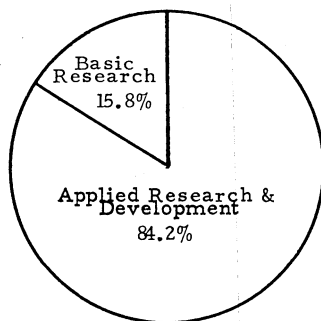


BASIC AND APPLIED RESEARCH AND DEVELOPMENT^{1/}

Prescription drug manufacturers allocated 15.8 percent of their research and development funds to basic research in 1965 (see Chart 11). U.S. expenditures of firms responding to this section amounted to \$231 million,^{2/} or 71 percent of the \$327 million spent by all 77 firms analyzed throughout most of this report.

Chart 11
Basic and Applied
Research and Development, 1965



^{1/} Based on responses from 42 member firms only. Data presented in this section constitute neither the total number of R&D performers nor total expenditures in the U.S. A more complete coverage of PMA membership comparable to earlier sections in this report would undoubtedly increase the number of firms allocating funds to basic and other types of research as well as total expenditures for such activities. For various reasons, particularly related to the difficulty firms experience in carefully identifying basic research operations and related costs within their research effort. There was a smaller response to this section of the research and development survey.

^{2/} Reporting 42 firms spent \$36.5 million for basic research and \$194.7 million for applied research and development.

BASIC RESEARCH^{1/}

Twenty-nine companies spent \$36.5 million for basic research.^{2/} The ten largest respondents accounted for two-thirds of this total.

Firms conducting or financing basic research allocated 19.3 percent of their total research and development expenditures for original investigations. A smaller ratio of 15.8 percent is obtained when the additional 13 firms with only applied research and development programs are included in the analysis. The latter were mostly smaller firms (see Chart 13).

Table 23

IMPORTANCE OF BASIC RESEARCH TO
DIFFERENT SIZE FIRMS, 1965

Sales Group (millions of dollars)	Firms with & without Basic Research		Firms with Basic Research	
	Number of Firms	% Spent for Basic Research	Number of Firms	% Spent for Basic Research
\$100 & over	10	16.5%	9	18.8%
\$30-under \$100	11	14.8	8	21.5
Less than \$30	<u>21</u>	<u>13.8</u>	<u>12</u>	<u>19.0</u>
Average, All Firms	42	15.8%	29	19.3%

^{1/} Based on responses from 42 member firms.

^{2/} Reporting companies' own funds spent for original investigations conducted within and outside of company facilities, excluding all government funds.

APPLIED RESEARCH AND DEVELOPMENT EXPENDITURES^{1/}

In 1965, more than half of the industry's applied research and development funds were directed toward the creation of drugs to be effective in three classes: (1) central nervous system and sense organ disorders; (2) parasitic and infective diseases; and (3) neoplasms, endocrine system and metabolic diseases. Table 24 is a breakdown by therapeutic purpose of the reporting firms' applied research and development expenditures in the United States.

Table 24

DISTRIBUTION OF APPLIED RESEARCH AND
DEVELOPMENT EXPENDITURES BY
THERAPEUTIC PURPOSE, 1965

	Company Financed U.S. R&D Funds		
	Number of Firms	Expen- ditures (millions)	Per- centage
<u>Research for the Discovery and Development</u>			
<u>For Human Use of:</u>			
Drugs for central nervous system and sense organs (37)		\$ 37.1	19.0%
Drugs affecting parasitic and infective diseases . . . (21)		33.9	17.4
Drugs for neoplasms, endocrine system and metabolic diseases (27)		32.8	16.8
Drugs acting on cardiovascular system (36)		18.8	9.7
Drugs acting on digestive or genito-urinary systems . (32)		15.1	7.8
Biologicals (13)		8.4	4.3
Drugs acting on respiratory system (26)		5.5	2.8
Vitamins, nutrients and hematinics. (17)		4.6	2.4
Diagnostic agents. (20)		4.0	2.1
Drugs acting on skin. (17)		3.4	1.7
Other pharmaceutical preparations. (25)		18.5	9.5
<u>Research for the Discovery and Development</u>			
<u>For Animal Use of:</u>			
Pharmaceutical preparations. (18)		9.9	5.1
Biologicals. (12)		2.7	1.4
TOTAL	(42)	\$194.7	100.0%

^{1/} Based on responses from 42 member firms.

Company Size and Applied Research and Development: Table 25 shows the "typical" allocation of the applied research and development dollar for a research-minded firm in a particular sales group. The largest funds were directed to discovery of drugs affecting parasitic and infective diseases by manufacturers with global sales of \$100 million and over. Next in importance was research for the discovery of drugs acting on central nervous system and sense organs, a field equally important to the medium to smaller firms.

Table 25

AVERAGE COMPANY APPLIED RESEARCH AND
DEVELOPMENT DOLLAR ALLOCATION,
BY SALES GROUP, 1965

<u>Research for the Discovery and Development</u> <u>For Human Use of:</u>	Sales Group		
	<u>\$100 million</u> <u>and over</u>	<u>\$30-\$100</u> <u>million</u>	<u>Less than</u> <u>\$30 million</u>
Drugs acting on central nervous system and sense organs	19.3%	17.0%	23.4%
Drugs affecting parasitic and infective diseases	21.1	13.5	3.1
Drugs affecting neoplasms, endocrine system & metabolic diseases	18.6	16.3	6.3
Drugs acting on cardiovascular system	8.1	12.3	13.0
Drugs acting on digestive or genito- urinary systems	6.6	8.3	14.3
Biologicals	4.8	4.0	1.7
Drugs acting on respiratory system	2.7	2.6	4.3
Vitamins, nutrients & hematinic drugs	2.4	2.0	3.6
Diagnostic agents	1.1	1.8	9.6
Drugs acting on skin	1.2	1.4	6.5
Other pharmaceutical preparations	5.6	18.5	9.5
<u>Research for the Discovery and Development</u> <u>For Animal Use of:</u>			
Pharmaceutical preparations	6.7	2.0	3.0
Biologicals	1.8	0.3	1.7
TOTAL, Applied R&D	<u>100.0%</u>	<u>100.0%</u>	<u>100.0%</u>
Number of Firms Reporting: (42)	(10)	(11)	(21)

MANPOWER^{1/}

Over 16,400 research and development personnel were employed by the pharmaceutical industry in 1965. About one-fourth held doctoral degrees. Scientists constituted 54 percent of the research and development staff and technicians and supporting personnel 46 percent.

Relationship of Research and Development Expenditures to Scientific and Professional Staff: A National Institutes of Health analysis (see footnote below) states that, "the proportion of scientific and professional staff to the total research and development staff appears to be an inverse function of the total volume of sales, with the larger organizations employing a relatively smaller percentage of scientific staff to the total research and development staff."

PMA analyses of the relationship between research and development manpower and research and development spending corroborate the National Institutes of Health findings. Table 26 illustrates that the correlation between the size of the research and development budget and the ratio of scientific and professional staff to the total research and development staff is negative. Data in Table 27 give further credence to the aforementioned National Institutes of Health hypothesis. The table indicates that research and development performers with large budgets employ relatively a smaller percentage of doctoral level staff.

^{1/} No attempt is made in the current study to deal with R&D manpower in detail. A comprehensive analysis of this subject appeared in the Resources for Medical Research Report No. 8, March 1966, "Trends in R&D Manpower in the Pharmaceutical Industry 1959-1965 and 1968," prepared by the National Institutes of Health of the U.S. Department of Health, Education and Welfare based on data provided by and in cooperation with PMA. The purpose of this section is to analyze the relationship between R&D expenditures and R&D manpower.

Table 26

U. S. R&D MANPOWER BY R&D BUDGET GROUP AND
TYPE OF STAFF, 1965

<u>Classi- fication of R&D, Budget^{1/}</u>	<u>All R&D Personnel</u>	<u>Scientific and Professional Personnel</u>	<u>Technicians and Supporting Personnel</u>	<u>Percent Scientific of all R&D Personnel</u>
A	6,110	3,190	2,920	52%
B	4,805	2,405	2,400	50
C	2,795	1,630	1,165	58
D	2,050	1,305	745	64
E	320	215	105	67
F	325	180	145	55
G	<u>35</u>	<u>20</u>	<u>15</u>	<u>57</u>
TOTAL	<u>16,440</u>	<u>8,945</u>	<u>7,495</u>	<u>54%</u>

Table 27

U. S. R&D MANPOWER BY R&D BUDGET
AND EDUCATIONAL LEVEL, 1965

<u>Classi- fication of R&D, Budget^{2/}</u>	<u>All R&D Personnel</u>	<u>Doctoral Personnel</u>	<u>Less than Doctoral Personnel</u>	<u>Percent Doctoral of all R&D Personnel</u>
A	6,110	1,430	4,680	23%
B	4,805	985	3,820	20
C	2,795	610	2,185	22
D	2,050	525	1,525	26
E	320	105	215	33
F	325	95	230	29
G	<u>35</u>	<u>15</u>	<u>20</u>	<u>43</u>
TOTAL	<u>16,440</u>	<u>3,765</u>	<u>12,675</u>	<u>23%</u>

^{1/}See page 39, Table 19.^{2/}ibid.

Average R&D Expenditures Per R&D Staff Person: With a working force of 16,440 during 1965, the industry spent \$365 million for research and development activities. Thus, an average of \$22,200 was spent to finance the activities of each member of the R&D team, including all scientific, professional and supporting staff. The average is nearly double for each professional or scientific individual -- \$40,800. A more significant figure may be the amount of money spent to support a doctoral-level scientist -- \$97,000. The above averages were somewhat lower when calculated solely on the basis of intramural spending. The over-all average dropped to \$17,600; while the per scientist figure was \$32,300. Each doctoral-level scientist had nearly \$76,700 at his command (see Table 28).

Table 28

INTRAMURAL R&D EXPENDITURES PER R&D PERSON
BY R&D BUDGET, 1965

Classification of R&D ^{2/} Budget	All R&D Personnel	Scientific and Professional Personnel	Doctoral Personnel
A	\$19,300	\$36,900	\$82,300
B	16,700	33,400	81,900
C	17,000	29,200	77,700
D	16,100	25,200	62,600
E	16,500	24,500	51,300
F	13,500	24,700	45,600
G	<u>13,000</u>	<u>22,400</u>	<u>30,800</u>
Average, All Firms	\$17,600	\$32,300	\$76,700

^{1/} The National Science Foundation average for 1964, latest year available, was \$31,700. According to the National Science Foundation the ratio has increased every year since 1957. 1963 -- \$31,100; 1962 -- \$29,200; 1961 -- \$28,100; 1960 -- \$26,700; 1959 -- \$25,900; 1958 -- \$23,300; and 1957 -- \$21,200. The National Science Foundation, Surveys of Science Resources Series, "Basic Research, Applied Research, and Development in Industry, 1964", NSF 66-28, June 1966.

^{2/} See page 39, Table 19.

Relationship of R&D Budget and Expenditures Per Scientist:

Table 28 indicates that there is a direct relationship between the size of the R&D budget and expenditures per scientist. For instance, a doctoral-level scientist in a Group A or B company had about \$82,000 at his disposal, including his staff's salaries.^{1/} However, other scientists had less to work with. A Group E company scientist with a doctoral degree was "allocated" about \$51,000. His colleagues with a G company received only \$31,000 each.

The relationship between magnitude of the research and development budget and the per person expenditures is demonstrated equally well by the "scientific and professional personnel" data. Here the range of variance is not as great. Nevertheless, per scientist allocations show a declining trend as we progress from Group A to Group G. The "all-persons" average does not show the same trend. In spite of this, the over-all average diminishes as the company research and development budget is reduced. For example, the average for Group A was the highest — \$19,300. Not much difference was observed among the averages for Groups B, C, D, and E; each of which was within the \$16,000 to \$17,000 range. The two smallest (F and G) groups averaged between \$13,000 and \$13,500.^{2/}

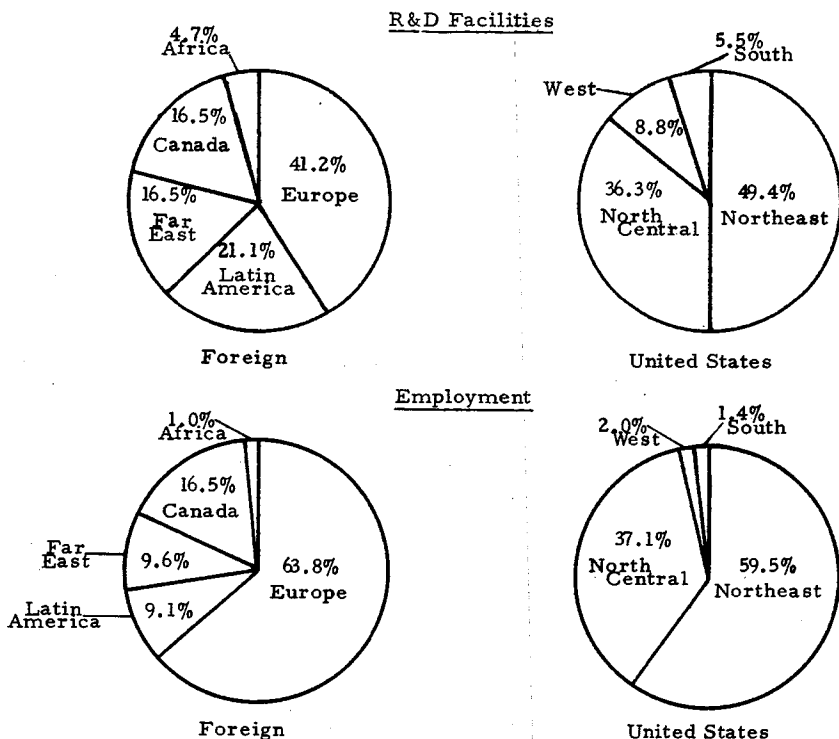
^{1/} Wages constitute 55 percent of total research and development costs (36 percent for scientists and 19 percent for research and development supporting personnel), according to the National Science Foundation. Material and supplies and other related research and development costs account for the remainder.

^{2/} PMA observations regarding the relationship between the research and development budget and expenditures per scientist are in line with those of the National Science Foundation. The Foundation found "a direct relationship in the cost ratio and R&D program size."

FACILITIES

The ethical pharmaceutical industry research laboratories provided employment for 18,600 people, 16,500 in the United States and 2,100 abroad. Respondent PMA member firms reported 176 research and development facilities in 20 states and 20 foreign nations.

Chart 12
Regional Distribution of
Research and Development, 1965



Foreign Research and Development Facilities: At the end of 1965 the United States ethical pharmaceutical industry had 85 research laboratories in 20 foreign nations. Most of these facilities were located at the manufacturing plant site. Only 16 were physically separate from manufacturing operations.

Thirteen research laboratories were located in the United Kingdom. This small segment accounted for more than half of the industry's combined research and development personnel in all foreign countries. Canada, with a larger number of research facilities, but a smaller number of research and development personnel, was the second region of major concentration (see Chart 12).

Drug research facilities abroad employed 2,100 persons in 1965 (see Table 29). Research and development laboratories operating at a different address from that of the manufacturing plant employed an average of about 15 scientists and supporting personnel.

Table 29

UNITED STATES RESEARCH AND DEVELOPMENT
FACILITIES ABROAD, 1965^{1/}

Region & Country ^{2/}	Number of R&D Facilities		T O T A L	Employment in R&D Facilities
	Outside Mfg. Plant	Within Mfg. Plant		
WESTERN EUROPE				
United Kingdom	3	10	13	1,135
France	2	5	7	60
Germany	1	5	6	35
Italy	-	3	3	10
Other ^{3/}	3	3	6	90
Regional Total	9	26	35	1,330
CANADA	2	12	14	345
PACIFIC & FAR EAST				
Australia ^{4/}	1	5	6	75
Other ^{4/}	3	5	8	125
Regional Total	4	10	14	200
LATIN AMERICA				
Mexico	1	5	6	95
Argentina	-	5	5	40
Brazil	-	3	3	15
Other ^{5/}	-	4	4	40
Regional Total	1	17	18	190
AFRICA	-	4	4	20
TOTAL	<u>16</u>	<u>69</u>	<u>85</u>	<u>2,085</u>

^{1/} Even though reported by only 19 PMA member companies with research facilities abroad, the following data is believed representative of the general dispersion of the U.S. ethical drug industry foreign research facilities and related employment. Complete coverage of the industry would not appreciably increase the employment figures reported.

^{2/} Countries are listed by region in descending order by number of employees.

^{3/} Includes facilities in Belgium (2), Switzerland (2), Netherlands (1), and an unspecified nation (1).

^{4/} Includes facilities in India (2), Japan (2), Philippines (2), Taiwan (1), and an unspecified nation (1).

^{5/} Includes facilities in Colombia (1), Peru (1), and an unspecified nation (1).

United States Research and Development Facilities: At the end of 1965 the ethical pharmaceutical industry research and development facilities were located in 20 states. However, more than four-fifths of the research and development facilities, and almost all of the scientists and supporting personnel were located in only half of these states (see Table 30).

The major portion of the industry's research facilities were located in three states of the Northeastern region. About one-half of the 91 major research centers were based in that area. These facilities also accounted for nearly 60 percent of the industry's total research and development personnel. The North Central region ranked second with 33 research facilities and 37 percent of the industrial staff engaged in research and related activities (see Chart 12).

Three states included in the Northeastern area -- New Jersey, New York and Pennsylvania -- were the leading drug research centers of the nation for 1965. Within the borders of these three neighboring states were included one-half of all research laboratories. New Jersey alone provided employment for 4,650 scientists and supporting personnel.

On the average a research laboratory was staffed with 60 people. Average employment for a research facility physically separate from the manufacturing plant site was considerably higher -- 150. However, a research facility located at the same address as the manufacturing operations averaged a smaller research staff of about 50.

Table 30

 UNITED STATES
 RESEARCH AND DEVELOPMENT FACILITIES, 1965^{1/}

Region and State ^{2/}	Number of R&D Facilities		T O T A L	Employment in R&D Facilities
	Outside Mfg. Plant	Within Mfg. Plant		
NORTHEAST				
New Jersey	4	15	19	4,650
New York	5	9	14	2,490
Pennsylvania	2	8	10	2,335
Other ^{3/}	-	2	2	355
Regional Total	11	34	45	9,830
NORTH CENTRAL				
Indiana	2	4	6	2,265
Illinois	1	8	9	1,665
Michigan	2	3	5	1,570
Ohio	-	5	5	425
Nebraska	-	3	3	30
Other ^{4/}	-	5	5	175
Regional Total	5	28	33	6,130
WEST				
California	-	7	7	330
Other	-	1	1	5
Regional Total	-	8	8	335
SOUTH ^{5/}				
	1	4	5	235
TOTAL	17	74	91	16,530 ^{6/}

^{1/} 52 respondents.^{2/} States are listed in descending order by number of employees.^{3/} Includes facilities in Connecticut (1) and Rhode Island (1).^{4/} Includes facilities in Iowa (1), Kansas (1), Missouri (1), and Wisconsin (2).^{5/} Includes facilities in Arkansas (1), Maryland (1), Virginia (2), and Texas (1).^{6/} Because it includes a larger number of persons with R&D supporting functions, the total employment figure on this page differs slightly from the R&D manpower data cited elsewhere in this report.

SELECTED DEFINITIONS

Basic Research: The National Science Foundation defines basic research as "original investigations for the advancement of scientific knowledge... which do not have specific commercial objectives, although they may be in fields of present or potential interests to the reporting company." The National Science Foundation studies using this definition show the "drug industry" to be the leader among industries engaging in basic research.

Bulk: For use as a pharmaceutical or medicinal product in further manufacture or in packaging, or for processing in animal feeds (but not as nutritional ingredients), or in prescription compounding, etc.

Company Financed Research and Development Expenditures: The total cost (worldwide) incurred for all pharmaceutical, biological and medical research and development activity financed by PMA member firms. These figures include cost of salaries, other direct costs, service, routine supplies, and supporting costs, plus a fair share of overhead (administration, depreciation, space charges, rent, etc.).

Excluded are costs of drug or medical research and development conducted on grant or contract for other companies, government agencies, and so on. Conversely, total outlays for all research and development work contracted to others (manufacturers, independent research laboratories, academic institutions, etc.) are included.

Company or firm is defined to include the parent company and affiliated, subsidiary or other related organizations under the same parent ownership.

Domestic U. S. Sales to Governments: Sales or shipments made directly to federal, state or local government agencies, hospitals and clinics.

Domestic U. S. Sales to Private Sector: Sales through regular marketing channels other than government agency administration or distribution.

Employment: Total number of full-time employees and full-time equivalent of those working part-time in ethical drug facilities.

Employment Abroad: Total number of full-time employees, whether U.S. citizens or not, of PMA member firms or any wholly-owned overseas corporations, or corporations in which PMA member firms had a substantial or controlling interest (ethical pharmaceutical manufacturing firms only).

Employees Engaged Primarily in Production and Product Control: Workers up through the working foreman level engaged in fabricating, processing, assembling, receiving, inspection, quality control, handling, packing, warehousing and storage, shipping, maintenance, repair, janitorial, watchman service, production development, record keeping, and other services associated with the production operations.

Employees Engaged Primarily in Research and Development: Personnel engaged in research, research administration, clinical evaluation and development; excludes personnel in promotion, sales, market research, business administration, production and quality control.

Ethical Pharmaceuticals: Products, including biologicals and medicinal chemicals, used for the cure, alleviation, mitigation, treatment, prevention or diagnosis of disease in humans or animals, and promoted primarily to the medical, pharmacy and allied professions; including products for "over-the-counter ethical" sales as well as for ultimate dispensing "by prescription only".

Government Grants and Contracts for Company Conducted Drug Research and Development: Included are dollar amount of grants and contractual payments received by member firms from governmental agencies for drug and medical research and development.

Manufacturing Plants: The definition of a plant is synonymous with that of the Bureau of the Census. By "production plant" is meant each location of a manufacturing, packaging or processing facility or group of such facilities geographically contiguous. Excluded are sales branches, administrative offices, research laboratories, warehouses, etc., which have no production, packaging or processing facilities. Employment figures for plants encompass all personnel, research and development staff, etc., as well as production workers.

Quality Control: Encompasses: (1) Employment and cost data on direct quality control activities. Includes all full-time employees responsible for sampling and testing of raw materials as they are produced, or while in storage; investigation of complaints; disposition of returned goods; selection and weighing of components; proper sanitation and storage of raw and finished materials; inspection of labels, contents, packages, etc.; maintenance in the final product of the desired purity, uniformity, potency and stability; and (2) Employment and cost data on indirect quality control activities. Includes the full-time equivalent of production workers and other employees who have inspection or quality control functions incidental to their primary assignments; pro-rated according to hours, facilities, etc., devoted to quality control functions as share of total labor time, and so on.

Research and Development: The term includes basic and applied research as well as development activities carried on or supported in the pharmaceutical, biological, chemical, medical and related sciences, including psychology and psychiatry, if the purpose of such activities is concerned ultimately with the utilization of scientific principles in understanding human diseases or in improving health.

Activity in pursuit of the following objectives is included:

- (1) Planned search for new knowledge, whether or not the search has reference to a specific application.
- (2) Application of existing knowledge to problems involved in the creation of a new product or process, including work required to evaluate possible use.
- (3) Application of existing knowledge to problems involved in the improvement of a present product or process.

For practical purposes, any scientific or technical activity which could result in a new drug, as defined in the Federal law, would certainly be considered research and development. Chemical synthesis of substances which might become drugs would be included in this definition and so would all clinical evaluation of new or old drugs.

The question, "When does development end and production begin?" is often asked. If the primary objective is to make further improvements on the product or process, then the work

comes within the definition of research and development. If, on the other hand, the product or process is substantially "set", and the primary objective is to develop markets or to do preproduction planning, or to make engineering changes in production equipment, then the work is not defined here as research and development. Routine quality control activities are not included; figures or estimates in development of quality control are included, where available.

Research and Development Facilities: The R&D facility is defined in very broad terms. It may be a five-man research laboratory within a manufacturing plant with 5,000 employees, or a research building housing 300 research workers and physically separate from manufacturing facilities. If located at the same address and in the same building, regardless of the number of research laboratories within it, the facility is counted as one. Research facilities at different locations (addresses) are listed separately, even if several such facilities are administered from one central research building.

Research and Development Scientific and Professional Staff: Includes all persons whose work requires the application for research and development of knowledge, skills, and scientific techniques, in the life, physical, engineering, or mathematical sciences, acquired through the completion of a four-year college course (or its equivalent) with a major in these fields or in medicine or other health professions. Excludes persons who have formal training in the sciences but who are not actively engaged in research and development.

Research and Development Technicians and Supporting Personnel: Includes persons who may hold some academic degree at the bachelor's level or above. Technicians include persons actually engaged in technical work at a level which requires knowledge of the life, physical, engineering, or mathematical sciences comparable at least to that acquired through technical institutes, junior colleges, or other formal post-high school training less extensive than four-year college training, or through equivalent on-the-job training or experience. Supporting Personnel includes persons who provide literature, clinical, statistical, or other services specifically for R&D staff.

Sales: Sales figures are reported as billed (before deducting cash discounts on sales and other marketing expenses), less returns

and allowances. Includes sales value of products bought and resold without further processing or repackaging as well as the dollar value of products made from own materials for other manufacturers' resale. Excluded are all royalty payments, interest and other income.

Sales Abroad: Actual sales consummated in foreign countries other than "Sales for Export to Other Firms". Such sales by affiliates, subsidiaries, distributors, sales offices, and other operations abroad are reported in dollars, computed at December 31, 1965, rate of exchange (when possible). Where a partially-owned subsidiary or joint venture is involved, the firm's share is determined on a proportionate profit-sharing basis.

Sale for Export: Reported "f. o. b. U. S. port":

- (a) To Other Firms: excludes intra-firm transactions; includes sales to third parties only.
- (b) Intra-Firm Transactions: includes "sales" and shipments to subsidiaries or affiliates for further handling, processing, or packaging by them. Reported as "net billed value", not end sales values.

Senator NELSON. Dr. Van Riper, please proceed.

STATEMENT OF DR. HART E. VAN RIPER, VICE PRESIDENT FOR MEDICAL AFFAIRS, GEIGY PHARMACEUTICALS, ARDSLEY, N.Y.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, D.C.

Dr. VAN RIPER. Thank you, Mr. Chairman.

I have submitted a statement for the hearing on November 16, and to conserve time, I have eliminated certain sentences in the statement that I will read today, but you may follow the statement that I have submitted in context.¹

I am Hart E. Van Riper, M.D., vice president for medical affairs of Geigy Pharmaceuticals, division of the Geigy Chemical Corp., Ardsley, N.Y. I was graduated from the University of Pennsylvania, being awarded a bachelor of arts degree in 1926 and a degree of doctor of medicine in 1930.

After an internship and residency in pediatrics, I was certified by the American Board of Pediatrics and practiced my specialty in Madison, Wis., from 1933 to 1941.

From 1941 to 1944, I served as Assistant Director for Maternal and Child Health, the Children's Bureau, at that time a bureau in the Department of Labor.

From 1944 to 1945, I was medical director of the Jackson Memorial Hospital, Miami, Fla.

From 1945 to 1956, I was medical director at the National Foundation for Infantile Paralysis, and during this period was concerned with the research that culminated in the field trials that established the safety and efficacy of the Salk poliomyelitis vaccine.

Since 1956, I have been associated with Geigy Pharmaceuticals and for 7 years, as medical director, I have been responsible for the clinical investigation of new drugs and the filing of new drug applications with the Food and Drug Administration.

In my statement I would like to outline briefly some of the activities of the research-oriented companies in the pharmaceutical industry in preparing safe and effective medicines for the treatment, cure, or prevention of disease. I hope to give you some idea of the vast amount of time, effort, talent, and money expended in the clinical phases of drug research.

In an article entitled "The Evaluation of New Drugs," which appeared in the Archives of Internal Medicine, volume 119, Drs. Barron and Bukantz, authors of this scientific paper, state that "it is presently estimated that approximately 4 years will elapse between the time a drug is recommended for development by the corporation's scientific advisory board and submitted as a new drug application (NDA) to the FDA for review and approval for marketing." This period may

¹ The complete prepared statement and attachments submitted by Dr. Van Riper for presentation on Nov. 16, 1967, begins at p. 2360, *infra*.

be extended several additional years before a drug product is finally approved. The orderly progression in the development from a chemical compound to a drug product; that is, from the early toxicity tests in a mouse to a safe and effective drug product in man, is an extremely time-consuming and costly procedure. It is estimated that for each drug product that receives an effective NDA, in excess of 6,000 chemical agents are investigated for their potential usefulness in the treatment or prevention of disease.

The enactment of the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act in 1962 added a second basic statutory requirement, proof of therapeutic effectiveness, to the 1938 amendments. Prior to 1962 the statute was primarily concerned with a need to demonstrate safety of a drug product.

Senator NELSON. What is the status presently of the question of the therapeutic effectiveness of the drugs that went on the market prior to 1962?

Dr. VAN RIPER. Mr. Chairman, those are currently under review by a committee of the National Science—the National Academy of Science, National Research Council. I understand approximately 20 of those drugs have had their final panel review and have been submitted to the Food and Drug Administration for action.

Senator NELSON. To determine therapeutic effectiveness?

Dr. VAN RIPER. Possibly effective or not effective.

Senator NELSON. Twenty of them. How many more are there for review?

Dr. VAN RIPER. I understand there are some 1,200 or more. They hope to have completed a review of about 400 by July 1, 1968. We were so advised about a month ago.

Senator NELSON. Under the law as I understand it, there was no requirement in the marketing of drugs prior to the Kefauver-Harris amendment in 1962 that proof of therapeutic efficacy be made; is that correct?

Dr. VAN RIPER. That was not required under the law; no, sir. But I believe that most companies were not interested in the investment of marketing a drug that was not effective.

Senator NELSON. I don't know about that. We don't know, as of this date, how many are on the market today that are not therapeutically effective, do we?

Dr. VAN RIPER. We do not. That is the purpose of this current review.

Senator NELSON. So for a majority of the drugs on the market in America today, therapeutic effectiveness has not been formally proved; is that correct?

Dr. VAN RIPER. That is right—not under the law. There has been under the law, I think, clinical evidence, Mr. Chairman, that would indicate there are probably not many ineffective drugs. Now, in hearing the discussions by the review committee, they did indicate that certain indications for some drugs might be questioned and might require further clinical investigation to establish the claim that had been allowed until now.

Senator NELSON. I would assume, in any event, that there must be a mass of clinical evidence on widely used drugs that were discovered prior to 1962, is there not?

Dr. VAN RIPER. That's right. And that was all submitted by the company that markets the drug at the time they made the information available for this review.

Senator NELSON. This committee isn't attempting itself, then, to do independent clinical studies of these drugs.

Dr. VAN RIPER. No. They are simply reviewing the clinical evidence that has been published, or it may be in the hands of the company that markets the drug, though it has not been published.

Senator NELSON. Do they have any kind of a timetable on how soon they expect to report on the balance?

Dr. VAN RIPER. We were told a month ago they hope to complete their reviews in about a year. Then those reviews will be submitted to the Food and Drug Administration who in turn will make a review and make final judgment as to whether the drug is effective, not effective, or probably effective.

Senator NELSON. Am I correct that if under the law any one of them turns out not to be therapeutically effective, it may be taken off the market? Is that what the law is?

Dr. VAN RIPER. Dr. Leahy has advised us they would undoubtedly give the company time to conduct clinical research to determine its effectiveness.

Mr. CUTLER. Senator, the law would require that the Food and Drug Administration at that point afford the company an opportunity for hearing.

Senator NELSON. I am talking about the end result. What will be done if the FDA concludes that there is no proof.

Mr. CUTLER. If FDA concludes—with the exception of a small class of grandfather drugs—if FDA should conclude that there is inadequate evidence of therapeutic effectiveness, it could require the drug to be taken off the market.

Senator NELSON. Have they grandfathered some drugs?

Mr. CUTLER. You did grandfather some drugs.

Senator NELSON. Not I.

Mr. CUTLER. The Congress did.

Senator NELSON. Some old drugs that professional oldtimers can't get along without?

Mr. CUTLER. It is a very complicated question and there is disagreement today as to just how many drugs are grandfathered. But it is a small number.

Senator NELSON. OK. I don't want to catch my wife paying for any of them, that's all.

Dr. VAN RIPER. The current regulations have placed under much closer scrutiny the evaluation of chemical substances employed in the treatment of human disease.

The first phase of a drug's evaluation is confined to study in appropriate species of animals. As much as a year may be required to establish the systemic absorption, tissue distribution, metabolism and elimi-

nation as well as the pharmacologic action and toxic potentials in laboratory animals. The biochemist, the pharmacologist, and the toxicologist must establish the basic data that warrants the first administration of the drug to man. It is unfortunate that in the present state of the art that this information gained from animal experimentation can only be considered an indicator of its potential action in man.

When the information that has been accumulated from the extensive animal research warrants the trial of the potential drug in man, a special form (FDA Form 1571)¹ is completed for submission to the Food and Drug Administration. A sample copy of a blank form is attached for your information. The assembly of the information required to complete this form may require as much as 2 months and constitutes a "Notice of Claimed Investigational Exemption for New Drug" (IND). The filing of this IND informs the FDA that the pharmaceutical company is prepared to initiate limited studies in man to determine whether or not the information gained from the animal studies can be confirmed.

The IND filed with the FDA represents a body of information gathered on a chemical entity or its combination products through animal experimentation. The cost involved in preparation and submission, however, reflects but a fraction of the total research expenditure to this point in the development of a marketable product. The man-hours of laboratory personnel, cost of animals, laboratory space, and equipment utilized in the screening of perhaps hundreds of compounds to discover a potentially safe and effective new drug product represents the hidden costs of drug research.

Prior to the 1962 amendments to the Food, Drug, and Cosmetic Act, it was the sole responsibility of the manufacturer to exercise his judgment in establishing the reasonableness and safety of first administering an entirely new drug product to man. Today, however, he shares that decision with the FDA which has the added responsibility of reviewing the information set forth on form 1571 and concurring in the decision to enter into phase I in the process of drug development. The IND is a total profile, containing all information that is known with respect to the chemical structure of active ingredients, biologic activity, pharmacologic action, dosage form, that is, tablet, capsule, or liquid, detailed process of manufacture and means of identifying ingredients both qualitatively and quantitatively, facilities for production, and a data sheet that provides all pertinent information for a prospective investigator.

The development of a drug product must necessarily be tailored to the chemical and physical nature of the active ingredients, anticipated therapeutic effects, the route of administration, the duration of action, and the ratio of pharmacologic and physiologic action to toxic potential. These developmental steps require an average of 12 months and are not instituted without the cautious control of persons experienced in the several disciplines that will influence the total procedure.

¹ See attachments for FDA Forms 1571, 1572, 1573, and FD356H, beginning at p. 2364, *infra*.

The following table shows a representative time schedule detailing the several integrated steps that must transpire after 1 to 5 years of basic research from the time of selection of the potential clinical candidate to the institution of the broadscale clinical trials.

The same procedures and time schedule are involved in the case of a combination product containing a new drug substance. The sponsor, in the majority of instances a pharmaceutical manufacturer, having already filed FDA Form 1571, is now required to obtain FDA Form 1572 from each investigator. The investigator in signing confirms his understanding of the nature of the drug product he will study; guarantees supervision of every aspect of the study by himself or one or more named associates who are directly responsible to him; describes the facilities available to him; and confirms his understanding that the product will be administered only to volunteers or patients to whom he has made a full disclosure of its actions, the purpose of administering it, and the benefits to be derived from the study, and from whom an informed consent has been obtained for the administration of the drug product.

The investigator, in signing FDA Form 1572, accepts all of the limitations on the investigational use of the experimental drug product as set forth in the sponsor's brochure. He further agrees to report promptly any event of clinical importance which may be observed in the subjects included in the study whether or not, in his judgment, the event is related to the product's administration. It is the responsibility of the sponsor to report these events to the FDA with an evaluation of the observation.

Phase I is a carefully restricted trial of the drug product in normal man, a relatively few volunteers who agree to take the drug product hopefully to confirm the information already established in a variety of animal species. Those qualified to investigate a drug product in this area of development must necessarily be carefully selected and knowledgeable in regard to drug action as it may affect all body systems and functions. This phase may involve no more than two investigators and perhaps 10 to 20 persons.

Phase II studies are warranted when the probably working-dose range has been ascertained and the human tolerance to the product has been established. At this phase of the investigation, a few selected patients suffering from the illness for which the product may be indicated are given the drug.

It is the customary practice in the industry that a single physician employee be assigned to monitor the investigations. He is responsible for the supplies of the investigational drug product, the filing of an FDA Form 1572 for each investigator, along with a protocol detailing the purpose of the particular study, its duration, and the numbers of patients expected to participate. Should an investigator, at any time or for any reason, elect to deviate from the protocol, the change must be reported to the FDA.

Studies during this period are most critical. The drug product must

demonstrate that it is both safe and effective. Critical judgment gained through experience and knowledge of conditions for which the drug product is indicated is essential for a proper evaluation upon which will be based a decision to proceed with the extensive and expensive clinical trials required for the eventual submission of the New Drug Application.

This monitoring of the investigation of an entirely new chemical for use in medicine demands the attention of a physician who possesses scientific curiosity, an in-depth knowledge of the clinical condition for which the drug product is being investigated, and clinical judgment in respect to the therapeutic agents already available to the practicing physician for the treatment or control of the clinical condition under investigation.

An additional responsibility is an administrative chore, for it involves the constant attention to the details of drug supply and preparation of progress reports to the FDA showing the continuing toxicological, teratological, and carcinogenic investigations are being correlated and integrated with the studies in man. Indeed, it is a complex exercise not to be undertaken by the inexperienced or uninformed.

Senator NELSON. May I interrupt for a moment? In this first full paragraph on the page you refer to the qualifications of the physician to monitor such an investigation. Are you referring to the doctor who does the experimenting?

Dr. VAN RIPER. I was referring in that instance to the physician employed by the pharmaceutical company.

Senator NELSON. What qualifications do you seek for the performance of clinical tests done pending approval of your application?

Dr. VAN RIPER. You try to pick out individuals who have, through scientific qualification, established a reputation in a particular field. If you are investigating an analgesic, you certainly go to someone in the field. If you are investigating a drug in cardiology, you go to a cardiologist. It is a highly selective process.

Senator NELSON. Is that a requirement of the law?

Dr. VAN RIPER. It is not a requirement of the law. But it is essential to good clinical investigation.

Senator NELSON. Does the FDA require, along with the submission of your accumulated clinical testing, submission of the qualifications of the doctor?

Dr. VAN RIPER. Those are submitted before you ever are permitted to begin the investigation.

Senator NELSON. They approve your proposal and the physicians who are to participate prior to your starting a clinical test?

Dr. VAN RIPER. Mr. Chairman, they don't actually give you written approval. But it does give them an opportunity—for instance, should they see you are using an investigator in whom they would have some doubts as to his qualifications, it provides them an opportunity to at least warn you that they think you have made a bad choice.

Senator NELSON. But it is a practice in the industry to seek physicians who have expertise in the disease area with which the drug is concerned?

Dr. VAN RIPER. That is right.

The ethical manufacturer of drug products, having established the safety and therapeutic action of the product under investigation, must make the final decision. Does this product represent a significant advance in therapeutics? What makes this drug product a useful therapeutic agent for the physician in his practice? What is the ratio of clinical effectiveness to the toxic potential?

At this stage of development the producer of a new drug product has a very substantial financial investment that has resulted in only a minimum of information on which to predict the commercial value. Also, this one drug product containing an active ingredient which has shown promise among the thousands that have been synthesized, has alone progressed to this stage of development.

Approximately 3 years after the decision to investigate a new drug product, plans are made for carrying out a phase III, broadly based, clinical trial. Prior to the initiation of this phase of the study, detailed analyses and review of the data derived from the phase II studies are completed. Any further modifications of the clinical data sheet, which are a consequence of new observations during the phase II period, are incorporated in a further revision of the clinical data sheet. At this point, a copy of FDA Form 1573 is sent to selected clinical investigators throughout the country. (A sample copy of this form is attached for your information.) This study provides a wide experience of use in all ethnic and socioeconomic groups in the total population. This is a broad test of the efficacy of the product in the specific clinical situations for which it is intended to be used. The sample of patients must be large enough to yield data upon which judgment can be made concerning the safety and efficacy of the product. As many as 150 (or more) clinicians may participate and the total number of patients under their observation will frequently exceed 1,500 and often 3,000. Although it is estimated that an additional 18 to 24 months will be required for the completion of the phase III trial, it is likely that more than 4 years will pass between the initiation of clinical research on a product and the completion and filing of its NDA. During this period the monitor maintains close contact with each investigator so that he is informed of developments throughout the clinical trial and obtains periodic reports of the progress of the trials.

A sample copy of the New Drug Application Form FD 356 H is included as an attachment. The detailed information required to complete this application can be appreciated in part by review of the form. FDA approval of an NDA does not terminate the monitoring of the drug product by the medical department of the sponsoring firm. Once the drug product is available on prescription, there is no way of preventing its being used in dosages and for indications not included in the approved labeling. A drug product may be used improperly resulting in failure in therapeutic response or causing drug reactions. Both drug failures and adverse effects must be carefully investigated and reported to the FDA. These reports must be submitted every 3 months for the first year of distribution, every 6 months during the second year, and once a year thereafter. Any contraindication to use or toxic effect not already detailed in the

labeling must be investigated and reported within 15 days after such knowledge is available to the producers.

No one has a greater interest or responsibility in the safety and effectiveness of a drug product than the manufacturer, who can ill afford to market a drug that will demonstrate a toxic response not commensurate with its effectiveness. To insure the continuing flow of all essential information in respect to an FDA approved drug product the pharmaceutical manufacturers support the Armed Forces Institute of Pathology in its investigation of tissue reaction to possible toxic drug effects and the American Medical Association's Council on Drugs and its panel on hematology of the registry on adverse reactions.

More than 700 doctors of medicine are engaged full-time by PMA member firms. There is a grave responsibility in the overall development of a new prescription drug product. Less than an honest appraisal of the product and constant surveillance of the claims made for it by its marketers could destroy a scientific reputation that was not obtained without great effort.

Senator NELSON. Thank you very much, Doctor. We certainly appreciate your taking the time to come here and present your very valuable testimony to the committee. We regret the great imposition on your time.

(The complete prepared statement and attachments submitted by Dr. Van Riper for presentation on November 16, 1967, follows:)

STATEMENT OF DR. HART E. VAN RIPER, VICE PRESIDENT, GEIGY PHARMACEUTICALS

THE CLINICAL EVALUATION OF NEW DRUGS

Mr. Chairman and members of the committee, I am Hart E. Van Riper, M.D., Vice President for Medical Affairs of Geigy Pharmaceuticals, Division of the Geigy Chemical Corporation, Ardsley, New York. I was graduated from the University of Pennsylvania, being awarded a bachelor of arts degree in 1926 and a degree of doctor of medicine in 1930. After an internship and residency in pediatrics, I was certified by the American Board of Pediatrics and practiced my specialty in Madison, Wisconsin from 1933 to 1941. From 1941 to 1944, I served as Assistant Director for Maternal and Child Health, The Children's Bureau, at that time a bureau in the Department of Labor. From 1944 to 1945, I was Medical Director of the Jackson Memorial Hospital, Miami, Florida. From 1945 to 1956, I was Medical Director at the National Foundation for Infantile Paralysis, and during this period was concerned with the research that culminated in the field trials that established the safety and efficacy of the Salk poliomyelitis vaccine. Since 1956, I have been associated with Geigy Pharmaceuticals and for seven years, as Medical Director, I have been responsible for the clinical investigation of new drugs and the filing of new drug applications with the Food and Drug Administration.

In my statement I would like to outline briefly some of the activities of the research-oriented companies in the pharmaceutical industry in preparing safe and effective medicines for the treatment, cure or prevention of disease. I hope to give you some idea of the vast amount of time, effort, talent and money expended in the clinical phases of drug research.

In an article entitled, "The Evaluation of New Drugs", which appeared in The Archives of Internal Medicine, Volume 119, June, 1967, scientists not associated with the pharmaceutical industry presented in considerable detail the steps that must be taken in the evaluation of a chemical compound from the chemist's laboratory to the finished pharmaceutical product on the pharmacist's shelf. Drs. Barron and Bukantz, authors of this scientific paper, state that "it is presently estimated that approximately four years will elapse between the time a

drug is recommended for development by the corporation's scientific advisory board and submitted as a New Drug Application (NDA) to the FDA for review and approval for marketing". This period may be extended several additional years before a drug product is finally approved. The orderly progression in the development from a chemical compound to a drug product, that is, from the early toxicity tests in a mouse to a safe and effective drug product in man is an extremely time consuming and costly procedure. It is estimated that for each drug product that receives an effective NDA, in excess of 6,000 chemical agents are investigated for their potential usefulness in the treatment or prevention of disease.

The enactment of the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act in 1962 added a second basic statutory requirement, proof of therapeutic effectiveness, to the 1938 amendments. Prior to 1962 the statute was primarily concerned with a need to demonstrate safety of a drug product.

The current regulations have placed under much closer scrutiny the evaluation of chemical substances employed in the treatment of human disease. The development of a new chemical entity for use as a therapeutic agent has also become a much more complicated and laborious process. The regulations have thus added materially to the cost and the time required to develop a new drug product.

The first phase of a drug's evaluation is confined to study in appropriate species of animals. As much as a year may be required to establish the systemic absorption, tissue distribution, metabolism and elimination as well as the pharmacologic action and toxic potentials in laboratory animals. The biochemist, the pharmacologist, and the toxicologist must establish the basic data that warrants the first administration of the drug to man. It is unfortunate that in the present state of the art that this information gained from animal experimentation can only be considered an indicator of its potential action in man. The orderly progression of drug development from "mouse to man" is fraught with both difficulties and disappointments.

When the information that has been accumulated from the extensive animal research warrants the trial of the potential drug in man, a special form (FDA Form 1571) is completed for submission to the Food and Drug Administration. (A sample copy of a blank form is attached for your information). The assembly of the information required to complete this form may require as much as two months and constitutes a "Notice of Claimed Investigational Exemption for New Drug" (IND). The filing of this IND informs the FDA that the pharmaceutical company is prepared to initiate limited studies in man to determine whether or not the information gained from the animal studies can be confirmed.

The IND filed with the FDA represents a body of information gathered on a chemical entity or its combination products through animal experimentation. The cost involved in preparation and submission; however, reflects but a fraction of the total research expenditure to this point in the development of a marketable product. The manhours of laboratory personnel, cost of animals, laboratory space, and equipment utilized in the screening of perhaps hundreds of compounds to discover a potentially "safe and effective" new drug product, represent the "hidden costs" of drug research.

Prior to the 1962 amendments to the Food, Drug and Cosmetic Act, it was the sole responsibility of the manufacturer to exercise his judgment in establishing the reasonableness and safety of first administering an entirely new drug product to man. Today, however, he shares that decision with the FDA which has the added responsibility of reviewing the information set forth on Form 1571 and concurring in the decision to enter into Phase I in the process of drug development. The IND is a total profile, containing all information that is known with respect to the chemical structure of active ingredients, biologic activity, pharmacologic action, dosage form, i.e., tablet, capsule or liquid, detailed process of manufacture and means of identifying ingredients both qualitatively and quantitatively, facilities for production, and a data sheet that provides all pertinent information for a prospective investigator.

The development of a drug product must necessarily be tailored to the chemical and physical nature of the active ingredients, anticipated therapeutic effects, the route of administration, the duration of action, and the ratio of pharmacologic and physiologic action to toxic potential. These developmental steps require an average of twelve months and are not instituted without the cautious control of

persons experienced in the several disciplines that will influence the total procedure.

The following table shows a representative time schedule detailing the several integrated steps that must transpire after one to five years of basic research from the time of selection of the potential clinical candidate to the institution of the broad-scale clinical trials:

Step I (4 to 6 months): Preparation of active ingredient, dosage form, animal toxicity, basic brochure, and filing of IND.

Step II (3 to 6 months): Human tolerance (phase I).

Step III (3 to 6 months): Refined dose range and efficacy (phase II).

Concurrent studies: Toxicity, biochemistry, metabolism, blood levels, and formulation.

Step IV (12 to 18 months): Controlled studies, potency, and safety determination of possible claims.

The same procedures and time schedule are involved in the case of a combination product containing a new drug substance. The sponsor, in the majority of instances a pharmaceutical manufacturer, having already filed FDA Form 1571, is now required to obtain FDA Form 1572 from each investigator. (A sample copy of this form is attached for your information.) The investigator in signing confirms his understanding of the nature of the drug product he will study; guarantees supervision of every aspect of the study by himself or one or more named associates who are directly responsible to him; describes the facilities available to him; and confirms his understanding that the product will be administered only to volunteers or patients to whom he has made a full disclosure of its actions, the purpose of administering it, and the benefits to be derived from the study, and from whom an informed consent has been obtained for the administration of the drug product.

The investigator, in signing FDA Form 1572, accepts all of the limitations on the investigational use of the experimental drug product as set forth in the sponsor's brochure. He further agrees to report promptly any event of clinical importance which may be observed in the subjects included in the study whether or not, in his judgment, the event is related to the product's administration. It is the responsibility of the sponsor to report these events to the FDA with an evaluation of the observation.

Phase I is a carefully restricted trial of the drug product in normal man, a relatively few volunteers who agree to take the drug product hopefully to confirm the information already established in a variety of animal species. Those qualified to investigate a drug product in this area of development must necessarily be carefully selected and knowledgeable in regard to drug action as it may affect all body systems and functions. This phase may involve no more than two investigators and perhaps ten to twenty persons.

Phase II studies are warranted when the probable working dose range has been ascertained and the human tolerance to the product has been established. At this phase of the investigation, a few selected patients suffering from the illness for which the product may be indicated are given the drug.

It is the customary practice in the industry that a single physician employee be assigned to monitor the investigations. He is responsible for the supplies of the investigational drug product the filing of an FDA Form 1572 for each investigator, along with a protocol detailing the purpose of the particular study, its duration and the numbers of patients expected to participate. Should an investigator, at any time or for any reason, elect to deviate from the protocol, the change must be reported to the FDA.

Studies during this period are most critical. The drug product must demonstrate that it is both safe and effective. Critical judgment gained through experience and knowledge of conditions for which the drug product is indicated is essential for a proper evaluation upon which will be based a decision to proceed with the extensive and expensive clinical trials required for the eventual submission of the New Drug Application.

This monitoring of the investigation of an entirely new chemical for use in medicine demands the attention of a physician who possesses scientific curiosity, an in-depth knowledge of the clinical condition for which the drug product is being investigated, and clinical judgment in respect to the therapeutic agents already available to the practicing physician for the treatment or control of the clinical condition under investigation.

An additional responsibility is an administrative chore, for it involves the constant attention to the details of drug supply and preparation of progress reports to the FDA showing the continuing toxicological, teratological and carcinogenic investigations are being correlated and integrated with the studies in man. Indeed it is a complex exercise not to be undertaken by the inexperienced or uninformed.

The ethical manufacturer of drug products, having established the safety and therapeutic action of the product under investigation, must make the final decision. Does this product represent a significant advance in therapeutics? What makes this drug product a useful therapeutic agent for the physician in his practice? What is the ratio of clinical effectiveness to the toxic potential?

At this stage of development the producer of a new drug product has a very substantial financial investment that has resulted in only a minimum of information on which to predict the commercial value. Also, this one drug product containing an active ingredient which has shown promise among the thousands that have been synthesized, has alone progressed to this stage of development.

Approximately three years after the decision to investigate a new drug product, plans are made for carrying out a Phase III, broadly based, clinical trial. Prior to the initiation of this phase of the study, detailed analyses and review of the data derived from the phase II studies are completed. Any further modifications of the clinical data sheet, which are a consequence of new observations during the Phase II period, are incorporated in a further revision of the clinical data sheet. At this point, a copy of FDA Form 1573 is sent to selected clinical investigators throughout the country. (A sample copy of this form is attached for your information.) This study provides a wide experience of use in all ethnic and socio-economic groups in the total population. This is a broad test of the efficacy of the product in the specific clinical situations for which it is intended to be used. The sample of patients must be large enough to yield data upon which judgment can be made concerning the safety and efficacy of the product. As many as 150 (or more) clinicians may participate and the total number of patients under their observation will frequently exceed 1,500 and often 3,000. Although it is estimated that an additional 18 to 24 months will be required for the completion of the Phase III trial, it is likely that more than four years will pass between the initiation of clinical research on a product and the completion and filing of its NDA. During this period the monitor maintains close contact with each investigator so that he is informed of developments throughout the clinical trial and obtains periodic reports of the progress of the trials.

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[Attachments]

FORM FD-1571 (4/67)
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

Form Approved
Budget Bureau No. 57-R0030

NOTICE OF
CLAIMED INVESTIGATIONAL EXEMPTION
FOR A NEW DRUG

Name of Sponsor _____

Address _____

Date _____

Name of Investigational Drug _____

To the Secretary of Health, Education, and Welfare
For the Commissioner of Food and Drugs
Washington, D.C. 20204

Dear Sir:

The sponsor, _____, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternatives for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug. Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the

preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of five copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of claimed investigational exemption for a new drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1575 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations, as follows:

a. *Clinical pharmacology.* This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and *in vitro* data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. *Clinical trial.* This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, in-

cluding completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. It is understood that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. It is understood that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

Very truly yours,

(Sponsor)

Per

(Indicate authority)

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

2366 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

FORM FD-1572 (8/64)

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR (Clinical Pharmacology)

TO SUPPLIER OF THE DRUG (Name and Address)

NAME OF INVESTIGATOR (Print or Type)

DATE

NAME OF DRUG

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(j) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.

1. A STATEMENT OF THE EDUCATION AND TRAINING THAT QUALIFIES ME FOR CLINICAL PHARMACOLOGY.

2. THE NAME AND ADDRESS OF THE MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL PHARMACOLOGY WILL BE CONDUCTED.

3. THE EXPERT COMMITTEES OR PANELS RESPONSIBLE FOR APPROVING THE EXPERIMENTAL PROJECT.

4. THE ESTIMATED DURATION OF THE PROJECT, AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

5. A GENERAL OUTLINE OF THE PROJECT TO BE UNDERTAKEN. (Modification is permitted on the basis of experience gained without advance submission of amendments to the general outline.)

(Continued on reverse)

6. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG:

- a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.
- b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended or terminated to return to the sponsor any unused supply of the drug.
- c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.
- d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effect which may reasonably be regarded as caused by, or is probably caused by, the new-drug shall be reported to the sponsor promptly; and if the adverse effect is alarming it shall be reported immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.
- e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date the new-drug application is approved for the drug; or if no application is to be filed or is approved until 2 years after the investigation is discontinued and the Food and

Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

- f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him,

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

- g. The investigator certifies that he will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

(Name of Investigator)

(Address)

FORM FD-1573 (8/64)

STATEMENT OF INVESTIGATOR

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATIONTO SUPPLIER OF DRUG (*Name and Address*)NAME OF INVESTIGATOR (*Print or Type*)

DATE

NAME OF DRUG

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.

1. THE FOLLOWING IS A STATEMENT OF MY EDUCATION AND EXPERIENCE:

- a. Colleges, universities, and medical or other professional schools attended, with dates of attendance, degrees, and dates degrees were awarded.

- b. Postgraduate medical or other professional training: Dates, names of institutions, and nature of training.

- c. Teaching or research experience: Dates, institutions, brief description of experience.

- d. Experience in medical practice or other professional experience: Dates, institutional affiliations, nature of practice, or other professional experience.

- e. Representative list of pertinent medical or other scientific publications: Titles of articles, names of publications and volume, page number, and date.

(If this information has previously been submitted to the sponsor, it may be referred to and any additions made to bring it up to date.)

2. IF ANY HOSPITAL, INSTITUTIONAL, AND CLINICAL LABORATORY FACILITIES, ETC., ARE AVAILABLE AND WILL BE EMPLOYED IN CONNECTION WITH THE INVESTIGATION, AN IDENTIFICATION OF EACH FOLLOWS:

(If this information has previously been submitted to the sponsor, reference to the previous submission will be adequate.)

(Continued on reverse)

3. THE INVESTIGATIONAL DRUG WILL BE USED BY THE UNDERSIGNED OR UNDER HIS SUPERVISION IN ACCORDANCE WITH THE PLAN OF INVESTIGATION DESCRIBED AS FOLLOWS: (Outline the plan of investigation, including approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and tests results obtained. This plan may include reasonable alternates and variations, and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)

4. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS, GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG:

- a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.
- b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated to return to the sponsor any unused supply of the drug.
- c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.
- d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.
- e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period

of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

- f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him, _____

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

- g. The investigator certifies that he will inform any subjects, including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

(Name of Investigator)

(Address)

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

FD-356H (REV. 6/67) DRUGS FOR HUMAN USE
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

Form Approved
Budget Bureau No. 57-R0003

NEW DRUG APPLICATION

(Title 21, Code of Federal Regulations, §130.4)

Name of applicant _____

Address _____

Date _____

Name of new drug _____

- ☐ Original application (regulation §130.4).
☐ Amendment to original, unapproved application (regulation §130.7).
☐ Supplement to an approved application (regulation §130.9).
☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. **Table of contents.** The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. **Summary.** A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. **Chemistry.**
i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. **Preclinical studies.** (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology, and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. **Clinical studies.** (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. **Evaluation of safety and effectiveness.** a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. **Copies of the label and all other labeling to be used for the drug** (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed

components of the finished drug: *Provided, however, That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.*

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infre-

quency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C. 20204), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

(Applicant)

Per

(Responsible official or agent)

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

STATEMENT OF LELAND W. BLAZEY, VICE PRESIDENT, MANUFACTURING, ENGINEERING, AND PURCHASING, McNEIL LABORATORIES, INC., FORT WASHINGTON, PA.

Mr. BLAZEY. Mr. Chairman, I would like to have my statement which was submitted for presentation on November 16 made a part of the record.

Senator NELSON. Your statement will be printed in full in the record. You may read from it or extemporize, or present it in any way you wish.

Mr. BLAZEY. I would prefer, Mr. Chairman, to abstract some paragraphs from it, and I will let you know what pages I have deleted as I proceed through it.¹

Senator NELSON. All right.

Mr. BLAZEY. My name is Leland W. Blazezy. I am vice president in charge of manufacturing, engineering, and purchasing for McNeil Laboratories, Inc. I am appearing today on behalf of the Pharmaceutical Manufacturers Association.

Senator NELSON. Where is McNeil Laboratories' home office?

Mr. BLAZEY. Fort Washington, Pa., just outside of Philadelphia.

Senator NELSON. Is this where your manufacturing is done?

Mr. BLAZEY. Yes.

Senator NELSON. All of it?

Mr. BLAZEY. Yes.

Mr. GORDON. That is a subsidiary of what company?

Mr. BLAZEY. Wholly owned subsidiary of Johnson & Johnson.

Senator NELSON. There is another rolcall. I have to answer it.

(Whereupon, there was a short recess.)

Senator NELSON. Go ahead. Sorry about the interruption.

Mr. BLAZEY. Since the early forties, I have worked with several pharmaceutical companies and have participated in some of our industry's pioneering efforts in design and process procedures relating to antibiotics, medicinal chemicals and pharmaceutical products.

As one who has been trained in the techniques of pharmaceutical manufacturing and engineering, I shall attempt to explain the great care which goes into the manufacturing operations of the research-oriented, quality-conscious companies in our industry.

In particular, I shall try to point up how this dedication to quality is a distinguishing characteristic of the most respected prescription drug manufacturers in this country.

To begin with, manufacturing facilities and equipment must be adequate for the highly technological science of making safe and effective drug products. But more than that, it is essential that we have top-caliber personnel in sufficient numbers to do this highly complex job.

Although the FDA's good manufacturing practice (GMP) regulations outline the general conditions under which prescription drugs are to be produced, there are wide differences in the actual operations of quality manufacturers and those of less responsible companies. The quality-conscious companies go well beyond basic FDA requirements.

¹ The complete prepared statement and attachment submitted by Mr. Blazezy for presentation on Nov. 16, 1967, begins at p. 2377, *infra*.

As a matter of fact, many of these firms did not find it necessary to make significant changes as a result of the 1962 amendments to the Food and Drug Act. Because of the high standards they had set for themselves over a period of many years, they were already in compliance with most of these new regulations.

As new medicinal agents have been discovered, our industry has recognized the need for constantly improving manufacturing methods and equipment. The advent of high-potency compounds, new formulation requirements, and more sophisticated medications has dictated change. Particularly during the last 10 to 20 years, the research-minded manufacturer has modified his physical plant and updated facilities in order to produce consistently safe and effective products.

These companies in our business usually are distinguished by stability of employment. Obviously, this is a most important factor in attracting good employees who are dedicated to the production of quality drugs. These workers are well-trained people who understand the rules and regulations under which the drug industry operates and who are proud of the part they play in their company's operations.

Buildings in which drugs are manufactured must be of suitable size and construction to house the necessary equipment and materials in such a manner that cross-contamination or mixup is avoided. In the better plants, provisions are made for cleaning the air and controlling temperature and humidity. One example of the great care that is taken to assure the most sanitary conditions possible is the sterilization of areas used for the production of hypodermic drugs. Much of the equipment used in these plants is custom-designed, and considerable engineering ingenuity is required.

Of paramount consideration are cleanliness and orderliness. For example, in my own company alone we have spent several hundred thousand dollars to separate operating equipment and functions, to provide a high degree of air filtration and dust control, and to insure the sanitation qualities of floors, ceilings and walls. This is typical of what the research-oriented companies are continuing to do to improve their operating areas.

Now, I should like to point out a few fundamentals about manufacturing methods and procedures of the quality-minded drug manufacturer. Our equipment must fulfill two important requirements:

First, we must be able to produce batches of a drug product with uniform consistency day in and day out.

Second, the equipment must be compatible with the chemicals involved and suitable for thorough cleaning to eliminate the possibility of contamination from product to product.

Clearly, maintenance of equipment is extremely important. For example, in the case of a tablet compression machine, where close tolerances are required, regular examination is essential to insure that each tablet produced meets the dose specified. Such care is part of the standard operating procedure of the quality-conscious, innovator-type of drug manufacturer.

All-important considerations for every capable drug manufacturer are: (1) Quality of raw materials used in the manufacturing process, and (2) in-process controls. I should like to elaborate on both of these points.

To assure the quality of a raw material, the careful company first insists that the supplier guarantee the quality and purity of the material, then makes double sure by conducting its own extensive tests.

This preoccupation with quality of raw materials applies to non-therapeutic as well as therapeutic substances: to nonofficial substances as well as those listed by the U.S. Pharmacopoeia is to assure the user of official medicinal substances of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity or adulterant that might be present.

In view of this undisputed fact, the quality-oriented pharmaceutical firm exerts additional efforts through the use of analytical know-how and in-process controls to give greater assurance of the identity, strength, quality, and purity of the ingredients which go into its products.

Throughout the drug manufacturing process, from raw materials through finished product, careful control must be exercised at every step of the way. Every quality-minded manufacturer follows a standing operating procedure which incorporates a system of checks and balances followed by quality audits.

Our standard procedures cover such important considerations as product and container identity, quarantine provisions, and storage conditions. Each product is covered by an appropriate batch record, and throughout the manufacturing operation great care is exercised to assure accuracy of weight, volume, and yield of each batch.

The packaging materials used are subjected to inspection, and particular care is exercised in the issuance of labels, cartons, and package inserts.

The warehousing of the finished product provides for proper storage, segregation, and identification by lot or batch number, as well as systematic rotation and inspection of stocks at regular intervals.

Another key factor in our standard procedures is the maintenance of records covering all manufacturing, packaging, and control operations concerned with a product. These records must be prepared with such care as to provide a history of each batch of every drug product.

The quality-conscious manufacturer continues his testing as long as a product is on the market.

Portions of each lot are retained and checks are made, even after the lot has reached the pharmacist's shelf, to make sure it measures up to the company's high standards.

As an illustration of the importance of checks and balances exercised during pharmaceutical manufacturing by some firms, I think it is interesting to note that in one of our own company's routine manufacturing operations we conduct some 687 inspections and tests during the course of making a finished product. Among these are 215 different inspections and tests on raw materials, 395 checkpoints and tests during the actual manufacturing, and 75 inspections and counts during the packaging operations.

The manufacturing principles I have discussed have been followed by the leading prescription drug companies of this country for many years. It is generally agreed by those who have firsthand knowledge of these research-minded pharmaceutical manufacturers that their plants stand out in their communities as models of modern industrial facilities.

Control of air pollution and maintenance of waste treatment facilities are among the important contributions such companies make toward their environment.

In concluding, Mr. Chairman, I should like to emphasize that the manufacture of quality drug products is a time-consuming and exacting process, requiring the best personnel and facilities. The reputable and responsible drug manufacturers of this country go as far as present-day technology permits in order to provide the highest quality prescription drugs for the medical profession and the public.

After all, it is not just the wood that makes the Stradivarius violin; it is the skill of the craftsman. It is not just the fabric that makes the fine suit; it is the skill of the tailor. So it is with prescription drugs. In the final analysis, differences in manufacturing process and controls can make the difference between good health and bad, between comfort and pain, and even between life and death.

Thank you.

Senator NELSON. I thank you.

(The complete prepared statement and attachment submitted by Mr. Blazey for presentation on November 16, 1967, follows:)

STATEMENT OF LELAND W. BLAZEY, VICE PRESIDENT, MANUFACTURING, ENGINEERING, AND PURCHASING, McNEIL LABORATORIES, INC.

MANUFACTURING CONSIDERATIONS IN QUALITY DRUG PRODUCTION

Mr. Chairman and members of the committee, my name is Leland W. Blazey. I am Vice President in charge of Manufacturing, Engineering and Purchasing for McNeil Laboratories, Inc. I am appearing today on behalf of the Pharmaceutical Manufacturers Association.

Since the early 40's I have worked with several pharmaceutical companies on technical assignments in development, engineering and production. Together with other technical personnel, I participated in some of our industry's pioneering efforts in design and process procedures relating to antibiotics, medicinal chemicals and pharmaceutical products.

I have also been responsible for directing the planning, engineering and construction on many projects dealing with chemical, pharmaceutical and research facilities in the United States and in foreign countries.

As one who has been trained in the techniques of pharmaceutical manufacturing and engineering, I shall attempt to explain the great care which goes into the manufacturing operations of the research-oriented, quality-conscious companies in our industry.

In particular, I shall try to point up how this dedication to quality is a distinguishing characteristic of the most respected prescription drug manufacturers in this country.

To begin with, manufacturing facilities and equipment must be adequate for the highly technological science of making safe and effective drug products. But more than that, it is essential that we have top-caliber personnel in sufficient numbers to do this highly complex job.

Although the F.D.A.'s Good Manufacturing Practice (GMP) Regulations outline the general conditions under which prescription drugs are to be produced, there are wide differences between actual operations of quality manufacturers and those of less responsible companies. The quality-conscious companies go well beyond basic F.D.A. requirements. As a matter of fact, many of these firms did not find it necessary to make significant changes as a result of the 1962 Amendments to the Food and Drug Act and the subsequent promulgation of GMP regulations. Because of the high standards they had set for themselves over a period of many years, they were already in compliance with most of these new regulations.

As new medicinal agents have been discovered, our industry has recognized the need for constantly improving manufacturing methods and equipment.

The advent of high-potency compounds, new formulation requirements, and more sophisticated medications has dictated change. Particularly during the last ten to twenty years, the research-minded manufacturer has modified his physical plant and updated facilities in order to produce consistently safe and effective products.

The research-oriented innovator type of company generally sets higher quality standards for its products than does the non-innovator. Moreover, a manufacturer of this type will not market a drug product until it has been clinically tested for safety and effectiveness. When one considers that there are many drug products which are classified by the F.D.A. as "old" drugs, for which no proof of safety and effectiveness is required prior to marketing, the extra care taken by the quality-conscious company can be more fully appreciated.

For those drug products which do require F.D.A. approval for safety and effectiveness, the quality company establishes the conditions of manufacture and control which assure that each batch measures up in every respect to the initial batch on which the F.D.A. submission was based. The importance of this procedure cannot be over emphasized.

The former Commissioner of the Food and Drug Administration, George P. Larrick, made some pertinent comments on the importance of manufacturing control before the Senate Subcommittee on Antitrust and Monopoly in 1960. At that time he said:

"* * * It requires a great deal of technical knowledge as well as properly utilized procedures to produce modern drugs that will meet all the requirements of modern medicine and of the law. Our experience has demonstrated the soundness of that position and it is even more true today as the complexity of drugs and their dosage forms increase. Adequate and extensive control from the time the raw materials enter the drug plant to the time the finished drug reaches the patient is essential if both patient and clinicians are to have confidence in the drug prescribed."

Mr. Larrick went on to say: "Our experience has shown that those who do not have proper controls are more like to produce substandard drugs. The point * * * is not whether drug manufacturers are large or small, but whether they have the scientific personnel and laboratory control to produce pure, reliable and safe drugs".

Assurance of quality in the manufacturing of drugs begins with people. For this reason, the quality-minded companies are extremely careful in their selection of the personnel who devise the formulas, test the components and finished preparations, inspect the final product, and perform the many other tasks involved in drug production. These men and women must have a high degree of training, knowledge, motivation and experience.

The research-conscious innovator companies in our business usually are distinguished by stability of employment. Obviously this is a most important factor in attracting good employees who are dedicated to the production of quality drug products. These workers are well-trained people who understand the rules and regulations under which the drug industry operates and who are proud of the part they play in their company's operations.

Laws and regulations are no substitute for the care exercised by men and women of integrity. You simply cannot legislate quality into drug products, any more than you can eliminate traffic fatalities and injuries by making new laws. There are many excellent traffic laws already on the books—local, state, and federal—yet the death toll on our highways continues unabated. In the final analysis, it's the human factor which counts. And so it is with the production of quality drug products—the people a company employs make a big difference.

As an example, in our own manufacturing plant, more than 33 percent of our employees have been with the company longer than fifteen years. They are without a doubt among our most valuable assets. In recognition of this fact, we invest in numerous fringe benefits and special programs designed to demonstrate the high regard we have for our people. In addition, we strongly support safety programs, provide tuition assistance to upgrade the education of employees, and conduct training programs to assure top-level performance.

Because of the importance of employees in the production of top-quality drug products, the more responsible manufacturers go out of their way to provide the best of working conditions. Particular attention is paid to buildings and equipment.

Buildings in which drugs are manufactured must be of suitable size and construction to house the necessary equipment and materials in such a manner that cross-contamination or mixup is avoided. In the better plants, provisions are made for cleaning the air and controlling temperature and humidity. One example of the great care that is taken to assure the most sanitary conditions possible is the sterilization of areas used for the production of parenteral products. Much of the equipment used in these plants is custom-designed and considerable engineering ingenuity is required.

Of paramount consideration are cleanliness and orderliness. For example, in my own company alone we have spent several hundred thousand dollars to separate operating equipment and functions, to provide a high degree of air filtration and dust control, and to insure the sanitation qualities of floors, ceilings and walls. This is typical of what the research-oriented companies are continuing to do to improve their operating areas.

Now I should like to point out a few fundamentals about manufacturing methods and procedures of the quality-minded drug manufacturer. Our equipment must fulfill two important requirements:

First, we must be able to produce batches of a drug product with uniform consistency day in and day out. Secondly, the equipment must be compatible with the chemicals involved and suitable for thorough cleaning to eliminate the possibility of contamination from product to product. Clearly, maintenance of equipment is extremely important. For example, in the case of a tablet compression machine, where close tolerances are required, regular examination is essential to insure that each tablet produced meets the dose specified. Such care is part of the standard operating procedure of the quality-conscious, innovator type of drug manufacturer.

All-important considerations for every reputable drug manufacturer are: (1) Quality of raw materials used in the manufacturing process and (2) In-process controls. I should like to elaborate on both of these points.

To assure the quality of a raw material, the careful company first insists that the supplier guarantee the quality and purity of the material, then makes doubly sure by conducting its own extensive tests. Many companies even conduct their own inspections of suppliers' plants.

This preoccupation with quality of raw materials applies to non-therapeutic as well as therapeutic substances; to non-official substances as well as those listed by the U.S. Pharmacopoeia and the National Formulary. In this connection, the following statement is made by one of these official compendia: "While one of the primary objects of the Pharmacopoeia is to assure the user of official medicinal substances of their identity, strength, quality and purity, it is manifestly impossible to include in each monograph a test for every impurity or adulterant that might be present". In view of this undisputed fact, the quality-oriented pharmaceutical firm exerts additional efforts through the use of analytical know-how and in-process controls to give greater assurance of the identity, strength, quality, and purity of the ingredients which go into its products.

Throughout the drug manufacturing process, from raw materials through finished product, careful control must be exercised at every step of the way. Every quality-minded manufacturer follows a standing operating procedure which incorporates a system of checks and balances followed by quality audits.

Included in these standard operations is a process for written procedures and specifications covering all raw materials and finished products. Items such as methods of sampling and analysis, and criteria for acceptance, are specified. All manufacturing formulas and working directions are as explicit as we can make them.

Our standard procedures cover such important considerations as product and container identity, quarantine provisions, and storage conditions. Each product is covered by an appropriate batch record, and throughout the manufacturing operation great care is exercised to assure accuracy of weight, volume, and yield of each batch.

Special care is exercised in the production of sterile products to avoid microbial contamination.

The packaging materials used are subjected to inspection, and particular care is exercised in the issuance of labels, cartons, and package inserts.

The warehousing of the finished product provides for proper storage, segregation, and identification by lot or batch number, as well as systematic rotation and inspection of stocks at regular intervals.

Another key factor in our standard procedures is the maintenance of records covering all manufacturing, packaging, and control operations concerned with a product. These records must be prepared with such care as to provide a history of each batch of every drug product.

One of the most important parts of our system of in-process controls is the testing required to assure the identity, strength, quality, and purity of all raw materials and finished products. Periodic checks are made even after it has reached the pharmacist's shelf to make certain it measures up to the company's high standards. The quality-conscious manufacturer continues his testing as long as a product is on the market.

As a final step in this system of controls, the manufacturer must provide for the proper disposition of returned goods.

As an illustration of the importance of checks and balances exercised during pharmaceutical manufacturing by some firms, I think it's interesting to note that in one of our own company's routine manufacturing operations we conduct some 687 inspections and tests during the course of making a finished product. Among these are 215 different inspections and tests on raw materials, 395 check-points and tests during the actual manufacturing, and 75 inspections and counts during the packaging operations.

The manufacturing principles I have discussed have been followed by the leading prescription drug companies of this country for many years. It is generally agreed by those who have first-hand knowledge of these research-minded pharmaceutical manufacturers that their plants stand out in their communities as models of modern industrial facilities. Control of air pollution and maintenance of waste treatment facilities are among the important contributions such companies make toward their environment.

In 1965, the Pharmaceutical Manufacturers Association joined with the Food and Drug Administration and the University of Wisconsin in providing training in the principles and procedures of modern drug manufacture. In his opening address, the Dean of the University's School of Pharmacy stated:

"Today, this 'know-how' (of drug making) exists and is constantly expanding as new, more complex and sophisticated drugs and dosage forms are introduced. Unfortunately, at the present time this know-how is confined to a relatively small segment of the total pharmaceutical industry."

In concluding, Mr. Chairman, I should like to emphasize that the manufacture of quality drug products is a time-consuming and exacting process, requiring the best personnel and facilities. The reputable and responsible drug manufacturers of this country go as far as present-day technology permits in order to provide the highest-quality prescription drugs for the medical profession and the public.

LELAND W. BLAZEY

Education:

Hobart College, 1936, AB—Biology and Chemistry.

Ohio State University, 1941, M. Sc.—Chemical Engineering.

Graduate Studies, University of Rochester, Administration; Princeton University Extension, Chemical Engineering.

Experience:

Vice Principal and Instructor: Shortsville High School, 4 years.

Merck & Co., Inc.—Positions from 1941–1958 in order, 17 years Supervisor in Pilot Plant and Chemical Engineering Division; Chemical Design Engineer; Manager Production Standards; Manager Industrial Engineering; Manager Design and Construction.

Merck Sharp & Dohme, Pharmaceutical Division: Chief Industrial Engineer.

Merck & Co., Inc., Chemical Division: Assistant Director of Engineering.

McNeil Laboratories, Inc. (1958 to present, 9 years): Director of Engineering, Vice President of Manufacturing and Engineering.

Professional Organizations:

American Institute of Chemical Engineers.

American Chemical Society.

Honorary Scientific: Society of Sigma Xi.

Trade Associations:

Member Production and Engineering Section, P.M.A., former Chairman.

Member Parenteral Drug Association.

Other:

Member of Board of Directors, Easter Seal Society for Crippled Children and Adults.

Chairman of Montgomery County Business and Industry Campaign, Easter Seal Society.

Senator NELSON. Nobody questions the importance, the great significance of research-oriented companies in the drug industry. I assume it is also true that a company that is not research-oriented may meet all of the same production standards as any research-oriented company. Is that correct?

Mr. BLAZEY. I think that is possible.

Senator NELSON. I forgot to ask Dr. Van Riper—I notice in a report of the FDA before 1964 Geigy had contracted-out for the production of its entire line of drugs. One of the contractors was Strong Cobb Arner. I notice that Strong Cobb Arner produce drugs for a number of companies. And I notice that either Grays or Peoples—one of those two chains—has advertised that they are putting in a full line of Strong Cobb Arner's generic drugs.

They also stated in their ad that the average cost of these drugs would be 50 percent or more below the average prescription cost for a trade name drug.

Is there any doubt in your mind, for example, about the quality of the generic drugs produced by this company?

Dr. VAN RIPER. I might say, Mr. Chairman, that Strong Cobb Arner no longer manufacture for Geigy. They did up to 1964.

Senator NELSON. I think this was 1964. But it said, "still employ these contractors but will eliminate them entirely in 1 year's time." That was dated 1964. But this report states that at one period contract manufacturers produced Geigy's entire line of drugs.

Dr. VAN RIPER. That is right, sir.

Senator NELSON. There wasn't any doubt in your mind about the quality of the drugs that Geigy got from Strong Cobb Arner, or any of the other generic producers, was there?

Dr. VAN RIPER. There was none, sir. But we maintained one of our personnel constantly in the production plant of Strong Cobb Arner.

Senator NELSON. Did you find any difficulty in getting quality products from them?

Dr. VAN RIPER. Not as far as I know.

Senator NELSON. The point I wanted to make is that certainly it ought to be clear that a company may produce high quality drugs under proper quality control without being in the research field, or without producing trade name drugs. Is that not correct?

Mr. CUTLER. I think it is correct, Mr. Chairman. Strong Cobb Arner is a PMA member, and we are not trying to suggest in any way it does not have excellent quality controls and produce good quality drugs. It so happens that you need scientists to achieve good quality control, and the companies that have scientists, most of them like to do research. So, the two do tend to go hand in hand.

Senator NELSON. Okay.

Do you have anything else?

Mr. CUTLER. No, sir.

Senator NELSON. At this time, I have an article that I will ask be put in the record at this point, by Dr. Mark J. Brauer and Dr. Wil-

liam Dameshek on the occurrence of hypoplastic anemia and myeloblastic leukemia following chloramphenicol therapy.

(The article above-referred to follows:)

[From the New England Journal of Medicine, vol. 277, No. 19, Nov. 9, 1967, pp. 1003-1005]

HYPOPLASTIC ANEMIA AND MYELOBLASTIC LEUKEMIA FOLLOWING CHLORAMPHENICOL THERAPY*

REPORT OF THREE CASES

(By Mark J. Brauer, M.D.,† and William Dameshek, M.D.‡)

Boston

A pathogenic relation between aplastic anemia and myeloblastic leukemia has long been suspected. It is well known that certain agents capable of producing aplastic anemia in man can also induce leukemia. Prime examples are benzene^{1,2} and irradiation.^{3,4} In addition, cases of leukemia developing during the course of hereditary hypoplastic syndromes have been recorded.^{5,6} The broad-spectrum antibiotic chloramphenicol⁷⁻⁹ has become the most commonly cited cause of acquired aplastic anemia. To date, only 1 case report of acute myeloblastic leukemia following aplasia secondary to chloramphenicol administration has been published.¹⁰ The purpose of this communication is to present 2 additional cases of chloramphenicol-induced aplastic anemia of long standing that developed into acute myeloblastic leukemia. In addition, a patient in whom an indolent, pancytopenic myeloblastic leukemia followed the prolonged use of chloramphenicol for the treatment and prevention of head colds is reported.

CASE REPORTS

CASE 1. J.D. (N.E.M.C.H. 178-415), a 38-year-old woman, was initially investigated 8 years before admission when, after a 6-week course of chloramphenicol (total dose, 84 gm), marked pallor developed. The pretreatment hemoglobin level was 12 gm per 100 ml, and the white-cell count 8000. Shortly after chloramphenicol therapy the hemoglobin was 7.2 gm per 100 ml, the white-cell count 2200, and the platelet count 100,000. Peripheral blood examination showed a predominance of mature lymphocytes (69 per cent) with no primitive white-cell forms. In addition there was mild red-cell anisocytosis. Aspiration of the bone marrow produced a fatty hypocellular sample with small spicules. The myeloid-erythroid ratio was increased, primarily owing to severe red-cell hypoplasia. Granulocytic precursors and megakaryocytes were also decreased in number. No vacuolization of bone-marrow elements nor increase in immature forms was apparent. Lymphocytes and reticular elements were relatively increased. A diagnosis of chloramphenicol-induced hypoplastic anemia was made, but no specific therapy was initiated.

Splenectomy was performed in 1959 because of worsening pancytopenia and bleeding. The spleen was of normal size and showed no abnormal features. Bone-marrow aspiration was not repeated. After splenectomy there was no marked change in the peripheral blood picture. The hemoglobin values ranged between 6 and 8 gm per 100 ml, and the white-cell counts around 2500. Treatment consisted of adrenocorticosteroids, androgens and occasional blood transfusion until 1963, when the patient gave birth to a normal male child. Thereafter, transfusion requirements rose sharply. This was attributed primarily to decreased red-cell production. Thirty-eight units of whole blood were given from March, 1965, until 1966. A hemogram performed in April, 1966, revealed a hemoglobin of 7.0 gm per 100 ml, a white-cell count of 15,000 and a platelet count of 50,000. The

*From the Blood Research Laboratory, New England Medical Center Hospital, and the Department of Medicine, Tufts University School of Medicine (requests for reprints should be addressed to Dr. Dameshek at the Mount Sinai Hospital, 100th Street and Fifth Avenue, New York, N.Y. 10029).

Supported by a fund from the grant (CA 04168-09) from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

†Attending physician and hematologist, New England Medical Center Hospital; senior instructor in medicine, Tufts University School of Medicine.

‡Attending hematologist, Mount Sinai Hospital; professor of medicine, Mount Sinai School of Medicine, New York City.

differential count showed a predominance of immature blast forms, some of which contained Auer rods.

On clinical examination in May, 1966, the patient was extremely pale and incoherent, with marked purpura. There was evidence of congestive heart failure and a severe neurologic deficit related to brain hemorrhage. The peripheral white-cell count was 37,900, with 15 per cent myeloblasts. Aspiration of the bone marrow produced a specimen almost totally replaced by myeloblasts. Shortly after admission the patient died. Permission for post-mortem examination was not granted.

This patient with chronic aplastic anemia after chloramphenicol was observed for eight years. The terminal development of acute myeloblastic leukemia suggested a causal relation.

CASE 2. L.R. (N.E.M.C.H. 169-853), a 57-year-old woman, was first seen 15 years before admission for recurrent attacks of dysuria diagnosed as "cystitis." Multiple urologic examinations gave no evidence of obstruction or intrinsic abnormality. For 8 years before admission it had been her custom to take chloramphenicol for her attacks. Short courses taken *ad lib* always produced impressive clinical improvement. Over this period an estimated 500 to 700 capsules were consumed (approximately 175 gm). Routine blood counts performed during annual examinations were reported as "within normal limits."

An anal fistula developed after hysterectomy in February, 1964. She was intermittently treated with chloramphenicol until May, with little improvement. At that time the hemoglobin level was 8.4 gm per 100 ml, and the white-cell count 2500. No platelet count was recorded. A sternal puncture yielded a fatty specimen with marked hypocellularity. Erythroid precursors were almost totally absent. Granulocytic elements, although diminished, showed no "shift to the left" nor clusters of immature cells. No vacuolization of young forms was seen. Megakaryocytes were also markedly diminished. A diagnosis of chloramphenicol-induced bone-marrow hypoplasia was made.

The patient was treated with adrenocorticosteroids, androgens and blood transfusions from August 1964, until February, 1965, without improvement of blood findings.

On examination in February, 1965, she appeared chronically ill with marked pallor, widespread purpura and pulmonary congestion. The liver and spleen were not enlarged. A major finding was a massive perirectal abscess. The hemoglobin was 7.3 gm per 100 ml, the white-cell count 5800, and the platelet count 21,000. The differential count showed 25 percent myeloblasts. Bone-marrow aspiration revealed a hypercellular specimen completely replaced by myeloblasts.

Therapy with 6-mercaptopurine had no beneficial effect, and she died in another hospital. No post-mortem examination was performed.

In this case, chronic chloramphenicol ingestion was held responsible for the development of aplastic anemia. Acute granulocytic leukemia was observed one year later.

CASE 3. V.D., a 61-year-old woman, was first seen on October 26, 1964. At a routine checkup on October 5, when she was asymptomatic and showed no physical abnormalities, a blood count revealed leukopenia and granulocytopenia. The history revealed further that the patient had been plagued by several "heavy colds" every year and that she had been advised by her family doctor in August, 1963, to take chloramphenicol, 4 capsules daily, "at the earliest sniffle." In the course of the past 14 months she had taken by actual count 60 capsules (15 gm) of the drug. There was no history of any other drug or chemical contact and no history of x-ray exposure except for a few single dental x-ray examinations. The family and past histories were noncontributory.

On examination the patient looked very well. However, the liver edge was palpable 3 fingerbreadths below the right costal margin, and a few ecchymoses were present. The hemoglobin was 11.5 gm per 100 ml, the red-cell count 3,890,000, the hematocrit 37 per cent, reticulocyte count 2.2 per cent, and the platelet count 225,000; the white-cell count was 2200, with 15 percent neutrophils, 80 per cent lymphocytes; and 5 per cent monocytes. The sedimentation rate was 10 mm per hour. Bone-marrow aspiration revealed hypocellularity to normocellularity. Large numbers of primitive pale-staining cells were present, and primitive monocytoïd cells were increased. The diagnosis of hypoplasia of the bone marrow, with primitive cell (myeloblastic) leukemia, was made. An alternative diagnosis of "maturation arrest of the granulocyte series" induced by chloramphenicol was entertained. No therapy was advised except for discontinuance of the antibiotic.

The patient was observed at intervals during the following year. During the first 6 months she continued asymptomatic. Gradually, increasing pancytopenia developed. Symptoms of gingival hyperplasia, bouts of diarrhea, and bouts of fever occurred in June and July, 1965. In mid-October, a severe nasopharyngitis, cellulitis of the left ear and rapidly progressive anemia appeared. The bone marrow was now almost completely replaced by myeloblasts and promyelocytes. Therapy with 6-mercaptopurine was instituted, and antibiotics and transfusions were given. In early December, 1965, generalized sepsis due to a coagulase-positive staphylococcus was present, and the patient died on December 7.

This woman of sixty-one, always in good health except for head colds, took 60 capsules of chloramphenicol during fourteen months as a prophylactic measure against further colds. This was successful, but pancytopenia and the indications in the bone marrow of hypoplasia and of primitive cell (myeloblast) leukemia developed. Chloramphenicol was discontinued. The patient was well for about six months, and then the various clinical manifestations of acute leukemia developed and she died fourteen months after the diagnosis had been made.

DISCUSSION

Hypoplastic anemia has been defined in various ways by various observers. We prefer to reserve this term for cases showing pancytopenia of the blood and well defined hypoplasia of the bone marrow. Those with increased cellularity of the marrow and blood pancytopenia may indicate other conditions ranging from maturation arrest to the DiGuglielmo syndrome or leukemia. In the aplastic anemia that follows the administration of chloramphenicol, 2 main forms may be discriminated. In the first the onset is acute, seemingly dose related and frequently associated with a normocellular bone marrow, which exhibits vacuolization of erythroblasts and granulocytic precursors. Moderate anemia, reticulocytopenia, increased plasma iron and delayed plasma iron clearance have been observed in this sitting.⁹ Unless the dosage of drug has been inordinately high, this type is usually reversible when the drug is discontinued. Work in mammalian cell-free systems suggests that prolonged exposure to chloramphenicol and high blood levels of unbound drug are both important factors in inhibiting protein synthesis through interaction with messenger RNA. This may help to explain the bone-marrow hypofunction.¹¹

The second form, or "late-onset type," may not be dose related. It is characterized morphologically by hypoplasia or severe aplasia of the bone marrow. In most patients manifestations of marrow depression develop after the drug has been stopped, often weeks or months later. In such cases, indications of marrow injury remain long after the last trace of the drug have disappeared. Conceivably, injury to a large number of stem cells might explain such an effect. An interval would then be required before the stem-cell pool became depleted and cytopenia was manifest. That some patients, because of a metabolic abnormality or deficiency, may be more susceptible than others to the action of chloramphenicol or its degradation products, is an attractive but unproved possibility. In fact, there is no ready explanation at present for the apparent susceptibility of some persons to the development of serious disorders of the marrow after chloramphenicol or other agents.

The development of leukemia in the course of aplastic anemia is of considerable interest. Although most large series of acquired aplastic anemia¹²⁻¹⁴ contain no such reports, examples may be found with benzene toxicity,^{1,2} after radiation,^{3,4} after administration of phenylbutazone,^{15,16} during the hypoplastic phase of paroxysmal nocturnal hemoglobinuria¹⁷ and in hereditary hypoplastic syndromes.^{5,6} The development of paroxysmal nocturnal hemoglobinuria during aplastic anemia¹⁸ is of additional interest. This may be but another example of the development of abnormal cell lines in a previously injured bone marrow.

The induction of leukemia by chemicals (including drugs) may be mediated through chromosomal injury. In line with this is the recent observation by Castoldi and Mitus¹⁹ of chromosomal vacuolization in patients receiving chloramphenicol. Inconstant chromosomal changes have been observed in several series of cases of acute leukemia.^{20,21} Similar changes have been found to follow radiation⁴ and benzene²² and to occur in hereditary states.²³ The chromosomal vacuolization seen after chloramphenicol may be a comparable lesion. Another possible explanation is that the leukemia is a secondary, perhaps reparative, response to aplastic anemia. A tendency to neoplasia of hypoplastic tissues has

been recognized repeatedly in human pathology. Examples include atrophic gastritis and leukoplakia. Perhaps analogous to the potential of these disturbed tissues to transform into carcinoma is the eventual emergence of leukemia in the chronically aplastic bone marrow.

Finally, another explanation for the development of leukemia in these cases deserves consideration. Aplastic anemia and leukemia may both be thought of as growth disturbances of the bone marrow (myeloproliferative disorders). Thus, they may occur either together or sequentially as phases of the same pathogenetic mechanism. Block et al.²⁴ had the unique opportunity to observe 12 patients for as long as twenty-seven months before the development of acute myelogenous or stem-cell leukemia. Most of the patients in this "preleukemic" phase displayed variable degrees of marrow hypoplasia as well as peripheral cytopenias. Blair and his associates²⁵ reported a similar experience in 16 cases of "atypical leukemia." Thus, it may be hypothesized that in some cases aplastic anemia and leukemia simply represent different expressions of the same fundamental disturbance. It is now reasonably clear that an "insult" to the bone marrow, as from chloramphenicol or another chemical, may either destroy totally or partially. Partial destruction of some cells may serve only to "knock out" one or two enzyme systems but not prevent cell reproduction. Under these circumstances, a new self-perpetuating cell line (clone) may develop—that is, leukemia, when white cells are concerned, or paroxysmal nocturnal hemoglobinuria with erythroblastic involvement. We have recently remarked upon the relation of paroxysmal nocturnal hemoglobinuria and aplastic anemia, particularly in association with chloramphenicol toxicity.²⁶

The syndrome of aplastic anemia, regardless of cause, may lead to early death from hemorrhage or infection or may result in chronic bone-marrow malfunction. The development of leukemia and of paroxysmal nocturnal hemoglobinuria has been associated with the latter process. It is evident that chloramphenicol can result in this sequence of events. The continued widespread use of this drug, particularly in the less developed countries, and even among the highest-income groups of this affluent country, often for trivial reasons, may be a factor in the causation of some forms of leukemia, particularly of the relatively indolent, hypoplastic type.

SUMMARY AND CONCLUSIONS

The development of myeloblastic leukemia during the course of chloramphenicol-induced pancytopenia in 3 patients is described. Leukemia has been reported in a wide variety of clinical states commonly characterized by variable degrees of bone-marrow hypoplasia. Factors responsible for the development of aplastic anemia and drug-induced leukemia are considered. Chloramphenicol, by primary or secondary means, appears causally related to the blood dyscrasias in the cases presented. As stated so many times, indications for the routine or even common use of this drug in the treatment of infection must always be carefully scrutinized.

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Senator NELSON. We appreciate very much your taking the time to come here, gentlemen. I apologize for having to make some of you make an extra trip because we could not complete the testimony the last time.

I realize that this was an imposition upon your time and I regret it. But I do appreciate your contributions to the record.

I think that all of the prepared testimony presented was certainly well done, well prepared, and will be a valuable asset to the record.

Thank you very much.

Mr. CUTLER. Mr. Chairman, we appreciate the time and attention you have paid to us. As you know, we do have a number of economic witnesses prepared to deal with such subjects as prices and profits, and I understand from Mr. Gordon that he will give us a date at some point in the near future for those witnesses.

Senator NELSON. We certainly will. As I said the last time, if additional time is needed we will take an additional day or two, or whatever is required, for purposes of presenting for the record whatever you desire to put into the record. With all your expertise, you are a very formidable group for me to contend with.

Mr. CUTLER. Let's hope we are educating one another.

(Whereupon, at 5:35 p.m., the subcommittee was adjourned, subject to the call of the Chair.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, FEBRUARY 6, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:15 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. We will now open the hearings of the Monopoly Subcommittee.

During the course of the Monopoly Subcommittee hearings on prescription drugs, the committee's attention has been called to a number of cases in which the administration of certain drugs has resulted in serious side effects.

A short time ago an industry witness, in relating to the committee the effectiveness of the company's broad spectrum antibiotic, Chloromycetin, concurred in the statement that the drug had been the cause of serious blood dyscrasias, some of which have resulted in death.

The "Physicians' Desk Reference" says that chloramphenicol "should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections, such as colds, influenza, or viral infections of the throat, or as a prophylactic agent," and so forth.

Yet, the manufacturer of Chloromycetin reported total domestic sales of \$45,000,000 in 1966, and a total sales of \$70 million worldwide.

There is a growing mountain of evidence that Chloromycetin is being widely overprescribed.

Dr. William Best, who has studied 408 cases of adverse reactions to the drug, has surfaced information on the indications for which doctors generally prescribe chloramphenicol.

In 30 percent of the cases cited, he found that the drug had been administered for "relatively trivial indications for which the drug should never have been used." He says that many complications occurred in patients who "should not have received chloramphenicol."

Recently FDA Assistant Commissioner Theodore O. Cron acknowledged that physicians in large numbers continue to ignore label warnings about misuse of the drug.

Dr. William P. Cregar, addressing the San Diego Academy of General Practice, said that the drug "is the leading cause of" the often fatal aplastic anemia and that physicians "are using it far too much."

One of our witnesses today, Dr. William Dameshek, has been quoted in a widely read book on drugs that:

Promiscuous use of the drug should be avoided and use restricted to impelling circumstances; i.e., for conditions in which no other antibiotic is currently effective.

The American Medical Association Registry on Blood Dyscrasias, which provides reliable data on the subject, reported in July 1967 that in 96 percent of the 408 cases of aplastic anemia brought to its attention, it was strongly suspected that chloramphenicol was the causative agent—and its possible link in the remaining 4 percent was not ruled out.

The report says the drug is believed to be the cause of death in 50 percent of these 408 cases.

A physician, Dr. Albe M. Watkins, whose son died from aplastic anemia caused by chloramphenicol, stated:

I do not know of one single victim who would not be alive today had he only been permitted to get well by himself, by nature, without the use of this antibiotic.

In a case in March 1967, a Federal district court awarded the heirs of a California woman \$180,000 in damages because she was disfigured after taking the drug. A dentist had prescribed the drug for an infection which followed extraction of several teeth.

The California woman claimed Chloromycetin produced aplastic anemia and so disfigured her that friends could not recognize her. She said she had to shave daily, grew a "buffalo hump," and developed severe acne. She later died of complications of the disease.

On February 20, 1967, a two-page advertisement appeared in the Journal of the American Medical Association which described the use of Chloromycetin to the doctor. In 1,300 words of warning and in a large, black-bordered box, the ad warned the physician that—

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia * * *) are known to occur * * * chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its anti-bacterial effects.

And it went on to warn against use for minor infections.

I asked the quality control director of the Parke, Davis Co. if he agreed that the warning was necessary and appropriate.

He concurred that the warning was important and had to be an integral part of the ad; that the drug had dangerous side effects; that deaths had occurred which were directly attributable to the use of the drug.

Then I showed him an advertisement for Chloromycetin run by Parke, Davis in the British Medical Journal on February 11, 1967—9 days prior to the American ad.

Not a single word of warning appeared in the British ad. No mention was made of the drug's potentially fatal side effects to at least alert the British physician.

I asked the drug company representative why there was no warning.

His counsel replied that the company complies with the law of the country where it advertises, and the British do not require the warning.

Because of the effect this lack of complete disclosure has on unfortunate victims in other parts of the world, on our trading partners, and on our friends in the underdeveloped countries, this committee has asked several distinguished authorities on blood diseases and disorders to testify to the committee about the uses and dangers of chloramphenicol.

Our first witness this morning is Dr. William Dameshek, a very distinguished professor of medicine now at Mount Sinai School of Medicine in New York.

Doctor, we appreciate your taking the time to come here today and the committee is well aware of your distinguished credentials. We will print prior to the printing of your statement, the biography which you have supplied to us.

(The biography of Dr. Dameshek follows:)

SHORT BIOGRAPHY

William Dameshek, M.D. (New York, New York).

Born: May 22, 1900.

Harvard Medical School, 1923.

Titles:

Professor of Medicine, The Mount Sinai School of Medicine, N.Y.C.
 Attending Hematologist, The Mount Sinai Hospital, N.Y.C.
 Professor Emeritus, Tufts University School of Medicine (Mass.)
 Editor in Chief (and Founder) of BLOOD—The Journal of Hematology.
 President of the International Society of Hematology, 1954–56.
 President, American Society of Hematology, 1964.
 Extraordinary Professor of Medicine, National University of Mexico.
 Professor, Honoris Causa, University of Santiago, Chile.
 Commander, Order of Carlos Finlay, Cuba.

Awards:

Certificate of Merit, American Medical Association, 1942.
 Billings Silver Medal, 1952, 1953.
 Premio Ferrata, 1958.
 Willard O. Thompson Gold Medal American Geriatrics Society, 1968.

Professional Societies:

American Academy of Arts and Sciences.
 American Association of Immunologists.
 American College of Physicians.

Fellow:

American Society of Clinical Investigation.
 American Society of Hematology.
 New York Academy of Sciences.
 American Society for Experimental Pathology.

Author of approximately 450 published articles, books and monographs on hematologic subjects.

Books:

The Hemorrhagic Disorders, Eds. I and II; Spleen and Hypersplenism.
 Chemotherapy of Leukemia and Leukosarcoma; Hemolytic Syndromes.
 Leukopenia and Agranulocytosis; Leukemia. Eds. I and II.

Family:

Wife, Mrs. William Dameshek (Rose T.)
 Daughter, Mrs. Elinor D. Reichlin (wife of Dr. Seymour Reichlin of Rochester, New York).
 Two grandsons.
 One granddaughter.

Senator NELSON. Dr. Dameshek, we are pleased to have you here this morning.

STATEMENT OF DR. WILLIAM DAMESHEK, PROFESSOR, SCHOOL OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK, N.Y.

Dr. DAMESHEK. Nice to be here, Senator.

Senator NELSON. Go ahead, Doctor.

Dr. DAMESHEK. What do you want me to do at this point?

Senator NELSON. If you will proceed to read your statement and then, at any time when you wish to extemporize or elaborate, we will be pleased to have you to do so. I realize that attempting to reduce all you wish to say in a printed statement throws a considerable amount of effort on you, but we will be pleased to have you elaborate at any point. If we happen to have some questions which occur to us while you are giving your statement, I am sure you will not mind an interruption. Otherwise, we will ask the questions at the conclusion of your statement.

Dr. DAMESHEK. I would like to introduce my statement by saying I have no personal vendetta against any pharmaceutical house that might be implicated in the use of this drug. I realize that pharmaceutical houses in this country are of considerable importance to the medical profession. They have done a great deal over the years in the research and development of drugs which we have used, as physicians, and I am fully aware of their importance and of their ethical responsibilities, and so on.

Senator NELSON. Let me say, Dr. Dameshek, the committee agrees with that statement. We have no particular vendetta against anybody, either. We are attempting here to get the best professional testimony on certain problems in this area from the most authoritative people in the country. We think this will be, in the long pull, a benefit to the companies as well as to the public and the medical profession.

Dr. DAMESHEK. I want to be, however, as objective as I possibly can. I realize that perhaps some of this objectivity may be lost in my own case possibly because I see the end results of some of the cases of chloramphenicol toxicity.

I am in the special field of what is called hematology, disorders of the blood, and I see cases of aplastic anemia, many of which have been treated with chloramphenicol, and these cases are very serious cases. Most of them die. So that I may be accused perhaps of looking through one end of the telescope whereas the cases of aplastic anemia that develop with the use of this drug are certainly relatively few.

Now, my statement here reads that chloramphenicol, or Chloromycetin as it is usually called, is a chemical or drug which was introduced as an antibiotic in 1948. It is a relatively simple compound and as such it was soon synthesized—a rare, if not unique, event in antibiotic studies, at least in soil antibiotics. Its formula is unique amongst antibiotics in that one part of the molecule contains a benzene ring to which is attached an NO_2 moiety. This means that the possibility of injury might occur. At least we have been alerted to that idea since the time of Kracke, who was a hematologist and student of drug reactions a good many years ago.

This idea was early commented upon, notably by Smadel, who was an investigator of drugs, as indicating a possible risk to the bone marrow—the bone marrow is the factory that produces blood cells—

and the blood; as other nitrobenzene drugs had been previously incriminated in the causation of toxic blood reactions.¹

The chloramphenicol story is an upsetting one from several stand-points: On the one hand, this drug is a great "broad-spectrum" antibiotic; no question about it. It works just as well and perhaps better when taken by mouth than many other antibiotics do when given by injection. On the other hand, it is at the same time a powerful anti-metabolite, which means a cell poison or a material which interferes with the growth of proteins, cells, and it has apparently a particular effect on the bone marrow which is the chief factory, as I have said here, of blood cell production.

Thus, one must subordinate one's desire to use it because of the risk, it may do harm. In other words, great caution, great restraint, must be exercised by each individual physician when he prescribes Chloromycetin for a particular infection. It gets upsetting, too, that many times this restraint is not used by the physician and as a result great injury, sometimes irreversible, results—in the form of disorders of the whole marrow—aplastic anemia—or of one or another of its components; the red cells, the white cells, or the platelets. Those are the cells that are produced in the bone marrow and come out in the blood.

Now, since the drug is often used without restraint, and especially in infectious states when either no drugs or less harmful drugs can be used just as well, one must consider the possibility of restricting its use to certain well-defined conditions. This is something new, I must say, in my own thinking because some years ago we thought a simple warning would do the trick. Some years ago we thought that we could educate the medical profession by editorials, by articles, and so on. But, I must say this has not worked, and we see cases of aplastic anemia in which the drug need not have been used.

Senator NELSON. Do you have any opinion as to why the warnings have not worked, as to why the cautionary statements about the limitations of this drug have not been effectively translated to a sufficient number of physicians who still do prescribe it?

Dr. DAMESHEK. I have no real solid opinion about this. I think many warnings are honored in the breach rather than the observance. That is, people might look at them, either ignore them or just think that maybe this time it will not do any harm, because the severe reactions to this drug are relatively few. What is more, this antibiotic happens to be an exceptionally good antibiotic and can be given by mouth so that pediatricians like to use it. What is more, we have an affluent society, as has been said, in this country at least, and there seems to be an impelling need to use drugs even for minor infections. It is the thing to do because, if a doctor does not supply or does not prescribe drugs, a family thinks there is something wrong with him. So that, I suppose, there are many reasons why these warnings are perhaps ignored.

Mr. GORDON. Dr. Dameshek, may I ask a question at this point? Why is the public so drug oriented? Could it be the large number of articles about drugs which appear in the lay magazines?

Dr. DAMESHEK. Well, again I do not know. I have no solid answer. Advertising is an important feature here naturally. We know about a

¹ See exhibit A, p. 2399, *infra*.

lot of things from advertising. Word of mouth, the idea that everything responds nowadays to miracle drugs, that this has captured the public fancy and naturally people want something for an illness. The doctor who goes away from a patient without prescribing a drug is often thought to be a little bit unusual. The patient might then go to a doctor who does prescribe a drug.

I think it is a rather complex, perhaps philosophical story.

Well, I was talking about restrictions and we will take that up towards the end of my statement. What these restrictions might be, who is to do the restricting, can undoubtedly be worked out.

Chloramphenicol, like most, if not all of the active medications we use in medicine, is associated with unwanted reactions particularly to cell systems which normally grow rapidly, as in the bone marrow. This drug, namely chloramphenicol, however, has particular value in serious or severe infections in which good, available antibiotics are hard to find. I should say in certain serious or severe infections. And one of them is typhoid fever, another is sudden severe septicemias in which interstitial organisms come out into the blood. This might occur in shock or when the blood count is low. And in certain resistant severe urinary infections.

Senator NELSON. Is chloramphenicol always indicated in every case of typhoid fever or would it depend upon the diagnosis of the condition of the particular patient?

Dr. DAMESHEK. I think we must say chloramphenicol is the best one for typhoid fever, although Ampicillin, a fairly recently introduced antibiotic related to penicillin, seems to be almost as effective and without the reactions of Chloromycetin.

Senator NELSON. What I was getting at is whether typhoid fever is always so serious a disease that a drug of some kind is always indicated?

Dr. DAMESHEK. Yes. That is a serious disease and it does not respond to the ordinary tetracyclines or the sulfa drugs, et cetera, and Chloromycetin seems to have a particular ability in controlling typhoid fever.

Senator NELSON. Does the medical profession have any good educated guesses as to how many cases of typhoid fever occur in this country annually?

Dr. DAMESHEK. Well, I would say it is a rare disease in this country. Something in the neighborhood maybe of a few hundred cases occur a year. It is a rare disease now.

Chloramphenicol is not indicated for colds, acne, that is pimples, grippe, influenza, and other common infections that are self-limited and in which either no treatment or such relatively harmless drugs as penicillin and the tetracycline drugs can be used.

Senator NELSON. Is it indicated for any of the upper respiratory infections?

Dr. DAMESHEK. I would say it is not indicated.

Senator NELSON. Not indicated?

Dr. DAMESHEK. Not indicated. Either the upper respiratory infections will get better themselves, which they do by and large, or else there are plenty of drugs around that could be used that do not have the effects on the blood-building machinery that this drug has.

So, I would say it is not indicated in the ordinary upper respiratory infections.

Large doses of the drug, for example, 6 grams a day, will regularly result in well-defined injury to the bone marrow and to the blood. Now, it can be demonstrated in something like 18 out of 20 cases. In other words, if large doses of the drug are used, almost everybody, will develop well-defined effects which can be measured following the use of the drug, and here it is not a matter of sensitivity. It is a matter of dosage. The pharmacologic action of the drug is one in which the bone marrow is affected by the drug.

Senator NELSON. And, are these effects usually permanent?

Dr. DAMESHEK. These are ordinarily reversible, or self-limited. But, I must say this, that I do not like to see them. That is No. 1. And No. 2, the possibility is present that once having had a reaction of this sort on the part of the bone marrow, that individual is, therefore, sensitized to future reactions, and finally there has not yet been a study made of those individuals who have developed reactions to 6 grams a day of the drug to see whether in the future they might have developed severe drug reactions.

Senator NELSON. Is 6 grams a day a program that is frequently prescribed?

Dr. DAMESHEK. It has been rather frequently used by specialists in infectious diseases. I cannot say how frequently. But, I do know from personal observation that it has been used by specialists in infectious disease for severe infection.

Senator NELSON. Is that, in your judgment, usually or always an excessive amount to be prescribed in any event?

Dr. DAMESHEK. No. The 6 grams may be effective whereas 2 grams may not be or 1 gram may not be. But, to say it is always effective, no. I do not think you can say it is always effective in clearing up any infection.

Senator NELSON. In your judgment, would that be considered an excessive dosage in most cases?

Dr. DAMESHEK. Well, to my way of thinking, it is an excessive dosage. I would say that. But, this is my own judgment.

Unfortunately there is some evidence from case studies, that the continued use of even small doses of Chloromycetin, or in some cases even a single 5- to 7-day course of drug, may eventually lead to bone marrow damage, eventually, 6 months, a year, year and a half. Repeated courses of drug at regular or irregular intervals has, in my experience, been more regularly followed by severe reactions such as aplastic anemia than when only one course is given. This is in my own experience.

Unfortunately, in most of the cases of severe aplastic anemia, that I have seen, Chloromycetin had been given for such infections as acne, upper respiratory disorders, mild urinary infections and, in fact, indiscriminately.

Senator NELSON. These are all cases, in your judgment, where it should not have been given at all.

Dr. DAMESHEK. Well, I would say this, that in most of the cases that I have seen, in fact, in most of the cases reported in the literature of severe drug induced reactions, the drug should not have been used. It

is as simple as all that because the indications for which the physician prescribed the drug were acne, upper respiratory infections, and the like, in which he could either have used no drug or have used a drug that does not cause these severe reactions.

The side effects of the drug depend upon the fact that it is an anti-metabolite or cell poison. Evidences of injury to red cell growth, white cell growth, platelet growth, and lymphocyte growth have been demonstrated from a variety of careful studies. Now, the lymphocyte is not a bone marrow cell in the accepted sense. The lymphocyte is at the center of a special grouping of cells which is concerned with immunity or helping the body either to prevent an infection or to prevent an infection from getting ahead.

Now, it has been demonstrated from a number of studies that this drug also affects these cells concerned with immunity, that is, the lymphocytes.

In general, the drug has demonstrated effects on the production of cell proteins, disturbance in transfer of the synthetic "message" from RNA to ribosome, that is, where proteins are produced within the cells. So that one can say in simple words that an actual "monkey wrench" has been thrown into the machinery of cell growth.

Thus, with lymphocytes, antibody formation is greatly reduced; with red cells, hemoglobin synthesis is delayed and cell maturity greatly slowed down. Similar disturbances occur with white cells of the marrow and with the megakaryocyte platelets. Those are the big cells in the marrow that produce platelets. Sorry about these big terms.

In most instances the entire marrow shows reactions and thus, all the elements of the blood are affected leading to the very serious condition of aplastic anemia, which is frequently fatal.

Senator NELSON. Would you describe aplastic anemia for the record?

Dr. DAMESHEK. Yes. Aplastic anemia is fundamentally a disturbance of bone marrow growth in which the growth of cells normally in the marrow is greatly reduced so that the bone marrow is finally producing something like 1 percent, 2 percent, 10 percent, possibly 25 percent of the normal number of cells produced. This leads, therefore, to a reduced number of red cells, a reduced number of white cells, a reduced number of platelets in the blood. The individual may be perfectly healthy in every respect but if his marrow is not working, he has very little blood. So that this becomes, then, a very important thing because without blood there can be no life. In some ways the blood is the central feature of life.

Senator NELSON. What does the term aplastic mean?

Dr. DAMESHEK. Lack of growth. Aplastic—plastic has to do with growth and "a" means lack of growth.

Senator NELSON. And in what percentage of cases is the disease aplastic anemia fatal?

Dr. DAMESHEK. Well, that is a difficult question to define because it is hard to define what is meant by aplastic anemia. If you say that aplastic anemia is a condition in which 75 percent of the bone marrow has been "knocked out," then I would say that the mortality rate for aplastic anemia varies between 50 to 75 percent, maybe more.

Senator NELSON. In the cases that you have seen where aplastic

anemia has developed from the use of the drug chloramphenicol, what percentage of those cases were fatal?

Dr. DAMESHEK. I would say something like 75 percent.

Senator NELSON. 75 percent?

Dr. DAMESHEK. Yes. I have seen mainly the severe cases.

Senator NELSON. One can live certain periods of time, I take it, then, with aplastic anemia depending upon the degree of inhibition of production of blood cells that has resulted.

Dr. DAMESHEK. Yes; and depending also upon the amount of treatment, notably the use of transfusions, because if the individual develops lack of blood, lack of red cells, this can be substituted by the use of transfusions, at least to some extent.

Senator NELSON. And what is the patient's condition even though he continues to live?

Dr. DAMESHEK. Well, as a result of the aplastic anemia, the individual becomes incapacitated as a rule. He cannot work, he cannot do his usual work. He is usually anemic. What is more, he is very apt to pick up infections because his white cell count is low. And the normal white cells which control infections are no longer there.

He is apt to bleed from his nose, his gums, get black and blue marks and bleed internally because he has very few platelets which control bleeding. So that he is in a rather bad way.

Now, in most instances the entire marrow shows reactions to the drug and thus all the elements of the blood are affected, leading to aplastic anemia which is frequently fatal. Overt or serious aplastic anemia develops only rarely in the wake of Chloromycetin therapy.

Now, how rarely it develops is by no means known. We have no exact statistics on this subject at all. There is no need, there is no requirement about reporting drug reactions at this time.

Senator NELSON. No requirement at all in the law?

Dr. DAMESHEK. No. No requirement as far as I know in any State, municipal, or governmental law regarding the reporting of severe reactions or drug reactions.

Senator NELSON. To depart from your testimony, would it be feasible at least, to have a reporting system developed by all the hospitals? Would it be useful?

Dr. DAMESHEK. Oh, I think it would. I see no great difficulties involved in that. If every hospital reported every case of aplastic anemia, and of every severe reaction to a drug or every severe possible or probable reaction to a drug, I think that would be quite feasible. I see no objection to that.

Senator NELSON. You would apply that to all serious reactions to all drugs?

Dr. DAMESHEK. All serious reactions; yes, I would. I think it would be a very valuable educational thing to have and very valuable thing to have in general.

Senator NELSON. If that were done by the hospitals, where would the best place be for the information to be accumulated so that it could be properly evaluated and disseminated?

Dr. DAMESHEK. Well, I can see the possibility of the patient having a probable or well-defined reaction to a drug reported to the admin-

istrator's office, for example—to the administration office in the hospital.

Senator NELSON. I am thinking that if this information would be valuable to the medical profession, where would hospitals ultimately report it?

Dr. DAMESHEK. Well, at the present time there is a voluntary agency for picking up reports of drug reaction that is handled by the American Medical Association, in their offices. That is one possibility.

Another possibility would be that such reactions would be reported to the Food and Drug Administration. That is another possibility that might be more official, I suppose.

Senator NELSON. As one who has had a great deal of experience working in hospitals, if you had some defined requirement that serious reactions to drugs be reported by the hospital, what kind of a paper-work problem would this be?

Dr. DAMESHEK. Oh, it would simply increase the paperwork which already is extremely high at hospitals. Some hospitals have more paperwork than others as I have found in my move from Boston to New York. So that this would simply increase the paperwork in New York by a very small fraction, in other places by a very large fraction.

It could be done. I see no reason why it could not be done.

Senator NELSON. It could be confined to reactions knowledge of which would be of some value. In other words, there are drugs where I suppose you have had enough experience so that everybody in the profession knows about all the possible reactions that could occur. I suppose that is one kind of situation.

Dr. DAMESHEK. I would think serious drug reactions—you take, for example, penicillin occasionally has drug reactions, that you are undoubtedly familiar with. You may get a skin rash or something of that sort. I doubt that anyone would want to report any more cases of drug rash with penicillin. But, when you talk about aplastic anemia or severe blood reactions, if I were an administrator of a hospital, I would like to know something about those reactions.

Senator NELSON. Since all the information is there in the hospital records on every patient anyway, what you would be talking about is that at the conclusion of some period, 6 months or a year of the appropriate professional people and specialists in the hospital, would decide which of these reactions were reactions knowledge of which would be of some value to medical knowledge and literature, and they would then report those possibly to the FDA and the AMA.

Dr. DAMESHEK. Right. Most hospitals already have the machinery set up. They have a drug committee which in some hospitals, I believe, functions with respect to drug reactions. So that the machinery is there in many hospitals and could easily be set up in other hospitals.

Senator NELSON. And, do I understand it to be your judgment that, if this kind of information were collected and properly submitted to the right places, whether it be FDA and AMA or wherever, it would be a valuable contribution to medical knowledge?

Dr. DAMESHEK. I would say it would be valuable because one of the functions of dissemination of knowledge is development of facts first, accumulation of facts, and then one can draw conclusions from those facts, yes.

Senator NELSON. I suppose it would be most valuable when a new drug comes on to the market, during the first few years of experience with it?

Dr. DAMESHEK. Yes; I would think so because a drug may be introduced, may get by all agencies as a fine drug without reactions, as this one did, and then in a few years case after case begins to pile up. It is a curious thing. The reactions do not seem to show themselves up for a while.

There can be no question that the continued widespread advertising of chloramphenicol and of promotional activities by detail men tend to increase the use of this drug. Although cautionary statements have been introduced in the advertising literature and also in the medication packet, there is no clear-cut evidence that these are heeded to any degree. With access to an excellent antibiotic like Chloromycetin, the practicing physician is apt to reason that in this particular instance, and in view of the relatively few overt reactions to the drug, this particular patient would probably withstand any serious damage. As in cigarette smoking, the warning statements are honored more in the breach than in the observance.

In some areas of the world, notably in less developed countries as in the Orient, Chloromycetin is used almost as freely as aspirin, from my experience there, and without the cautionary recommendations required in this country.

Senator NELSON. Are these drugs manufactured in this country?

Dr. DAMESHEK. As far as I know, they are. There may be other sources, I do not know. But I know that Chloromycetin is used widely in various Oriental countries like the Philippine Islands and in Formosa and in many other foreign countries.

Senator NELSON. Do you find a comparatively high incidence, then, of blood dyscrasias of various kinds in those countries where chloramphenicol is used extensively?

Dr. DAMESHEK. Well, the physicians I talked with in the countries I visited seemed to think that the incidence of aplastic anemia in their respective countries is increasing, is unduly prevalent.

I have a little statement here from an editorial I wrote a few months ago that talks about this.² I said:

Thus, in Manila, the Philippines, Dr. Allen Caviles, of the Philippines General Hospital—

One of the largest hospitals in Manila, but only one of them, this is only one hospital—

informed me that he had observed 71 cases of aplastic anemia in 3 years, 53 of which had been the subject of followup.

One of these had developed another interesting disease that I have here. I call it here PNH, in abbreviation:

In the same period nine cases of PNH had also been observed, five of them having previously been diagnosed as aplastic anemia.

Another doctor, Dr. Hwang, in Taipei, Taiwan, reported that he had observed 10 to 14 new cases of aplastic anemia annually in one large hospital and he thought that the incidence had been going up year by year. In both these areas, Chloromycetin had been used very freely for about everything.

² See exhibit B, p. 2400, *infra*.

Senator NELSON. Are the instructions about the precautions in using it as widely disseminated there as here?

Dr. DAMESHEK. I would be inclined to doubt that they were. I am not sure that they even have any cautionary statements about the use of chloramphenicol in these countries.

Senator NELSON. In the—

Dr. DAMESHEK. In the literature or in the package. I am not sure about that. I do not believe they have, but I am not sure about it.

Some of the disturbances which may be related to aplastic anemia, and which I have observed, are acute leukemia, which has been shown to develop in some cases of aplastic anemia after some time. And the peculiar disorder known as paroxysmal nocturnal hemoglobinuria, PNH, which I do not think I would go on and explain to you because it is rather complicated.

But, a few months ago we did report in the *New England Journal of Medicine* three cases of myeloblastic leukemia following Chloromycetin therapy and in these two cases the patients had used the drug, had developed aplastic anemia which was followed by the development of leukemia.

Senator NELSON. Were these cases in which the drug should not have been prescribed, in which it was not indicated?

Dr. DAMESHEK. The first one I came in contact with was a woman from one of the most affluent families in this country. I will not mention the name. And her doctor in this elegant community had given her Chloromycetin for a head cold and had told her to use this drug for every sniffle that she might get in the future. She proceeded to follow this prescription regularly. Her colds disappeared. But later on she developed aplastic anemia and eventually leukemia.

And, in the two other cases I have here, one had a urinary disturbance where she was asked to take—cystitis, so-called—she was asked to take the drug whenever she had a little burning of the urination. Eventually she developed aplastic anemia and then leukemia.

The other one was a woman who had had simply a 6-week course of Chloromycetin for an infection. I do not have it specified here what the infection was. I guess we did not know about it. But, these are newer developments in the followup of aplastic anemia.

There was another case recently reported from California, the same sort of thing.

Senator NELSON. Are each of these cases ultimately fatal?

Dr. DAMESHEK. Yes. This kind of leukemia is always fatal.

Senator NELSON. Was the second case that you mentioned one in which it should have been prescribed for the condition?

Dr. DAMESHEK. Well, this woman had a urinary infection and a lot of people use this drug in urinary infections. Now, whether it should not have been prescribed I am not sure, but she used it whenever she had a little burning of urination. I think she used it rather indiscriminately. That is about as far as I can go on that.

I discussed in an editorial of the *Journal of the American Medical Association* of a few years ago some of the problems relating to responsibility and to precautionary measures.³ That is, who is responsible for this or whose responsibility is it?

³ See exhibit C, p. 2401, *infra*.

Senator NELSON. You read from an editorial that you had written. Was that for the Journal of American Medical Association?

Dr. DAMESHEK. Oh, that last—

Senator NELSON. The first one you mentioned?

Dr. DAMESHEK. About the Far East?

Senator NELSON. Yes.

Dr. DAMESHEK. This was published in the journal "Blood."

Senator NELSON. Would you mind supplying that to us so that it can be printed at this point in the record of your testimony?

Dr. DAMESHEK. Yes. I have it here.

Senator NELSON. And then, would you supply for us the cases you just mentioned for printing in the record?

Dr. DAMESHEK. Yes.

Senator NELSON. We would appreciate it if you would give us copies of each of the reports or editorials that you refer to.

Dr. DAMESHEK. Fine. I think you have this one from "Blood," of which I—

Senator NELSON. That is attached to the back of your statement and will be printed, yes.

(The articles referred to follow:)

[Reprinted from Blood, the Journal of Hematology, vol. VII, No. 7, July 1952]

EXHIBIT A.—EDITORIAL

CHLORAMPHENICOL (CHLOROMYCETIN) AND THE BONE MARROW

New drugs, miraculous as they often appear to be initially, not infrequently have their tarnish rubbed off as we come to know them better. More often than not, this is the result of reactions of the drug upon the bone marrow and blood. Since 1931 when Kracke¹ and others suggested that agranulocytosis might be due to the administration of drugs such as aminopyrine, the medical profession has been alerted to the possibly deleterious effect of drugs containing the benzene ring, particularly when it is in combination with a nitrogen, amino, or nitrate group.

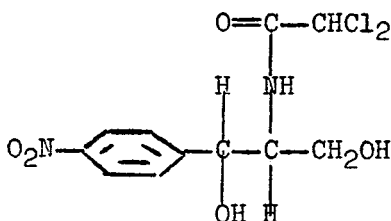
In Denmark, agranulocytosis ceased to exist for all practical purposes when a complete prohibition was placed on the import and sale of Pyramidon (aminopyrine) into that country. Later, when the first "miracle drugs" of present-day medicine, i.e., the sulfonamides were introduced, it was found that they too might result in various types of bone marrow reactions and thus in total or selective cytopenias. These reactions occurred with both the intermittent administration of the drug ("hypersensitivity?") or after long continued administration.² With the advent of the soil antibiotics, this particular problem appeared to be solved, and in fact, penicillin administration soon became the standard mode of therapy for agranulocytosis.

Penicillin, remarkable though it was in quelling many gram positive infections, was ineffective in controlling such diseases as tuberculosis and the gram negative infections. This resulted in a wide search throughout the world for other therapeutic molds, as a result of which streptomycin, aureomycin, terramycin and chloramphenicol (Chloromycetin) were found and developed. The latter three agents became known as the "broad spectrum" antibiotics since they prove to be active against both gram positive and gram negative bacteria, certain rickettsiae and even against some viruses. Of the group, chloramphenicol, originally derived from a soil bacterium found in Venezuela, had the simplest formula and was the only one that could be synthesized. Isolated in 1948, it was introduced into medical practice the following year.

The chemical formula of chloramphenicol is pictured (Merck Index, 1952) as:

¹ Kracke, R. R. and Parker, F. P.: J. Lab. & Clin. Med. 19: 799, 1934.

² Dameshek, William: Leukopenia and Agranulocytosis, New York, Oxford, 1944.



Shortly after its introduction, at least one observer, Smadel,³ called attention to the nitrobenzene radical in the drug and warned of its possible toxic effects on blood-forming apparatus. Early reports indicating possible toxic hematologic reactions of Chloromycetin were largely minimized, especially since in the great majority of the cases in which the drug was used, no ill effects were noted. Furthermore, it was not clear in some of the cases whether Chloromycetin was the sole responsible agent. Recently, however, we have been apprised of a rapidly increasing number of cases from all parts of the country,⁴ and we ourselves have observed a striking instance of hypoplastic anemia following the long term administration of Chloromycetin for mild acne of the face. Although it is likely that a number of cases are in the process of publication⁵ there has been as yet only one article⁶ in 1952 dealing with aplastic anemia following prolonged administration of the drug. Many of the cases have been shown to be irreversible and therefore fatal. Although most of the reports are still in the status of "personal communications," there seems to be no question as to their authenticity or their relationship on a circumstantial basis to chloramphenicol administration. It appears from the various reports that severe myelotoxic reactions have followed both the lengthy administration of the drug and its intermittent use.

It seems increasingly clear that a real danger exists in the uncritical use of this drug by the medical profession. A recent pamphlet⁷ recognizes this possibility but places the emphasis upon the very large number of cases and the millions of administrations in which no harmful effects have apparently been observed. There can be no doubt regarding the relatively small proportion of severe hematologic reaction, thus indicating a possible allergic susceptibility on the part of some. However, to the luckless individual who develops pancytopenia, the 10-percentage figure means very little.

In the instance of a valuable drug with potential toxic effects, the ultimate safety of the patient must transcend all other considerations. With the use of Chloromycetin the physician is assuming an admittedly small but nevertheless "calculated risk," and should, therefore, be on the watch for possible hematologic reactions, particularly during long term administration.

Chloromycetin appears to offer a potential hazard to the bone marrow, at least in some individuals, and it would, therefore, seem wise to use it only for short term administration and when there is a clear and impelling need for this particular medication. Its indiscriminate use for trivial infections and as a household remedy must be deplored.

It is unfortunate that no good method has yet been devised to measure in advance the tendency of new drugs to cause hematologic reactions. Certainly in the case of chloramphenicol, careful animal and human studies on the metabolic disposition and toxicity of the drug gave no hint that it might induce severe bone marrow reactions. Much thus remains to be done in the important field of drug sensitivity particularly as it relates to the bone marrow and blood.

WILLIAM DAMESHEK.

[Excerpt from editorial—Blood, vol. 30, No. 2 (August), 1967]

EXHIBIT B

During a recent trip to the Far East where aplastic anemia appears to be unduly prevalent (perhaps because the use of chloramphenicol is relatively uninhibited), it was evident that the incidence of PNH was also unduly high. Thus, in Manila, the Philippines, Dr. Allen Caviles of the Philippines General Hos-

³ Smadel, J. E.: *Am. J. Med.* 7: 671, 1949.

⁴ The U.S. Food and Drug Administration has collected about 40 cases (with 9 deaths) in which severe hematologic reactions occurred following use of chloramphenicol.

⁵ Smiley, R. K., Cartwright, G. E. and Wintrobe, M. M.: *J.A.M.A.* In press.

⁶ Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O. and Kahn, Julius: *J.A.M.A.* 149: 231, 1952.

⁷ Chloromycetin from the Hematologist's Point of View, Detroit, Parke, Davis, 1952.

pital informed me that he had observed 71 cases of aplastic anemia in three years, 53 of which had been subject to follow-up; one of these had developed PNH. In the same period, nine cases of PNH had also been observed, five of them having been previously diagnosed as aplastic anemia. Dr. Tien-tse Hwang in Taipei, Taiwan, reported that he had observed 10-14 new cases of aplastic anemia annually, as well as seven cases of PNH at the two hospitals where he worked, one of them the large National Defense Hospital. Among the first 10 cases of hypoplastic anemia he had seen in 1966, one of them subsequently developed PNH. From these several observations, the factor of coincidence for the two apparently disparate conditions of aplastic anemia and PNH seems unlikely.

[Reprinted from J.A.M.A., vol. 174, No. 14; 1953-1954, 1960]

EXHIBIT C.—CHLORAMPHENICOL—A NEW WARNING

In one month recently, I saw 4 new cases of aplastic anemia. Although they ranged in age from 3 to 63, and came from different sections of the country, they had one common denominator: chloramphenicol had been used in the recent past for minor respiratory infections. There was no history of the use of other antibiotics or potentially toxic drugs and since the anemia and the other manifestations appeared a few months after the last administration of chloramphenicol, it seemed clear that this drug was responsible for the marrow aplasia.

In our recently studied series of aplastic anemia (seen within the past 3 years) 8 of 30 had received significant amounts of chloromycetin, almost invariably for minor infections. Of the most recent 10 cases of aplastic anemia, 5 had followed therapy with chloramphenicol. The tragic thing about all these seriously ill cases, most of whom died, is *that the drug need never have been given.*

It is becoming increasingly clear that chloramphenicol, an excellent broad-spectrum antibiotic, has antimetabolic effects as well—that is, it may injure the intrinsic "machinery" of certain rapidly proliferating cells, notably of the bone marrow. Thus, Rubin and associates, using radioactive techniques, demonstrated a depressant effect of chloramphenicol on erythropoiesis; this occurred in 5 of 15 subjects receiving ordinary doses and in all of 4 cases with cancer who were given unusually large doses of the drug.¹ In another study by Saidi and Wallerstein² 10 of 22 cases treated with chloramphenicol for various infections developed striking vacuolization of nucleated red cells in the bone marrow, associated with a maturation arrest phenomenon and marked reduction in blood reticulocytes. The possibility is present that these temporary changes could go on to complete or partially complete destruction of the bone marrow providing (a) that sufficient drug was used or (b) the patient became sensitized in some manner and was given a second course of drug therapy at another time. It is thus conceivable that both an immediate or direct effect as well as an indirect or hypersensitivity mechanism may be responsible for the marrow reactions seen.

Following the introduction of chloramphenicol in 1948 and the reports of the first cases of aplastic anemia between 1950 and 1952, many editorials and reports of special ad hoc meetings appeared. Evidently the medical profession was profoundly influenced; in any event, the sales of chloromycetin declined sharply, reaching their lowest level in 1954. This lull was short-lived. By 1958, there was a five-fold increase in the sales of the drug and by 1960, enough chloramphenicol was being distributed, and presumably used, in the United States to supply 3,732,416 persons with 10 Gm. courses of the drug! (These data were supplied through the kind cooperation of Dr. Harry Carnes, Parke Davis & Co., Detroit, Mich.)

To those of us who see cases of aplastic anemia following the use of various possible etiologic agents, chloramphenicol stands out as the most important single historical factor. To be sure, evaluation of histories and even of statistics relating to both the incidence of aplastic anemia and of chloramphenicol as an etiologic agent is difficult. Nevertheless the importance of the chloramphenicol-aplastic anemia relationship persists, and one must naturally be concerned with the possibility that an increased incidence in aplastic anemia may result as use of the drug increases so rapidly. Is the pharmaceutical house which introduced and for there can be no question that this respected company has gone to every effort popularized the use of chloramphenicol to be taken to task? This seems unfair to ferret out statistics of case reports, to carry out experimental work in various animals and even to note the effects of marrow transplantation in chemically induced aplastic anemia of monkeys.

¹ Rubin, D.; Weisberger, A. S.; Botti, R. E.; and Storaasli, J. P.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity. J. Clin. Invest. 37: 1286-1292 (Sept.) 1958.

² Saidi, F., and Wallerstein, R. O.: Effect of Chloramphenicol on Erythropoiesis. To be published.

Is it the physician, then, who is largely responsible? In a way he is, for with out his prescription, the drug would not be administered. Certainly, if he regards chloramphenicol lightly, to be dispensed like aspirin, for every minor cold and respiratory infection, he is not without blame. But are there certain mitigating factors? Some say that a person ill is a person to be treated! The urge to make a person comfortable and to cure his illness as quickly as possible is an urge each of us has. It follows then that a good antibiotic of the broad spectrum variety and which can be readily administered is something to be used at every opportunity. This is part of the mores in this affluent society of ours. We have potent medicines; the patient is ill; we must treat! The days of simple herb medicines and of simple galenicals have long since passed. More often than not, the newer synthetics, most of them composed of molecules with benzene rings and nitrogen, NH, NH₂, or NO₂ groupings—are used, and all of them, it should be said, are potentially harmful.

What then can be done? A few suggestions may be offered: (1) Physicians must be warned, and in no uncertain terms by means of articles, editorials, meetings, announcements; not once, but repeatedly that chloramphenicol is not only a potent antibiotic but apparently an antimetabolite as well, having effects not only on bacteria but on the bone marrow. (2) By some means, whether by regulation or by self-discipline, promiscuous use of the drug should be avoided and its use restricted to *impelling circumstances*, i.e. for conditions in which no other antibiotic is currently effective. One realizes that this is more easily said than done, knowing the physician's individualistic nature. (3) The patient and the patient's family must be warned, either by the physician or by the druggist that this is a powerful drug; that it should be used only once; that its repeated use may result in serious blood reactions; that it should not be kept in the bathroom cabinet and used again if an apparently similar disorder supervenes. (4) The manufacturing drug house should instruct its detail men, our ubiquitous mentors, not to minimize the dangers of the drug, and to emphasize its value for certain specific conditions, and not for the whole gamut of infectious diseases. The journal advertising could be made more forceful regarding the necessity for guarding against use of the drug indiscriminately, and especially in minor infections, or in repeated courses; or off the bathroom closet shelf.

It might be wise for the patient or his family to have some knowledge of what antibiotic is being used in a given case. Perhaps we physicians might also consider, at least for many of the acute, self-limited infections, the more conservative course (radical by present-day standards) of giving no potent medications at all, but rather such symptomatic care as aspirin, fluids, and the like. After all, the body defenses are usually capable of handling most acute upper respiratory infections.

In any event, something must be done to reduce the incidence of grave insult to the bone marrow produced by some of the antibiotics. The practicing physician would do well to think twice before prescribing a potent antibiotic and to ask himself "Is this drug really necessary?"

WILLIAM DAMESHEK, M.D.

Dr. DAMESHEK. This is one on leukemia I did not put in.

Senator NELSON. If you will furnish that to the reporter.

Dr. DAMESHEK. Fine.

(The article referred to follows:)

[Reprinted from the New England Journal of Medicine, 277: 1003-1005 (Nov. 9), 1967]

HYPOPLASTIC ANEMIA AND MYELOBLASTIC LEUKEMIA FOLLOWING CHLORAMPHENICOL THERAPY*—REPORT OF THREE CASES

Mark J. Brauer, M.D.,[†] and William Dameshek, M.D.[‡]

A pathogenic relation between aplastic anemia and myeloblastic leukemia has long been suspected. It is well known that certain agents capable of producing

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†Supported by a fund from the grant (CA 04168-09) from the National Cancer Institute, National Institutes of Health, United States Public Health Service.

‡Attending physician and hematologist, New England Medical Center Hospital; senior instructor in medicine, Tufts University School of Medicine.

§Attending hematologist, Mount Sinai Hospital; professor of medicine, Mount Sinai School of Medicine, New York City.

aplastic anemia in man can also induce leukemia. Prime examples are benzene^{1,2} and irradiation.^{3,4} In addition, cases of leukemia developing during the course of hereditary hypoplastic syndromes have been recorded.^{5,6} The broad-spectrum antibiotic chloramphenicol⁷⁻⁹ has become the most commonly cited cause of acquired aplastic anemia. To date, only 1 case report of acute myeloblastic leukemia following aplasia secondary to chloramphenicol administration has been published.¹⁰ The purpose of this communication is to present 2 additional cases of chloramphenicol-induced aplastic anemia of long standing that developed into acute myeloblastic leukemia. In addition, a patient in whom an indolent, pancytopenic myeloblastic leukemia followed the prolonged use of chloramphenicol for the treatment and prevention of head colds is reported.

CASE REPORTS

CASE 1. J.D. (N.E.M.C.H. 178-415), a 38-year-old woman, was initially investigated 8 years before admission when, after a 6-week course of chloramphenicol (total dose, 84 gm), marked pallor developed. The pretreatment hemoglobin level was 12 gm per 100 ml, and the white-cell count 8000. Shortly after chloramphenicol therapy the hemoglobin was 7.2 gm per 100 ml, the white-cell count 2200, and the platelet count 100,000. Peripheral blood examination showed a predominance of mature lymphocytes (69 per cent) with no primitive white-cell forms. In addition there was mild red-cell anisocytosis. Aspiration of the bone marrow produced a fatty hypocellular sample with small spicules. The myeloid-erythroid ratio was increased, primarily owing to severe red-cell hypoplasia. Granulocytic precursors and megakaryocytes were also decreased in number. No vacuolization of bone-marrow elements nor increase in immature forms was apparent. Lymphocytes and reticular elements were relatively increased. A diagnosis of chloramphenicol-induced hypoplastic anemia was made, but no specific therapy was initiated.

Splenectomy was performed in 1959 because of worsening pancytopenia and bleeding. The spleen was of normal size and showed no abnormal features. Bone-marrow aspiration was not repeated. After splenectomy there was no marked change in the peripheral blood picture. The hemoglobin values ranged between 6 and 8 gm per 100 ml, and the white-cell counts around 2500. Treatment consisted of adrenocorticosteroids, androgens and occasional blood transfusion until 1963, when the patient gave birth to a normal male child. Thereafter, transfusion requirements rose sharply. This was attributed primarily to decreased red-cell production. Thirty-eight units of whole blood were given from March, 1965, until 1966. A hemogram performed in April, 1966, revealed a hemoglobin of 7.0 gm per 100 ml, a white-cell count of 15,000 and a platelet count of 50,000. The differential count showed a predominance of immature blast forms, some of which contained Auer rods.

On clinical examination in May, 1966, the patient was extremely pale and incoherent, with marked purpura. There was evidence of congestive heart failure and a severe neurologic deficit related to brain hemorrhage. The peripheral white-cell count was 37,900, with 15 per cent myeloblasts. Aspiration of the bone marrow produced a specimen almost totally replaced by myeloblasts. Shortly after admission the patient died. Permission for post-mortem examination was not granted.

¹ DeGowin, R. L. Benzene exposure and aplastic anemia followed by leukemia 15 years later. *J.A.M.A.* 185: 748-751, 1963.

² Vigilani, E. C., and Saita, G. Benzene and leukemia. *New Eng. J. Med.* 271: 872-876, 1964.

³ Cronkite, E. P., Moloney, W., and Bond, V. P. Radiation leukemogenesis: analysis of problem. *Am. J. Med.* 28: 673-682, 1960.

⁴ Lawrence, J. S. Is there incriminating evidence for . . . irradiation leukemogenesis. *J.A.M.A.* 199: 1049-1054, 1964.

⁵ Cowdell, R. H., Phizackerley, P. J. R., and Pyke, D. A. Constitutional anemia (Fanconi's syndrome) and leukemia in two brothers. *Blood* 10: 788-801, 1955.

⁶ Garriga, S., and Crosby, W. H. Incidence of leukemia in families of patients with hypoplasia of marrow. *Blood* 14: 1008-1014, 1959.

⁷ Registry on Adverse Reactions, Council on Drugs, American Medical Association.

⁸ Leiken, S. L., Welch, H., and Guin, G. H. Aplastic anemia due to chloramphenicol. *Clin. Proc. Child. Hosp.* 17: 171-181, 1961.

⁹ Yunis, A. A., and Bloomberg, G. R. Chloramphenicol toxicity: clinical features and pathogenesis. *Prog. in Hemat.* 4: 138-159, 1964.

¹⁰ Mukherji, P. A. Acute myeloblastic leukemia following chloramphenicol treatment. *Brit. M. J.* 1: 1286, 1957.

This patient with chronic aplastic anemia after chloramphenicol was observed for eight years. The terminal development of acute myeloblastic leukemia suggested a causal relation.

CASE 2. L.R. (N.E.M.C.H. 169-853), a 57-year-old woman, was first seen 15 years before admission for recurrent attacks of dysuria diagnosed as "cystitis." Multiple urologic examinations gave no evidence of obstruction or intrinsic abnormality. For 8 years before admission it had been her custom to take chloramphenicol for her attacks. Short courses taken *ad lib* always produced impressive clinical improvement. Over this period an estimated 500 to 700 capsules were consumed (approximately 175 gm). Routine blood counts performed during annual examinations were reported as "within normal limits."

An anal fistula developed after hysterectomy in February, 1964. She was intermittently treated with chloramphenicol until May, with little improvement. At that time the hemoglobin level was 8.4 gm per 100 ml, and the white-cell count 2500. No platelet count was recorded. A sternal puncture yielded a fatty specimen with marked hypocellularity. Erythroid precursors were almost totally absent. Granulocytic elements, although diminished, showed no "shift to the left" nor clusters of immature cells. No vacuolization of young forms was seen. Megakaryocytes were also markedly diminished. A diagnosis of chloramphenicol-induced bone-marrow hypoplasia was made.

The patient was treated with adrenocorticosteroids, androgens and blood transfusions from August, 1964, until February, 1965, without improvement of blood findings.

On examination in February, 1965, she appeared chronically ill with marked pallor, widespread purpura and pulmonary congestion. The liver and spleen were not enlarged. A major finding was a massive perirectal abscess. The hemoglobin was 7.3 gm per 100 ml, the white-cell count 5800, and the platelet count 21,000. The differential count showed 25 per cent myeloblasts. Bone-marrow aspiration revealed a hypercellular specimen completely replaced by myeloblasts.

Therapy with 6-mercaptopurine had no beneficial effect, and she died in another hospital. No post-mortem examination was performed.

In this case, chronic chloramphenicol ingestion was held responsible for the development of aplastic anemia. Acute granulocytic leukemia was observed one year later.

CASE 3. V.D., a 61-year-old woman, was first seen on October 26, 1964. At a routine checkup on October 5, when she was asymptomatic and showed no physical abnormalities, a blood count revealed leukopenia and granulocytopenia. The history revealed further that the patient had been plagued by several "heavy colds" every year and that she had been advised by her family doctor in August, 1963, to take chloramphenicol, 4 capsules daily, "at the earliest snuffle." In the course of the past 14 months she had taken by actual count 60 capsules (15 gm) of the drug. There was no history of any other drug or chemical contact and no history of x-ray exposure except for a few single dental x-ray examinations. The family and past histories were noncontributory.

On examination the patient looked very well. However, the liver edge was palpable 3 fingerbreadths below the right costal margin, and a few ecchymoses were present. The hemoglobin was 11.5 gm per 100 ml, the red-cell count 3,890,000, the hematocrit 37 percent, reticulocyte count 2.2 percent, and the platelet count 225,000; the white-cell count was 2200, with 15 percent neutrophils, 80 percent lymphocytes; and 5 percent monocytes. The sedimentation rate was 10 mm per hour. Bone-marrow aspiration revealed hypocellularity to normocellularity. Large numbers of primitive, pale-staining cells were present, and primitive monocytoid cells were increased. The diagnosis of hypoplasia of the bone marrow, with primitive cell (myeloblastic) leukemia, was made. An alternative diagnosis of "maturation arrest of the granulocyte series" induced by chloramphenicol was entertained. No therapy was advised except for discontinuance of the antibiotic.

The patient was observed at intervals during the following year. During the first 6 months she continued asymptomatic. Gradually, increasing pancytopenia developed. Symptoms of gingival hyperplasia, bouts of diarrhea and bouts of fever occurred in June and July, 1965. In mid-October, a severe nasopharyngitis, cellulitis of the left ear and rapidly progressive anemia appeared. The bone marrow was now almost completely replaced by myeloblasts and promyelocytes. Therapy with 6-mercaptopurine was instituted, and antibiotics and transfusions were given. In early December, 1965, generalized sepsis due to a coagulase-positive staphylococcus was present, and the patient died on December 7.

This woman of sixty-one, always in good health except for head colds, took 60 capsules of chloramphenicol during fourteen months as a prophylactic measure against further colds. This was successful, but pancytopenia and the indications in the bone marrow of hypoplasia and of primitive cell (myeloblast) leukemia developed. Chloramphenicol was discontinued. The patient was well for about six months, and then the various clinical manifestations of acute leukemia developed and she died fourteen months after the diagnosis had been made.

DISCUSSION

Hypoplastic anemia has been defined in various ways by various observers. We prefer to reserve this term for cases showing pancytopenia of the blood and well defined hypoplasia of the bone marrow. Those with increased cellularity of the marrow and blood pancytopenia may indicate other conditions ranging from maturation arrest to the DiGuglielmo syndrome or leukemia. In the aplastic anemia that follows the administration of chloramphenicol, 2 main forms may be discriminated. In the first the onset is acute, seemingly dose related and frequently associated with a normocellular bone marrow, which exhibits vacuolization of erythroblasts and granulocytic precursors. Moderate anemia, reticulocytopenia, increased plasma iron and delayed plasma iron clearance have been observed in this setting.⁹ Unless the dosage of drug has been inordinately high, this type is usually reversible when the drug is discontinued. Work in mammalian cell-free systems suggests that prolonged exposure to chloramphenicol and high blood levels of unbound drug are both important factors in inhibiting protein synthesis through interaction with messenger RNA. This may help to explain the bone-marrow hypofunction.¹¹

The second form, or "late-onset type," may not be dose related. It is characterized morphologically by hypoplasia or severe aplasia of the bone marrow. In most patients manifestations of marrow depression develop after the drug has been stopped, often weeks or months later. In such cases, indications of marrow injury remain long after the last trace of the drug have disappeared. Conceivably, injury to a large number of stem cells might explain such an effect. An interval would then be required before the stem-cell pool became depleted and cytopenia was manifest. That some patients, because of a metabolic abnormality or deficiency, may be more susceptible than others to the action of chloramphenicol or its degradation products, is an attractive but unproved possibility. In fact, there is no ready explanation at present for the apparent susceptibility of some persons to the development of serious disorders of the marrow after chloramphenicol or other agents.

The development of leukemia in the course of aplastic anemia is of considerable interest. Although most large series of acquired aplastic anemia¹²⁻¹⁴ contain no such reports, examples may be found with benzene toxicity,^{1,2} after radiation,^{3,4} after administration of phenylbutazone,^{15,16} during the hypoplastic phase of paroxysmal nocturnal hemoglobinuria¹⁷ and in hereditary hypoplastic syndromes.^{5,6} The development of paroxysmal nocturnal hemoglobinuria during aplastic anemia¹⁸ is of additional interest. This may be but another example of the development of abnormal cell lines in a previously injured bone marrow.

The induction of leukemia by chemicals (including drugs) may be mediated through chromosomal injury. In line with this is the recent observation by Castoldi and Mitus¹⁰ of chromosomal vacuolization in patients receiving chloram-

¹¹ Weisberger, A. S., Wolfe, S., and Aremtrout, S. Inhibition of protein synthesis in mammalian cell free systems by chloramphenicol. *J. Exper. Med.* 12: 161-181, 1964.

¹² Lewis, S. M. Course and prognosis in aplastic anaemia. *Brit. M. J.* 1: 1027-1031, 1965.

¹³ Mohler, D. N., and Leavell, B. S. Aplastic anemia: analysis of 50 1: 1027-1031, 1965.

¹⁴ Scott, J. L., Cartwright, G. E., and Wintrobe, M. M. Acquired aplastic anemia: analysis of thirty-nine cases and review of pertinent literature. *Medicine* 38: 119-172, 1959.

¹⁵ Bean, R. H. D. Phenylbutazone and leukemia: possible association. *Brit. M. J.* 2: 1552-1555, 1960.

¹⁶ Dougan, L., and Woodliff, H. J. Acute leukaemia associated with phenylbutazone treatment: review of literature and report of further case. *M. J. Australia* 1: 217-219, 1965.

¹⁷ Hartman, R. C., and Jenkins, D. E. Personal communication.

¹⁸ Lewis, S. M., and Dacie, J. V. Aplastic anemia: paroxysmal nocturnal haemoglobinuria syndrome. *Brit. J. Haemat.* 13: 236-251, 1967.

¹⁹ Castoldi, G., and Mitus, W. J. Personal communication.

phenicol. Inconstant chromosomal changes have been observed in several series of cases of acute leukemia.^{20,21} Similar changes have been found to follow radiation⁴ and benzene²² and to occur in hereditary states.²³ The chromosomal vacuolization seen after chloramphenicol may be a comparable lesion. Another possible explanation is that the leukemia is a secondary, perhaps reparative, response to aplastic anemia. A tendency to neoplasia of hypoplastic tissues has been recognized repeatedly in human pathology. Examples include atrophic gastritis and leukoplakia. Perhaps analogous to the potential of these disturbed tissues to transform into carcinoma is the eventual emergence of leukemia in the chronically aplastic bone marrow.

Finally, another explanation for the development of leukemia in these cases deserves consideration. Aplastic anemia and leukemia may both be thought of as growth disturbances of the bone marrow (myeloproliferative disorders). Thus they may occur either together or sequentially as phases of the same pathogenetic mechanism. Block et al.²⁴ had the unique opportunity to observe 12 patients for as long as twenty-seven months before the development of acute myelogenous or stem-cell leukemia. Most of the patients in this "preleukemic" phase displayed variable degrees of marrow hypoplasia as well as peripheral cytopenias. Blair and his associates²⁵ reported a similar experience in 16 cases of "atypical leukemia." Thus, it may be hypothesized that in some cases aplastic anemia and leukemia simply represent different expressions of the same fundamental disturbance. It is now reasonably clear that an "insult" to the bone marrow, as from chloramphenicol or another chemical, may either destroy totally or partially. Partial destruction of some cells may serve only to "knock out" one or two enzyme systems but not prevent cell reproduction. Under these circumstances, a new self-perpetuating cell line (clone) may develop—that is, leukemia, when white cells are concerned, or paroxysmal nocturnal hemoglobinuria with erythroblastic involvement. We have recently remarked upon the relation of paroxysmal nocturnal hemoglobinuria and aplastic anemia, particularly in association with chloramphenicol toxicity.²⁶

The syndrome of aplastic anemia, regardless of cause, may lead to early death from hemorrhage or infection or may result in chronic bone-marrow malfunction. The development of leukemia and of paroxysmal nocturnal hemoglobinuria has been associated with the latter process. It is evident that chloramphenicol can result in this sequence of events. The continued widespread use of this drug, particularly in the less developed countries, and even among the highest-income groups of this affluent country, often for trivial reasons, may be a factor in the causation of some forms of leukemia, particularly of the relatively indolent, hypoplastic type.

SUMMARY AND CONCLUSIONS

The development of myeloblastic leukemia during the course of chloramphenicol-induced pancytopenia in 3 patients is described. Leukemia has been reported in a wide variety of clinical states commonly characterized by variable degrees of bone-marrow hypoplasia. Factors responsible for the development of aplastic anemia and drug-induced leukemia are considered. Chloramphenicol, by primary or secondary means, appears casually related to the blood dyscrasias in the cases presented. As stated so many times, indications for the routine or even common use of this drug in the treatment of infection must always be carefully scrutinized.

Senator NELSON. I am sorry to interrupt you.

Dr. DAMESHEK. Fine. I do not mind at all.

²⁰ Baikie, A. G., Jacobs, P. A., McBride, J. A., and Tough, I. M. Cytogenetic studies in acute leukaemia. *Brit. M. J.* 1: 1564-1571, 1961.

²¹ Klossoglou, K., Mitus, W. J., and Dameshek, W. Chromosomal aberrations in acute leukemia. *Blood* 26: 610-641, 1965.

²² Pollini, G., and Colombi, R. Il dono cromosomico midollare nell'anemia aplastica benzolica. *Med. d. lavoro* 55: 241-255, 1964.

²³ Bloom, G. E., Warner, S., Gerald, P. S., and Diamond, L. K. Chromosome abnormalities in constitutional aplastic anemia. *New Eng. J. Med.* 274: 8-14, 1966.

²⁴ Block, M., Jacobson, L. O., and Bethard, W. F. Preleukemic acute human leukemia. *J.A.M.A.* 152: 1018-1028, 1953.

²⁵ Blair, T. R., Bayrd, E. D., and Pease, G. L. Atypical leukemia. *J.A.M.A.* 198: 21-26, 1966.

²⁶ Dameshek, W. Riddle: what do aplastic anemia, paroxysmal nocturnal hemoglobinuria (PNH) and "hypoplastic" leukemia have in common? *Blood* 30: 251-254, 1967.

As I say, I discussed in an editorial of the Journal of the American Medical Association in 1960 something about the responsibilities involved. Who is responsible and whose responsibility is it in the use of this drug. Is it, I say, the pharmaceutical house which introduced and popularized the use of chloramphenicol to be taken to task? This seems unfair because there can be no question that this respected company has gone to every effort to ferret out statistics of case reports, to carry out experimental work in various animals, and even to note the effects of marrow transplantation in chemically induced aplastic anemia in monkeys.

Is it the physician, then, who is largely responsible? In a way he is, because without his prescription the drug would not be administered. Certainly, if he regards Chloromycetin lightly, to be dispensed like aspirin for every minor cold and respiratory infection, he is not without blame.

But are there certain mitigating factors, which I have already mentioned? Some say that a person ill is a person to be treated. The urge to make a person comfortable and to cure his illness as quickly as possible is an urge each of us as physicians has. It follows, then, that a good antibiotic of the broad spectrum variety and which can be readily administered is something to be used at every opportunity. We have potent medications. The patient is ill. We must treat him. The days of simple herb medicines and galenicals—that is, ordinary medications made from herbs and other sources—those days have long since passed. More often than not the newer synthetics are almost invariably composed of molecules of benzene rings and nitrogen, $\square$ H, NH_2 , NO_2 groups and all of them it should be said are potentially harmful. So, I talked about these responsibilities but I must say that since 1960 I have modified my stand a little bit. I say, in retrospect, this by no means settles the question. The numerous warnings regarding the indiscriminate use of Chloromycetin have been practically without effect.

Senator NELSON. The printed warnings have been practically without effect?

Dr. DAMESHEK. As I see it. It is now about time to consider more radical measures such as restriction of the drug for a few specific indications. Should one stop its use altogether? This would surely be a wrong thing to do because the drug is a potent antibiotic and has a well-defined usage. Should one simply continue with a warning statement in the advertising and in the package? These seem to have little, if any, value. Should one attempt restriction of the use of the drug to various well-defined conditions? This, I would be in favor of, but who is to do the restricting? Should it be done by governmental means, either at National or State level? Should it be done by the practicing physician, or by whom? I would, myself, be in favor of including on the prescription blank for Chloromycetin a statement as to the diagnosis of the condition. The druggist looking at the prescription blank could then question, if need be, the physician as to the indication. This might hold up some of the prescription writing. This is one way, of course, but you have already, Senator, pointed out another way, through the hospital, where many patients go. That is a possibility. And, of course, we as physicians do not like restrictions. We are highly individualistic. But, on the other hand, we do allow the Government

to restrict us in the use of opiates and other such materials through a registry, and one wonders whether this sort of thing might be applicable here, that certain drugs like Chloromycetin might have to be written under a specific ruling or registry where the druggist could then control, to some extent, the situation.

Physicians are, of course, jealous of their prerogatives and perhaps rightly so. They are by nature individualists who object reflexly to restriction, but it is doubtful whether they would mind very much putting down the patient's diagnosis in general terms on the prescription blank. However, I am not so sure about that statement. To restrict that drug solely to hospital practice, as you suggest; this is possible. It may be of some interest to say that about half the doctors in this country are in hospital practice one way or another.

Senator NELSON. About half?

Dr. DAMESHEK. Yes; I would say so. About 100,000 of the 200,000 doctors, M.D.'s, in this country are in hospitals. That includes interns, residents, and the like; full-time physicians.

Senator NELSON. When you say limit it to hospital practice, do you mean limit it to administration to patients in a hospital?

Dr. DAMESHEK. I suppose if in a hospital one of the rulings of the drug committee or of the administration were that Chloromycetin should be restricted to diseases one, two, and three, this might then cut out some of the prescribing for this drug. This would cut out some of the prescribing for this drug for simple infections; but on the other hand, we realize that the simple infections—acne, head colds, grippe—are not treated in hospitals. They are treated on the outside.

Senator NELSON. Dr. Barbara Moulton, a physician who was formerly with the FDA, stated that in the case of a relatively small number of drugs, among which she included chloramphenicol, there should be established a special category of medicines that should be prescribed only with the written approval of a consultant except in emergencies or special circumstances. Would that be feasible?

Dr. DAMESHEK. Well, I think that is a bit unwieldy and I do not think that doctors by and large would like it. This would mean that every patient in a hospital or on the outside who has a disorder of an infectious type, and in which the physician wants to use the drug, would have to call in a consultant by law. I think that is a bit unwieldy.

Senator NELSON. If it is the case as you state, and as I believe both Dr. Lepper and Dr. Best have written, that there are many cases where the drug is being prescribed where it just simply is not indicated, I assume that this occurs because the doctor is not really aware of the caution which must be exercised, or for some reason does not believe that the warnings are very serious. Would it not be possible perhaps to have a committee decide that there are some categories of drugs such as this one which produce very serious side effects in a certain percentage of cases and that with regard to those drugs some special requirement be devised for the doctor in the prescribing of it to alert him that this drug is one in which there are serious side effects. You could probably notify all pharmacists so that there would be a couple of checks on the prescribing of these drugs. For example, prescription of such a drug could be limited to circumstances so that at least the doctor has a chance to take a second look if he is not aware of the

proper indications for the drug or has made a mistake. Would it be worth while to have some kind of control that would not be too cumbersome, but that still would control overprescription?

Dr. DAMESHEK. Well, Senator, I think you are absolutely right. I have come to the reluctant conclusion in the last few years that some type of restriction is essential in the use of this drug. How that restriction is going to take place or should take place, I am not sure. Certainly, physicians do not object to a registration number for the prescription of narcotics and, when they write morphine sulphate, they have to put their registration number down and they have to write out who it is being supplied for, and so on. The druggist then knows that this is a special type of prescription and he will not give it out for anything but a well-defined cause. He knows that. So there is restriction already in the medical profession with respect to certain drugs and I can see myself that this idea of a special registry for special drugs which have an undue proportion of serious reactions, I can see that such a registry could be begun and utilized. Exactly how, I do not know, either.

Senator NELSON. Do the doctors find any particular difficulty in complying with the regulations applicable to the prescription of morphine or any other narcotic? Is it a particularly cumbersome procedure for them to have to follow?

Dr. DAMESHEK. No. I do not think so. Once a year one has to make out a check for \$1 to the U.S. Government on a blank furnished by the Government with respect to narcotics, and one has to put down on a prescription your registration number and the name and address of the patient and your own name and address. That is about it. And that is not much of a restriction, I do not think.

Senator NELSON. Would you have any guess as to how many drugs ought to be in such a special category? You include chloramphenicol as one of those special drugs. Do you have any idea of what we are talking about in terms of numbers—half a dozen, a dozen—or any notion about which drugs you would include?

Dr. DAMESHEK. I would think there might be half a dozen to 10 drugs or so that might come in this category.

Senator NELSON. If the procedure followed with respect to certain other drugs like morphine is effective, why would not it be feasible, after appropriate consultation with members of the medical profession and the FDA, to agree that there are a half dozen or more drugs which ought to be used with special caution and, therefore, they would be handled in the same way that morphine is handled? Would that be feasible, in your judgment?

Dr. DAMESHEK. Well, I think there is something good that might be said about this. I personally do not think it would restrict anyone's individual liberty to do this sort of thing and I think it might be distinctly valuable.

Senator NELSON. Would it have in your judgment, the effect of putting a doctor on notice that the prescription of such a drug has been considered a serious enough matter so that there is a special requirement with respect to this drug? Is it your judgment that he would then be alerted to examine the literature carefully, if he had not al-

ready done so, to be sure that the drug was really indicated in the case for which he was prescribing it?

Dr. DAMESHEK. I would think it would conceivably act as a brake on the practicing physician. I could conceive that. If, in addition, the physician were asked to put down on the prescription blank the name of the disease, that might help even more. The two together, that is.

Senator NELSON. I am just exploring this extemporaneously here. You mentioned that a doctor might be reluctant to write the diagnosis out so that the patient would see it. Is this something that a physician might be concerned about sometimes?

Dr. DAMESHEK. No. I do not see how a doctor can be reluctant about putting the disease down if it is typhoid fever or a severe infection. The only time I suppose he might be reluctant would be in the case of acute leukemia where infection, serious infection, may develop due to one cause or another. He might not like to put the diagnosis of acute leukemia down, but on the other hand, he could put down serious infection, I suppose.

Senator NELSON. If the doctor followed the same procedure as he would with morphine so that pharmacists would also know that it was a special case, and at the time the pharmacist would make a specific record on a form as to the diagnosis, do you think that would be helpful?

Dr. DAMESHEK. Yes. I think it would reduce—certainly it would stop, I would think, the use of the drug for cases of acne, colds, grippe, influenza, and minor infections in general. It seems to me it would.

Now, the question of the mechanics of this I am not so sure about. I do not want to try to make any exact recommendations. That is not in my line really.

Mr. GORDON. Dr. Dameshek, if the doctor would under ordinary conditions prescribe this drug, say, for a cold, why would writing it down on a prescription blank discourage him from doing what he had intended to do or would have done in the first place?

Dr. DAMESHEK. Because I would think if the doctor knows that he should not be giving this drug for a cold, and, therefore, if he puts down a cold and the patient happens to be one of these rare birds that develops aplastic anemia, this prescription and the cold might be held against him in future times.

Mr. GORDON. Well, are you saying, Dr. Dameshek, that the doctor frequently knows he should not be prescribing Chloromycetin for a particular illness and yet he still does so?

Dr. DAMESHEK. I dislike to say anything against the medical profession, being a member of that august profession myself. I doubt that the doctor is ignorant of all the statements that have been made over the years about Chloromycetin. So that this is what I base my statement on.

Senator NELSON. Might he not have been influenced by the advertising which is designed in such a way as to indicate that it is a marvelous antibiotic and has over the years covered up the side effects to some extent? Unless the drug company wasted its money, then the advertising must have some influence.

Dr. DAMESHEK. Yes, I suppose so, but advertising might be construed as a form of brainwashing and I doubt that intelligent people, whether they are presidential candidates or doctors, should be brainwashed to that extent.

Senator NELSON. But, they might be.

Dr. DAMESHEK. Oh, yes.

Senator NELSON. You were just near the end of your statement.

Dr. DAMESHEK. Should a simple—I say here in my typed statement “to restrict the drug solely to hospital practice would not do very much because about half of the doctors in the country are in hospitals and they are apt to make as many errors of judgment in this regard as outside physicians.” Well, I think it might do something. We discussed this previously. Should a simple method such as including the diagnosis on a prescription blank not prove successful, then a more radical approach might have to be used—one which almost completely restricts the drug to situations which are wholly acceptable for chloramphenicol therapy and for chloramphenicol therapy alone, as determined by one or another agency or committee. When lives are to be placed in jeopardy, even a few lives, one realizes, I should say this, that the reactions to this drug are few, relatively few, in comparison to the number of administrations, and this has been pointed up by many as an excuse for giving the drug. But in a democracy such as ours, every life is worth a great deal and the individual who does get this disease, aplastic anemia, is more apt to die than not, and, therefore, it seems to me that, even though the reactions are very few, the lives that are lost from this drug, whether they are 100 or 200 a year in this country—I do not know the statistics—those are well worth saving and since the great majority of drug reactions have occurred in the past in response to the use of the drug for minor infections, I think we could save some lives, and each life is worth a lot and when the person does develop aplastic anemia, it is a poor comfort to that individual to say, well, 10,000 people took the drug and only you got it.

Senator NELSON. Well, of course, if it is a case where it should not have been prescribed in the first place—

Dr. DAMESHEK. Well, it makes it all the more binding, all the more upsetting. When lives are to be placed in jeopardy, every precaution however frustrating, is desirable.

Well, that is the end of my statement and I—

Senator NELSON. Doctor, we appreciate very much your thoughtful statement. I have a few questions I would like to ask.

You, as well as a number of other experts in the field, have recited cases of serious side effects occurring in patients who should not have received the drug in the first place. It has been estimated by some that approximately 3,700,000 people in this country are given chloramphenicol annually for one reason or another. Considering the restrictions under which you and many other experts believe the drug ought to be administered, do you have an educated guess as to how many people legitimately should be receiving chloramphenicol in their treatment annually?

Dr. DAMESHEK. No. I think Dr. Best probably has some statistics.

I would say no more than maybe 10 percent of the people receiving the drug should have had it. I think Dr. Best in one of his articles takes this thing up and you might ask Dr. Best for a better—or best—answer to this.

Senator NELSON. But, it is your belief or guess that of the some 3,500,000 or so who do receive the drug each year only about 10 percent should have received it?

Dr. DAMESHEK. I would think so, but I must confess that this is not a very—it is a guess. That is about it. And, if you want to say educated, all right. I am agreeable to that.

Senator NELSON. Pardon me. I did not understand that.

Dr. DAMESHEK. If you want to say “educated” in front of a guess, that is all right.

Senator NELSON. Doctor, I have here two package inserts on chloramphenicol, in this case Chloromycetin. One of them is a package insert that is used in this country now and one is a package insert that is used in Great Britain. I would like to have one of the staff show these to you and get your comment as to the adequacy of the warning notices on these package inserts and then submit them for the record.

Dr. DAMESHEK. Yes. The warning in the packet for use in this country is, I think, a pretty good warning. It is a direct outgrowth of an ad hoc committee of which I am a member, I think a committee of the National Academy of Sciences, or the National Science Foundation, and we had a meeting, I think, in 1952, and another meeting in, I think, around 1959, and we practically wrote this thing and it was accepted by the pharmaceutical house, Parke, Davis & Co., and it reads as follows, if I may read it:

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias—

Abnormalities of the blood—

have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

And then, it says something about precautions:

It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

I think that is a very good statement.

Mr. GORDON. Dr. Dameshek, does the ordinary practicing doctor read it and remember what it says?

Dr. DAMESHEK. Now, now look, I cannot look into the minds of ordinary practicing physicians. There are no such things as “ordinary” practicing physicians in our country. There are practicing physicians and they are all people who have had an adequate training, it is hoped, and have passed all the various boards, it is hoped, and so on, and they

are all intelligent people, we believe. So that "does he read them?" I do not know. Does he bother with them? I do not know.

Senator NELSON. Does he see them is, I suppose, another question, since, unless it is an injectible, the package insert goes to the drugstore and the doctor does not see it at all, does he?

Dr. DAMESHEK. That is right. That may be. I had not thought of that. Yes, Senator. It is a possibility he may not even see it.

Mr. GORDON. Most important of all, as you stated, he does not pay any attention to it.

Dr. DAMESHEK. Now, look, do not lead me into this "does not even pay any attention to it." I do not know. I will not read his mind if you will excuse me on that. I cannot say.

Now, you wanted me to read about the British thing, is that right?

Senator NELSON. Yes.

Dr. DAMESHEK. In the British statement—yes; it is, Parke, Davis & Co., Hounslow, London, England—I can see here no statement about such a warning. There is certainly no warning here, and then there is a statement about side reactions and toxicity, and this is what it reads:

"Patients on treatment may complain of dry mouth and less often of nausea, diarrhea, or vomiting, although these are seldom sufficiently severe to justify withdrawal of the drug. Drug sensitivity reactions are also sometimes encountered. Cases of optic and peripheral neuritis have been reported in patients receiving high total dosage during prolonged therapy. While the incidence of blood dyscrasias associated with systemic Chloromycetin therapy is rare, cases of serious disorders including aplastic anemia have been reported. As with certain other drugs, adequate blood studies should be made when the patient receives prolonged or intermittent therapy."

Senator NELSON. Do you consider this as good a warning as the one used in this country, and is it adequate, in your judgment, as a warning?

Dr. DAMESHEK. Well, I have not gone over the data for drug sensitivity reactions due to chloramphenicol or drug reactions from chloramphenicol in England. I do not know if it has been adequate. I would say this is much less adequate than the American warning. And what is more, it takes up in a previous statement the idea that Chloromycetin is effective in a number of clinical conditions and lists a great many, which is true, but the side reactions and the toxicity are not dilated upon, shall we say.

Senator NELSON. Does it say in there that it should not be used for minor infections? I do not recall.

Dr. DAMESHEK. No.

Senator NELSON. It does not caution against that?

Dr. DAMESHEK. No.

Senator NELSON. Did you respond to my question: Would you consider that an adequate precautionary notice? Or maybe you have not had a chance to study it long enough.

Dr. DAMESHEK. Well, to my way of thinking, it is inadequate.

Senator NELSON. It is inadequate?

Dr. DAMESHEK. Inadequate.

(The material previously referred to follows:)

CHLOROMYCETIN[®] FOR ORAL ADMINISTRATION

(CHLORAMPHENICOL, PARKE, DAVIS & COMPANY)

WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Chloramphenicol is a broad-spectrum antibiotic which clinical experience has shown to have specific therapeutic activity against a wide variety of organisms. Its activity was demonstrated initially in culture filtrates from a species of soil organism collected in Venezuela, later designated as *Streptomyces venezuelae*. The antibiotic was subsequently isolated from culture filtrates, identified chemically and later synthesized.

Experimental development of bacterial resistance to chloramphenicol by staphylococci *in vitro* occurs comparatively slowly and only to a moderate degree. Strains of decreased susceptibility to chloramphenicol are relatively short-lived both *in vitro* and in man. In a survey of experimental and clinical experiences on susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria.

ANTIMICROBIAL AND PHARMACOLOGICAL PROPERTIES OF CHLORAMPHENICOL

Chloramphenicol is absorbed rapidly from the intestinal tract, producing detectable concentrations in blood within one-half

hour after administration and peak concentration in from 1 to 3 hours. Peak blood concentration is roughly proportional to the dose. Following absorption of the drug and attainment of equilibrium conditions with body fluids and tissues, concentration in blood falls approximately 50 per cent in succeeding 3- to 4-hour periods. **Chloromycetin Palmitate** requires enzymatic hydrolysis to chloramphenicol before absorption. Resulting blood concentration is similar to that produced by the oral administration of chloramphenicol.

Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva, and in milk, and it diffuses readily into all parts of the eye. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

Seventy to ninety per cent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 per cent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most nitro compounds in the blood are in the form of free chloramphenicol. Despite the small proportion of unchanged drug excreted in the urine, concentrations therein are relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of the drug are also found in bile and in feces.

DOSAGE RECOMMENDATIONS FOR ORAL CHLOROMYCETIN PRODUCTS

The majority of microorganisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over a major portion of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will achieve levels of this magnitude. Except in certain circumstances (e.g., premature and newborn infants) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, must be prescribed at recommended doses known to have therapeutic activity. The following recommendations apply to all oral preparations:

Adults

Adults should receive 50 mg./kg./day in divided doses at 6-hour intervals. Patients with infections due to moderately susceptible organisms or with severe infections often require doses up to 100 mg./kg./day.

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., septicemia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, dosage should be reduced to 50 mg./kg./day as soon as clinical response occurs. When prolonged high dosage is necessary, possible toxic side effects may occur. In this event the dosage should be immediately reduced or discontinued.

Premature and Newborn Infants

An initial dose of 25 mg./kg. may be given to rapidly achieve effective concentrations in blood serum. This should be followed by administration of 25 mg./kg./day in 4 equal doses at 6-hour intervals, which produces and maintains concentrations in blood and tissues adequate to control most infections. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. Full term newborn infants ordinarily may receive from 25 to 50 mg./kg./day equally divided into 4 doses at 6-hour intervals.

For comatose or gravely ill patients, chloramphenicol is available in several forms for parenteral administration.

These dosage recommendations are extremely important because blood concentration of chloramphenicol in the premature and newborn infant differs from that of an infant over one month of age. This difference is due to variations in the metabolic disposition of this and other drugs in this age group which in turn depends on the maturity of the metabolic function and status of the liver and the kidneys. When these systems are immature (or seriously impaired in adults) high concentrations of the drug are found which tend to increase with succeeding doses. Toxic reactions and some fatalities have occurred in the premature and newborn age group, these being associated with higher than recommended dosages. The following summarizes the clinical and laboratory studies that have been made:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.

(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol (100 mg./kg. daily or more).

(3) The symptoms appeared in the following order: (a) abdominal distension with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. This has been referred to in some institutions as the "gray syndrome."

(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses.

(6) No characteristic pathological changes attributable to the use of chloramphenicol were found in any of the organ systems, including the hemopoietic system.

(7) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Infants and Children with Immature Metabolic Processes

In young infants (those between one month and one year of age) and others, in whom immature metabolic processes are suspected, a dose of no more than 50 mg./kg. but not less than 25 mg./kg./day, will produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by available microtechniques.

SIDE EFFECTS OF CHLORAMPHENICOL THERAPY

Untoward reactions in man are infrequent with chloramphenicol. Reactions attributed to chloramphenicol may be considered under the following headings:

Blood Dyscrasias

Aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia have been associated with the administration of chloramphenicol.

The following statement is quoted from NEW AND NONOFFICIAL DRUGS 1960, evaluated by A.M.A. Council on Drugs, page 82:

"Although serious and even fatal blood dyscrasias are known to occur after the administration of chloramphenicol, current data seem to indicate that these reactions are rare. Blood dyscrasias have occurred with both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, the physician may use chloramphenicol in the treatment of serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used in treating colds, influenza, viral infections of the throat, or as a prophylactic agent to prevent bacterial respiratory disease."

When blood counts show unusual deviations such as leukopenia or thrombocytopenia, chloramphenicol should be discontinued.

Gastro-Intestinal Reactions

After several days of therapy, glossitis may occur. Stomatitis, when it occurs is generally mild and usually consists of congestion and tenderness of the buccal mucosa. This is an indication to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce

widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported after prolonged administration of chloramphenicol and in patients previously treated with the antibiotic. These conditions are usually mild and disappear when chloramphenicol therapy is stopped, although occasionally they are protracted.

The pathogenesis of pseudomembranous enterocolitis of the intestine is not clear, but commonly staphylococci have been implicated. This severe reaction occurs in patients already ill with pneumonia or peritonitis, or it may follow surgical operation. Pseudomembranous enterocolitis has been reported in a few patients receiving chloramphenicol.

Hypersensitivity Reactions

Angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in patients sensitive to chloramphenicol. Urticaria and vesicular lesions also have been observed. Dermal lesions, usually mild, ordinarily subside promptly when the drug is stopped.

The Jarisch-Herxheimer reaction has been reported after chloramphenicol therapy in patients with syphilis, brucellosis, and typhoid fever. In patients with typhoid fever treated with chloramphenicol, several investigators have recorded a "shock-type reaction" characterized by circulatory collapse, attributed to sudden release of typhoidal endotoxin in an already weakened patient. Unlike the Herxheimer reaction, temperature is usually depressed, but exacerbation of fever has been reported. Recrudescence usually appears within 24 hours of the start of chloramphenicol therapy and persists from 24 to 48 hours.

Neurotoxic Reactions

Headache, mild depression, "dazed feelings," internal ophthalmoplegia, mental confusion, and delirium have been described in patients receiving chloramphenicol for a variety of infectious diseases. Optic and peripheral neuritides as probable effects of prolonged chloramphenicol therapy have been reported. Analysis of these cases suggests that these neurotoxic reactions were related both to large total doses of chloramphenicol and long periods of administration. The range of total dosages of chloramphenicol was from 190 to 1600 Gm. Toxic symptoms appeared between 42 days and 22 months after the start of therapy. Five patients had blurred vision as the most prominent symptom and in a sixth the initial complaint was blindness. This latter was the only one with permanent impairment of vision. Peripheral neuritis resolved in all patients except one, who still had minor residual symptoms thirteen months after onset. If symptoms of decreased visual acuity or peripheral neuritis occur during therapy, prompt withdrawal of the drug is indicated and large doses of oral or parenteral vitamin B complex should be considered.

Other Reactions

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, particularly monilia. Constant observation of the patient is essential. If new infections

caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

CLINICAL USE OF CHLORAMPHENICOL

Rickettsial Diseases

The response of patients with rickettsial infections, including epidemic and murine typhus fevers, Brill's disease, scrub typhus fever, Rocky Mountain spotted fever, and rickettsial pox, has been dramatic with virtual elimination of mortality and marked shortening of the course of illness. Average length of the febrile period after administration of chloramphenicol is 2 days in patients with epidemic typhus fever and 3 days in those with other typhus fevers. Treatment should be given for a minimum of 6 days or 4 days after temperature returns to normal.

Relapse may occur when treatment is given only for 48 hours early in the disease. This can be prevented by giving additional doses on the fifth and sixth days after the initial course. Also, patients in relapse respond as readily to treatment as do those with primary infection.

In patients with Rocky Mountain spotted fever, defervescence occurs about the fourth day after therapy is started. Treatment should be continued for 24 hours after normal temperature is attained.

Typhoid Fever

Chloramphenicol has been established as the drug of choice for this disease. After therapy is started, fever subsides in 3 or 4 days regardless of age, severity of illness, or stage of disease. To lessen possibility of relapse, it is important that therapy be continued for from 8 to 10 days after reaching the afebrile period. Close observation of the patient for complications of the disease, and for aforementioned side effects of the drug, is essential. Results of chloramphenicol treatment for the carrier state are equivocal.

Other Salmonellosis

While chloramphenicol has proved to be a useful therapeutic agent in ameliorating and shortening the clinical course of salmonella infections other than typhoid, results are not as uniform. Recommended duration of treatment is the same as for typhoid fever.

Urinary Tract Infections

Treatment for infections of the urinary tract should be based upon sensitivity of bacteria and on anatomic factors contributing to the infection. The more common organisms encountered in the urinary tract infections are *Esch. coli*, *A. aerogenes*, *Ps. aeruginosa*, *Proteus* sp., *Staph. aureus* and *Strep. fecalis*.

Chloramphenicol has been found effective in treatment for about 70 per cent of urologic infections, particularly those caused by *Esch. coli*, *Strep. fecalis*, and *Proteus* sp. Relief of symptoms and repeated bacteriological studies should be depended upon to indicate duration of treatment.

Surgical Infections

Surgical infections such as post-operative wound infections, cellulitis, infected sinus tract, and peritonitis or intra-abdominal abscess from ruptured intestine, diverticulae, or appendix, usually are due to microorganisms sensitive to chloramphenicol. The antibiotic is given, adjunctively to surgical intervention, in the recommended dosage for an average of from 10 to 16 days.

Respiratory Tract Infections

Chloramphenicol may be employed for severe infections of the respiratory tract due to susceptible microorganisms and in the presence of contraindications to other agents. Patients on recommended doses become afebrile in from 18 to 72 hours; roentgenographic clearing will be slower.

Meningeal Infections

Many microorganisms causing meningitis are susceptible to chloramphenicol. The drug's high diffusibility results in effective concentrations in the cerebrospinal fluid. Institution of therapy cannot be delayed until results of laboratory tests are known. Many clinicians consider chloramphenicol alone (or in combination with other effective agents) the drug of choice for meningitis caused by *H. influenzae* as almost all strains are sensitive to this antibiotic. Parenteral dosage is recommended until the patient is afebrile, after which oral medication may be used. Medication should be continued for a minimum of seven days to avoid relapse.

Miscellaneous Infections

Chloramphenicol has proved to be useful and frequently effective in treatment for many diverse infections, including brucellosis, bartonellosis, relapsing fever, granuloma inguinale, plague, and ornithosis. Other effective therapeutic agents should receive consideration as the treatment of choice. Whenever definite contraindications to these are known, such as hypersensitivity, or clinical response is poor, the judicious use of chloramphenicol is warranted, keeping in mind aforementioned warnings, precautions, and side effects, particularly in patients requiring prolonged or intermittent treatment.

PACKAGE INFORMATION

Kapseals No. 379, Chloromycetin, each contain 250 mg. chloramphenicol, supplied in packages of 16 and 100.

Capsules No. 477, Chloromycetin, each contain 50 mg. chloramphenicol, supplied in packages of 25 and 100.

Capsules No. 480, Chloromycetin, each contain 100 mg. chloramphenicol, supplied in packages of 25 and 100.

Suspension Chloromycetin Palmitate, each 4 cc. represents 125 mg. chloramphenicol, (each cc. contains chloramphenicol palmitate equivalent to 31.25 mg. chloramphenicol with 0.5% sodium benzoate as preservative), in bottles of 60 cc.

PARKE, DAVIS & COMPANY



DETROIT, MICHIGAN, U.S.A.

Feb. 1961

AB

To the Medical Profession

CHLOROMYCETIN

CHLOROMYCETIN* (chloramphenicol B.P., Parke-Davis) is a pure crystalline substance originally isolated from cultures of *Streptomyces venezuelae* and now synthesised. Each CHLOROMYCETIN Kapseal* contains 0.25 G. CHLOROMYCETIN.

CHLOROMYCETIN is effective in a number of clinical conditions, including typhoid fever and other salmonellosis; bacillary dysentery (shigellosis) and other enteric infections; pertussis; urinary tract infections; respiratory infections (bacterial and viral pneumonias); peritonitis; brucellosis; ocular and aural infections; non-tuberculous meningitis; rickettsial infections (Q fever, typhus fever, scrub typhus fever), and venereal diseases.

DOSAGE AND ADMINISTRATION

General Dosage Schedule

CHLOROMYCETIN is readily absorbed from the gastro-intestinal tract following oral administration, blood-levels increasing proportionally with increased dosage.

Adults & Children: 50 mg. per kg. body-weight daily in divided doses at 6 hourly intervals (approximately equivalent to 3 G. [12 Kapseals] daily for a patient weighing 10 stone [63 kg.]). Patients with infections due to moderately susceptible organisms or with severe

*Trade mark

P.T.O.

infections often require doses up to 100 mg./kg. body-weight daily; in *children* however, this dosage should be reduced to 50 mg./kg. body-weight daily as soon as clinical response occurs. In typhoid fever it is important that therapy be continued for 8 to 10 days after reaching the afebrile period.

Administration of CHLOROMYCETIN to infants and young children is best accomplished by means of Suspension CHLOROMYCETIN Palmitate, a pleasantly flavoured suspension of a bitterless derivative of CHLOROMYCETIN containing in each teaspoonful (4 ml.) the equivalent of 125 mg. CHLOROMYCETIN.

SIDE REACTIONS AND TOXICITY

Patients on treatment may complain of dry mouth and less often of nausea, diarrhoea or vomiting, although these are seldom sufficiently severe to justify withdrawal of the drug. Drug sensitivity reactions are also sometimes encountered. Cases of optic and peripheral neuritis have been reported in patients receiving high total dosage during prolonged therapy. While the incidence of blood dyscrasias associated with systemic CHLOROMYCETIN therapy is rare, cases of serious disorders including aplastic anaemia have been reported. As with certain other drugs adequate blood studies should be made when the patient receives prolonged or intermittent therapy.

Further literature on request

PARKE, DAVIS & COMPANY HOUNSLOW, LONDON, ENGLAND

No. 1188 T

Senator NELSON. Doctor, I want to thank you very much for your very fine contribution to these hearings. We appreciate your taking the time to come today.

Dr. DAMESHEK. Thank you, Senator.

(Dr. Dameshek subsequently submitted the following information:)

FEBRUARY 7, 1968.

Dr. WM. DAMESHEK,
Mount Sinai Medical School,
New York, N.Y.

DEAR DR. DAMESHEK: This morning, while in Milwaukee, Wisconsin, I read an article in the Milwaukee Sentinel concerning your testimony before a Senate subcommittee, concerning the Parke, Davis drug, Chloromycetin. Frankly, this news release brought back to me all the unhappy memories and frustrations of the illness my daughter Marilyn, age five, suffered for nine weeks in 1955.

The diagnosis was, of course, aplastic anemia, and the patient passed on May 3, 1955.

Our physician, now deceased, had prescribed this particular drug for three years prior to Marilyn's final illness. *Sore throats, colds, minor fevers* were all handled with Chloromycetin. The drug, as you know, eventually destroyed totally her bone marrow, and the child's ability to manufacture proper blood was destroyed.

The latter was confirmed by autopsy, and cause of death was confirmed as "Chloromycetal Intoxication."

I brought the foregoing to Parke-Davis' attention; guilt was admitted, and blame was placed at the door of the doctor. I then asked Parke-Davis to show me brochures and sales techniques that brought to the medical profession proper information concerning the pros and cons in the use of the drug. In other words, I conceded that the drug certainly had great value in the treatment of spinal meningitis, nephritis, nephrosis, typhoid, etc., but I wanted to see that said drug was not oversold as a cure-all, but was used only for major problems. This information was denied me.

My next logical step was to call on the U.S. Pure Food and Drug Administration in Detroit. I was informed at that time that Chloromycetin had been withdrawn from the market sometime earlier than 1955, as a result of a rash of complaints resulting from its use. The Government had checked the drug for a year, while no sales were allowed, but had been unable to pinpoint a real connection between aplastic anemia and Chloromycetin. To me this was a typical conclusion of our unbelievable bureaucracy.

Perhaps, at this point, you may be wondering why I am writing you about something that happened in 1955. I will tell you why.

Mrs. Lenox and I were desolate at the death of our child. The only reason we were able to continue without undue rancor was that we hoped, by bringing our situation to the attention of Parke-Davis plus the U.S. Food and Drug Administration, that future mistakes of this sort would be obviated. Thirteen years later I see that not only has the situation not been corrected, but that there is actually an increase in this sort of thing.

Sincerely,

HARRY LENOX, Jr.,
Detroit, Mich.

P.S.—If you wish to read this letter in future sub-committee hearings, you have my full permission to do so.

FEBRUARY 8, 1968.

DEAR DR. DAMESHEK: Upon reading an article in the Daily News, Wed., Feb. 7th, I have some information which may be of some help.

About 5 years ago our little boy took sick. Our Doctor at that time kept saying what he had was a virus, cold, sore throat, and kept giving him the drug chloromycetin as an antibiotic.

Finally when the child appeared after many months with black and blue marks on his body, the Dr. finally took a blood count.

We then found out the dreadful news that our boy had leukemia.

He lasted 8 months after this. I for one think that there was some connection with this drug that brought on Leukemia on our child.

If there are any further questions you may wish to ask me please feel free to contact me.

I hope you continue your research in this field and maybe soon we can find a cure or some sort of vaccine.

I remain,

NAME WITHHELD.

Mr. GORDON. Mr. Chairman, the subcommittee has some articles on this subject which I ask be put into the record.¹

Senator NELSON. They will be put in the record. Materials submitted by the witnesses in the course of their testimony or at a later date will also be accepted for the record.

Our next witness is Dr. William R. Best. Dr. Best is with the Veterans' Administration. The committee is very pleased to have you here today. As I said to Dr. Dameshek, we would be happy to have you elaborate on any of the points you make if you feel it would be helpful to an understanding of your statement or if it would be enlightening for the record. So, you may proceed to present your statement as you please.

¹ See appendix I, p. 2653, *infra*.

**STATEMENT OF DR. WILLIAM R. BEST, CHIEF, MIDWEST RESEARCH
SUPPORT CENTER, VETERANS' ADMINISTRATION, EDWARD
HINES, JR., HOSPITAL, HINES, ILL.**

Dr. BEST. Thank you, Senator Nelson.

I have been asked to discuss chloramphenicol and some of the problems involved in its use in medicine. As Dr. Dameshek has indicated, this was originally isolated and came on the market back in 1948. Parke, Davis & Co. has been the principal supplier. It was early proven to be very effective against a wide variety of bacterial, rickettsial and viral infections.

It was only after about 3 years of wide use that it became evident that rare susceptible individuals would develop aplastic anemia, an extreme depression of the bone marrow, as Dr. Dameshek has said. Since this complication is often fatal, this knowledge led to a reassessment of the indications for its use and, in 1953, the American Medical Association established a central registry of drug-associated blood dyscrasias. "Blood dyscrasia" means "blood diseases."

Before discussing these issues further, however, it is pertinent for me to outline my qualifications for appearing before you on this issue.

I received my M.D. degree from the University of Illinois College of Medicine, Chicago, in 1947, and after this pursued 4 years of post-graduate training at its principal teaching hospital; the Illinois Research & Educational Hospital. My training was in the general field of internal medicine, and in the subspecialty of hematology, diseases of the blood. After 2 years of military service, I joined the faculty of the University of Illinois as an assistant professor of medicine at 90 percent time. The remainder of my time was as an attending physician at the Veterans' Administration Hospital, Hines, Ill., and as a hematology consultant in private practice.

I have functioned in several roles in these particular settings. As a physician in general medicine I have been responsible for treating a variety of patients in both outpatient and hospital settings and on many occasions in outlining the treatment of infections I have had to weigh the relative likelihood of good versus harm in the selection of antibiotic agents.

In hematology, as Dr. Dameshek will attest, the choice of antibiotics is terribly important because of the low levels of natural resistance characteristic of many patients with leukemia and similar conditions. On a number of occasions chloramphenicol alone or in combination has appeared to be the drug of choice in my patients, despite the known risks of adverse reactions. No serious side effects have occurred in any patient to whom I have prescribed this drug. As a hematologist, however, I have also been consulted in relation to patients who develop bone marrow depression as a result of medications given by other physicians for other diseases. Over the years the number of cases of aplastic anemia due to chloramphenicol for which I have been personally consulted is not large. My knowledge of this condition comes more from another avenue which I shall outline in a few moments.

As assistant professor and later associate professor of medicine, my responsibilities have included not only direct patient care, but

also medical research and the teaching of medical students, interns, and residents. Much of my research has been directed to ward clinical and laboratory studies in leukemia, pernicious anemia, and other blood diseases. I have been author or coauthor of more than 100 scientific publications, including articles in journals, chapters in books, and abstracts of presentations for professional meetings. In recent years my research interests have turned from hematologic topics toward the applications of statistics, mathematics, and computers to general medical research and practice. In keeping with these changing interests, on August 1, 1967, I became chief of the Midwest Research Support Center at Hines, Ill., one of four such regional centers established by the Veterans' Administration to offer consultation and support in experimental design, computer analysis and related areas to any medical investigator affiliated with the VA system. I have retained my appointment as associate professor of medicine at the University of Illinois on a nonsalaried basis. I have given up a partial consulting practice in hematology which I had up to that time.

Because of my dual interest in biostatistics as well as hematology, I was asked several years ago to become a member of the study group on drug-associated blood dyscrasias of the American Medical Association Council on Drugs, a group of volunteer hematologists. This group was concerned with the inferences which might reasonably be drawn from data submitted by diverse physicians to the previously mentioned registry. During my period of membership with this group, 1961-67, I played a major role in attempting to analyze and interpret various types of data which had been submitted to the registry. A principal study in this regard, prepared at the request of the study group, culminated in an article entitled "Chloramphenicol-Associated Blood Dyscrasias," published in the *Journal of American Medical Association*, volume 201, pages 181 through 188, July 17, 1967. I have a copy here and I believe that copies have been distributed to those present.

Senator NELSON. That is the one entitled "Chloramphenicol-Associated Blood Dyscrasias"?

Dr. BEST. That is correct.

Senator NELSON. That will be printed at the conclusion of your testimony in the record.¹

Dr. BEST. Fine. Much of what I shall say here will be based on that study of 408 patients who developed blood cell depression within 1 year of receiving this drug and who were reported to the registry during the years 1963 through 1964.

Senator NELSON. What was the source of these reports to the registry?

Dr. BEST. These are cases that are voluntarily submitted by physicians. The registry went through several phases. At the beginning there was a limited group of hematologists, about 50 over the country, who knew about the registry and who were contributing the cases they saw to it. After a period of time it was opened up and the attempt was made to get all physicians who would see a case to report it to the registry.

¹ See article, p. 2433, *infra*.

The registry is an iceberg peak of unknown proportion. We do not know what percentage of all cases occurring are represented. All we can say is that these are the cases that were reported to the registry. Undoubtedly, there are biases involved in this process. Some physicians have not known about the registry; others perhaps might feel that one reaction is too mild to bother reporting or that another reaction to a particular drug is so well known that it does not need further documentation. I am sure all sorts of biasing considerations like this go into it. Although we would like to draw inferences from this data, there is always a question as to just how much the trends we see in the registry reflect what the across-the-board experience is.

Senator NELSON. So this was a total of 408 cases. What period of time does this cover?

Dr. BEST. 1953 through 1964.

Senator NELSON. These were cases voluntarily submitted?

Dr. BEST. Actually, there are two sources of cases. One which accounted for the vast majority, something like 75 or 80 percent, were voluntarily submitted. Some of the people on the AMA staff also screened literature that came in through their library and whenever they found a report in the literature that would bear on this, they would add that to the registry, too. Some of these are culled from the literature, about 20 percent; about 80 percent were voluntary reports submitted by the physicians.

Senator NELSON. Those 80 percent, were they submitted by the original prescribing physician or a mix of the original prescribing physician and the specialist at the end of the line?

Dr. BEST. I would say the latter is the case most often, although I do not think we actually have figures on this. The impression I have is that a majority are physicians who took care of the patient after this complication developed. Probably in most cases this was a different physician than the one who had prescribed the drug originally.

Senator NELSON. So, we have no notion as to how many other cases there are?

Dr. BEST. No. The registry itself gives us no way of estimating that.

Senator NELSON. May I ask one more questions? Of the specialists who would be called upon to diagnose or treat a patient subsequent to the onset of the problem, do you have any notion of what percentage of those in the United States have cooperated in sending in cases?

Dr. BEST. I do not think I have any way to say. I do not know.

To continue with my prepared statement—it is in relation to the details of chloramphenicol-associated bone marrow depression that I should be considered most expert. The statements I would make in terms of the use, indications for use, other side effects and impressions with regard to promotional activity would reflect more my knowledge and judgment as a board-certified internist with a particular interest in these topics.

In making these statements I wish to make it clear that I am speaking on the basis of my independent judgment and not as a spokesman for the Veterans' Administration, for the University of Illinois College of Medicine or for the American Medical Association.

When should chloramphenicol be prescribed? A universal rule for making therapeutic decisions is to balance the likelihood of benefit

against the likelihood of harm, in terms of both frequency and degree, for all reasonable courses of action or inaction. That course which seems to offer the best balance should then be implemented. The physician must then periodically evaluate the apparent effect of his therapy on the course of the disease, making a new decision as to mode of treatment if the initially chosen method seems to be ineffective or detrimental. While this general principle is quite clear, details of implementation may be muddy. Exact figures often are not known regarding the likelihood of benefit or harm; optimal methods of balancing potential good against potential harm have usually not been spelled out.

The type of balance which has appeared to make most sense to those concerned about bone marrow depression following chloramphenicol is based on the following observations:

(1) Rare individuals, probably somewhere between 1 in 20,000 to 1 in 100,000, who receive courses of chloramphenicol will develop significant bone marrow depression. This is a rather broad range of estimates. Dr. Dameshek, if I remember, threw in a figure of maybe 1 in 10,000. It is a reflection of our ignorance that we do not really know what the exact figure is. There have been a couple of attempts made to outline just how frequently this occurs and the truth appears to be somewhere in this general range. It is not an extremely frequent thing, but it does happen.

(2) There is no known way of determining beforehand whether or not a given individual is likely to develop this complication from chloramphenicol.

(3) When bone marrow depression does occur, it is serious, carrying a mortality rate of about 50 percent. There is no really good method of treating this complication. Some who do not die of it suffer prolonged disability. Dr. Dameshek mentioned 50- to 75-percent mortality and I think that 75 percent would probably come closer for the severe cases. The so recent figure is based on an across-the-board estimate, including some mild as well as severe cases.

(4) Careful attempts to detect the early stages of marrow depression with the idea of stopping the drug and preventing death are doomed to failure in many cases. The first evidence of marrow depression has most often appeared after the drug was stopped, and in many cases has been seen weeks or months later. In a minority of cases periodic blood counts during therapy may permit a more favorable outcome through early detection.

(5) Thus, under our present knowledge, there is no way to prevent fatalities due to this complication in rare cases if the drug is to be used at all.

(6) However, chloramphenicol can be a very effective drug in combating a variety of infections. In some life-threatening infections it will be clearly superior to all other available agents.

Based on these propositions, the following conclusions appear warranted:

(a) When the greatest likelihood for control of a serious infection appears to be through use of chloramphenicol, it should be used. More lives will be saved through superior therapy than will be lost through adverse reactions to the drug.

(b) However, even an occurrence rate of one in 20,000 to one in 100,000 is too great a risk to take in relation to trivial infections or conditions which a less risky agent might better be expected to control.

Given a group of patients representing a wide range of infections, most informed physicians would agree on a subgroup corresponding to (a) in which chloramphenicol should be used. Typhoid fever and severe paratyphoid infections would certainly be included. Many would also name *Hemophilus influenza meningitis*. Life-threatening infections, such gram-negative septicemia in patients with leukemia, if there is laboratory evidence suggesting the superiority of chloramphenicol, would also be included.

MR. GORDON. Dr. Best, if I am not mistaken, you are saying here, are you not, that even in these serious cases, chloramphenicol should not be given perfunctorily but only after there is evidence showing that other therapeutic agents are ineffective or are contraindicated?

DR. BEST. This is the implication of what I have said.

However, I feel that situations will rarely arise in which I would give the drug even before I had the laboratory evidence. If the patient was dying and my hunch was that chloramphenicol would be the best drug, I would give it even before the laboratory reports were returned. If there is not this urgency, then I would certainly say that you should have definite laboratory evidence that it is the superior drug to use.

At the other pole, there would be agreement that corresponding to the trivial conditions of (b) one might name the common cold, viral infections, and many bacterial or rickettsial infections for which other effective agents with lesser toxic potentiality exist.

There would inevitably be a gray zone, in which some physicians would consider the drug indicated; others, not. This would include various acute and chronic infections of lungs, urinary tract, bowel, and elsewhere involving variable organisms, variable laboratory sensitivities, and variable prior therapeutic histories. Since medicine is not an exact science, I do not believe this gray zone can be meaningfully resolved by law or pontification. The individual physician must remain free to exercise his judgment within a general framework of principles such as I have outlined.

This is not to say that such discretion has necessarily always been the rule. Information on why chloramphenicol was originally given was available for 71 percent of the registry cases which I studied. The most frequent reasons together with corresponding percentages of this subgroup are: Lower urinary tract infections (14 percent), the common cold (12 percent), pneumonia (8 percent), kidney infection (6 percent), typhoid fever (4 percent), septicemia (3 percent), chronic bronchitis (3 percent), and ear and sinus infections (3 percent). I might add—not necessarily the next in line, but Dr. Dameshek did mention it—acne. Approximately 2 percent were treated for acne.

SENATOR NELSON. Is there any conceivable case where you could justify using chloramphenicol for acne?

DR. BEST. I cannot see it myself. Maybe somebody could defend it but I certainly could not.

In 26 percent of cases there was a serious acute or subacute infection fitting the (a) criteria for use of chloramphenicol, or, at the least, falling into the gray zone. Thirty percent of cases fit the (b) criteria,

relatively trivial indications for which the drug should not have been used. In the remainder of cases, there is not adequate information to say whether (a) or (b) would best fit, though one suspects that (b) would predominate. It should be pointed out that 26 percent of reports were from outside the United States, and that a number of the more serious infections such as typhoid fever are from this subgroup. Thus, in this country many of these complications have occurred in patients who, according to the criteria I have outlined, should not have received chloramphenicol.

Senator NELSON. It appears from your statistics that, eliminating the gray zone, the higher percentage of those given the drug should not have received it.

Dr. BEST. I am sure that this is true. It is difficult, with the amount of information sent to the registry, to always say whether there was a good indication or not. I gave the prescribing doctors the benefit of the doubt in any borderline case. I am sure that if you really examined each case with a fine-tooth comb, it would be a very significant majority in which you would say the drug should not have been used.

Senator NELSON. And these are all cases where serious blood dyscrasias occurred?

Dr. BEST. Yes, serious enough for them to be reported. Now, some are more serious than others. Something like 75 percent of these, I would say, were of a very definitely serious nature. Maybe 20 to 25 percent tended to be a milder variety of the same thing.

Mr. GORDON. I notice in the circular chart on page 183 of your article that in only 6.6 percent of the reported cases was chloramphenicol the drug of choice.

Dr. BEST. These are the cases of typhoid, paratyphoid, and hemophilus influenza, where, just by knowing the name of the infection, you could say, "All right, we will say that chloramphenicol is indicated." In getting the 26 percent figure, giving the physician the benefit of the doubt, I decided that in a serious acute or subacute infection, evidence was adequate to say, "Yes, this was a good drug to use in that instance." But, I could be wrong. Here again it is a matter of working with, in many cases, a sketchy sort of information that is submitted with the report to the registry.

Mr. GORDON. Well, in those cases where it was not the drug of choice, was there any follow up to see whether it should have been used? Was there any indication in the reports to the registry?

Dr. BEST. I might say that the policy of the registry has been generally to receive the reports and unless they are grossly inadequate in information, to not try to seek further followup information. This policy was designed to obtain continued cooperation of the physicians by minimal paperwork harassment. Thus, there are very few of these cases where an attempt was made to find out further information other than that which was submitted in the original report.

Despite periodic reminders in the medical literature of toxic potentialities, it is apparent that some physicians treat this possibility lightly. In some cases the attitude is, "I have never seen such a case; therefore, I do not have to worry about it." Being as rare as it is, the average physician could well treat many patients with chloramphenicol over a number of years and never see a resultant aplastic anemi. How-

ever, he takes a finite risk with each new patient given the drug, and for the patient who develops a fatal complication, it is 100 percent.

What part has advertising to the medical profession played in the ways in which physicians prescribe this drug? Here I can only give my casual observations and opinions. Chloramphenicol has apparently been one of the major products of Parke, Davis & Co., for many years, and they have continued to keep its name before the medical profession. In thumbing through recent issues of the *Journal of the American Medical Association*, I find a two-page spread on Chloromycetin in about every third issue. I find similar spreads in many other professional magazines, both those obtained on subscription and those which are sent to physicians unsolicited. Two similar, two-page advertisements are used in their present campaign. I have these ads here. The first of these says, "When it counts—Chloromycetin may be indicated in certain severe respiratory infections."

The second begins, "When it counts . . . Chloromycetin can be useful in urinary tract infections." These advertisements are similar in that the left-hand page is designed to catch the eye; about one-quarter of the right-hand page cautiously outlines the indications for chloramphenicol in the particular type of infections; and the remaining three-quarters of a page is used in discussing dangers, precautions, and side effects. For example, there is a prominent area surrounded in black. I will not read what it says, because it repeats in detail, almost verbatim the precautions that Dr. Dameshek read as part of the package insert.

It is my opinion that these advertisements do represent an honest and informative appraisal of the problems related to consideration of this antibiotic for these types of infections. If the physician heeds the admonitions, he will be following the principles I outlined earlier.

Parke, Davis & Co. have sponsored a second campaign, an advertisement appearing as recently as July 1967 in *MD magazine*, *Hospital Physician*, and other places as well. These are one-page advertisements depicting the physician in various hospital settings. I have three examples here. The headlines are "When it Counts," "Among the Most Significant Drugs in Use Today," and "A Name You Can Count On When It Counts."

These are followed by the word "Chloromycetin," other identification items relating to the company, and then the phrase is given: "Complete information for usage available to physicians upon request." That is all.

These advertisements give no hint as to either uses or adverse reactions. They serve only to keep the product's name in the mind of the physician. While not misleading, they are certainly in no way informative.

Senator NELSON. There are no warnings or precautions in these ads?

Dr. BEST. No warnings. It just says "complete information is available." It does not say what it is good for but it does not say what harm it may cause either.

Senator NELSON. Well, since the idea, I assume, is to promote the use of the drug, would you not think that they ought to be required to list what it should be used for and to include cautionary statements in the ad?

Dr. BEST. I would think so.

I also turned to the 1960 Physicians' Desk Reference, a yearly compilation of pharmaceuticals which the various drug companies wish to bring to the attention of physicians. The writeups for particular drugs are usually abbreviated versions of the product package inserts. I chose 1960 as a year during which the possibility of toxic marrow depression was well known but which was prior to the recent tightening of controls by the Food and Drug Administration. The writeup says: "Chloromycetin is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy." Though not as detailed as the precautions mentioned in recent advertising, this description did point to the danger of marrow depression.

So far, the only adverse effects to Chloromycetin which I have mentioned are those related to bone marrow depression. This is because it is the area with which I am most familiar and because it is the type of reaction most frequently associated with a fatal outcome. As an aside, I might mention that in the Registry on Blood Dyscrasias, chloramphenicol has been associated with a plastic anemia more commonly than has any other group of drugs. Nonetheless, there are a variety of other types of reactions which can occur to this antibiotic. These include, in addition to minor symptoms such as fever, diarrhea, or minimal skin reactions, the following:

- (1) Anaphylactic reactions.
- (2) The "gray syndrome" in newborn infants. This is characterized by a distended abdomen, shock, and a bluish-white skin color. It can be fatal.
- (3) Severe skin reactions.
- (4) Optic neuritis with loss of vision, usually reversible.
- (5) Overgrowth of nonsusceptible bacteria or fungi.

Most such complications are readily reversible on stopping the drug. Some can be fatal or permanently disabling. None occur very often.

It should be pointed out that no antibiotic is 100 percent safe. All have potential side effects, some fatal. Penicillin and its variants probably constitute the most widely used group of antibiotics. Fatal anaphylactic reactions to the penicillins have undoubtedly been more numerous than have deaths from aplastic anemia following chloramphenicol. Unfortunately, we do not have adequate information to precisely evaluate the relative risks of such reactions under standard regimens of therapy. In regard to penicillin, I might say that one estimate has been that there are somewhere from 100 to 300 fatalities a year due to anaphylactic reactions to penicillin. I am sure this far exceeds the number of fatalities due to chloramphenicol. Of course, penicillin is much more widely used than chloramphenicol. A recent study in Boston hospitals showed the order of use of some of the more common antimicrobial agents. Penicillin and its analogs were far and away the No. 1 drug. The sulfa drugs occurred next in line among the drugs to be mentioned. The sulfa drugs can also cause severe and even fatal side reactions. Chloramphenicol was the third in this group, and the tetracyclines were No. 4. Tetracyclines have

much less serious types of side reactions, and in many cases the spectrum of activity is quite similar to that of chloramphenicol.

In summary, chloramphenicol is a very useful drug in a variety of serious infections. In rare patients it may produce fatal bone marrow depression or other serious reactions. Since there is no way to predict or prevent these reactions in individual patients, the physician must exercise judgment in weighing the possible benefits against the possible deleterious effects of therapy with chloramphenicol as with any other agent. There appears to be continued need for re-emphasis of potential dangers to the medical profession. However, I believe that attempts at legislative controls on the prescription of this drug would in the long run do more harm than good.

Senator NELSON. Is not the real issue here, however, that there is a clearly defined group of cases which you, as well as Dr. Dameshek and other distinguished authorities have testified to, in which the drug just simply should not be used. And in a substantial percentage of cases that you have studied from the registry, the drug was in fact improperly used and serious as well as fatal consequences were the result? Is that not correct?

Dr. BEST. That is true.

Senator NELSON. So, an important part of the problem here is that the drug is being prescribed in cases where it just simply should not be prescribed.

Dr. BEST. Yes; this is true. The danger I foresee is that controls would prevent it from being prescribed in cases where it should be prescribed.

Senator NELSON. You heard the discussion with Dr. Dameshek indicating that there ought to be some method at least of effectively communicating the warnings to the doctor or perhaps controlling the use of the drug. As to the possible method we discussed—that is, setting aside a group of drugs to be in a special category, and following the procedure used, say, in the prescribing and dispensing of morphine, would you find that to be a procedure that might be feasible?

Dr. BEST. I think so. Perhaps my summary statement against controls is a little too strong. Certainly, I would hate to see the pendulum swing over to the point where the drug could not be used. Let us put it this way: I think a certain amount of reasonable controls might be a good thing and acceptable. It depends on just how much of what one might interpret as harassment would be involved. A type of control parallel to that on the prescription of narcotics would seem to me reasonable; yes.

Senator NELSON. Well, the history of cases that have been called to your attention, as well as those reported, your study indicates that 30 percent of those you studied concerned people who should not have received the drug. So you do have specific cases where patients are either made seriously ill for the balance of their life or suffer a fatal disease as a consequence of inappropriate prescription of the drug.

As I mentioned earlier, when Dr. Dameshek was testifying, it appears, both from your statistics and considering the amount of the drug sold, that a large number of the people to whom the drug is being administered, should not have it.

Do you have any estimate or any guess to make as to how many people in this country ought to be receiving this drug annually?

Dr. BEST. Well, the best thing I can do is guess. I do not have any really solid figures on which to make such a statement. As stated in my article there is somewhere in the neighborhood of 30 percent who you could probably make a reasonably good case that they should have had the drug.

Senator NELSON. Should have had the drug?

Dr. BEST. Should have had it. Another about 30 percent where they should not, and then the remaining middle 40 percent we do not know, and my guess is that most of the middle one should not have had it, either. Obviously, there are some biases involved in those who were reported to the registry, and the chances are the bias would be towards reporting the cases where the drug was given for more serious diseases rather than less serious ones, so that just to kind of reach into the air and pull out a figure, I think the one that Dr. Dameshek mentioned of perhaps 10 percent of all that is given as having a good reason to be given is probably as good a guess as I would want to make but I do have to say that it is a guess.

Senator NELSON. That would mean, then, that the guess is also that 90 percent—

Dr. BEST. Ninety percent, probably some other drug or no drug at all would have been the better thing to use.

Mr. GROSSMAN. Doctor, can I just ask you one question about the ramifications of this failure of the warning system. For example, Dr. Dameshek says that the numerous warnings regarding the indiscriminate use of Chloromycetin have been practically without effect. With regard to our entire drug system, do you think that we have a failure of our warning systems to work and do we need some kind of a change?

Dr. BEST. I do not agree with his statement in that case. I think it has not been without effect, to use a double negative. I think it has had an effect. I do not think it has had nearly as much effect as we would like it to have, but I think it has had an effect. I believe we would see a much worse situation if we did not have the warnings. This is based on conversations I have had with individual physicians. I know many who are very reluctant to use chloramphenicol because they are aware of these warnings.

It is just that we have not hit 100 percent of physicians as far as this philosophy is concerned. So, we would like to do better. But I would not say that we have had no effect as far as our warnings are concerned.

Mr. GROSSMAN. Would you say it is a minority of physicians or smaller group of physicians?

Dr. BEST. It is hard to say whether it is a minority or a majority. Certainly, among those that I am personally familiar with, and these tend to be those who are academically oriented, I would say the vast majority are aware of this danger and tread very lightly in the use of chloramphenicol.

Mr. GROSSMAN. What are the ramifications as far as other drugs are concerned? In other words, are warnings being heeded on other drugs? Is the same true in most of our other drugs? If it is not being done here to some degree, how can we believe that warnings are really effective at all on any—

Dr. BEST. I am sure they are only partially effective. I am sure nonetheless that the average physician when he uses a drug does become

aware of what the reported side effects are, what the possible dangers are. This brings us again to the question of considering and balancing the odds as to various possible outcomes. Many people would like to believe that the physician has a certain omnipotence, that everything is black and white; but it ends up that in making decisions he is always balancing odds.

Mr. GROSSMAN. Would the reporting system that has been talked about here this morning—would that tend to restrict the use of dangerous drugs to properly indicated conditions?

Dr. BEST. Would you repeat that question, please?

Mr. GROSSMAN. Well, Senator Nelson and Dr. Dameshek were talking about a reporting system. Do you think this would have a beneficial effect on limiting improper usage?

Dr. BEST. I am not sure how much effect the reporting system would have itself. It would produce—if a universal reporting system were involved—it would produce figures that would have a little more meaning than the ones that I have written about that are related to a voluntary reporting. In other words, we would have a better feeling for what the total number of cases are. I think that we still would not have the whole picture. I know that in a recent study in Philadelphia, for example, five of the medical-school-affiliated hospitals tried to set up their own reporting system to catch all of the adverse reactions occurring in all of these hospitals. People being people the way they are, when they went back to check and see how complete the reporting system was, even though the chief of each service told all of his residents and interns to report every case that came through, I think they reported somewhere in the neighborhood of 5 percent; about 95 percent still did not get reported even though this was the rule of the particular hospital.

Mr. GROSSMAN. Can I ask you how would you grade our warning system, then, today, not just this particular drug, but generally? Is it the best thing we can come up with? Is there a way you would specifically recommend to improve our system?

Dr. BEST. You mean by warning system, putting the warnings on the package inserts, putting them on the advertising, et cetera?

Mr. GROSSMAN. I am talking about the way we are doing it now. In other words, is this adequate?

Dr. BEST. Well, I think that—my own personal opinion is—Dr. Dameshek did not want to commit himself on it, but my position on it is that—the vast majority of physicians rarely read a package insert but they do read some of the material that comes through the mail—and there is a flood of it that comes to every physician. They do read some of the ads in the journals, and so on. I think that very many of them turn to things such as the Physicians' Desk Reference for information. If all of these sources stress the important side effects, the physician should become aware of them.

What use they make of this information is another question, but I think the information will get to them through these avenues. If you speak about only giving this information in the package insert, however, I think it will be missed by many.

Mr. GROSSMAN. Thank you.

Senator NELSON. I realize that both you and Dr. Dameshek were making what you conceded was a guess as to the percentage of cases in which chloramphenicol was prescribed and was indicated. You both were guessing about 10 percent, but even if it were 20 or 30 or 40 percent, it does obviously indicate that there is some breakdown in proper communication to the physician as to the proper use of this drug; does it not?

Dr. BEST. Yes, I think so.

Mr. GORDON. Dr. Best, I have one question. In a case in California—I think it was Love against Wolfe and Parke, Davis—the court held that even though the warning is given, it could be regarded as canceled out if a vigorous promotional campaign was being waged. How do you feel about that?

Dr. BEST. Well, I have trouble responding to that. That seems like a legal question.

Mr. GORDON. Well, do you feel that a vigorous promotional campaign, say especially by the detail men, could cancel out the effect of the written warning on the packages or at least mitigate it? I told you that the court found that there is substantial evidence that it did wash out the warnings. How do you feel about that?

Dr. BEST. Well, it seems to me that if all of this promotional activity included the warning on each particular aspect of the promotion, I cannot say that that would necessarily negate it. On the other hand, the reason they put on a strong promotional campaign obviously is to sell more drugs and I can see a grain of truth in the court's point of view in that the more somebody is brainwashed, the more they are apt to think of this particular drug without necessarily thinking of the warnings; but it is a hard thing to give an absolute answer to.

Senator NELSON. The report of the Kefauver hearings, dated June 27, 1961, comments on this exact point about chloramphenicol. I will just read briefly from it. The report says, starting on page 198:

"Despite the obvious importance of providing the physician on whom this responsibility rests with full and accurate information on side effects, the drug companies in their advertisements have tended to handle the matter in either one of two ways: ignore side effects entirely or note and then dismiss the subject with some sort of reassuring phrase. When the latter technique is employed, the physician is comforted with such language," and these are quotes from the advertising, "virtually free from side effects"; "with few significant side effects"; "with low incidence of side effects"; "minimum side effects"; "unexcelled freedom from major as well as minor side effects."

That, obviously, would not be correct.

"With no irreversible side effects." "Fewer and less severe side effects"; "absence of serious side effects specially noted"; "accompanied by fewer and milder reactions"; "incidence of side effects is lowest ever reported"; "by adherence to recommended dosages side effects will be generally infrequent, mild, transient"; "without clinically significant side effects"; "side effects minimal"; "serious reactions have been practically nonexistent"; "no serious side effects noted"; obviously incorrect.

"Relative freedom from untoward reactions"; "side effects are fewer and milder"; "fewer old and no alarming new side effects"; "fewer

and milder classic side effects"; "with minimal side effects"; "minimum incidence of certain side effects"; "relatively nontoxic"; "untoward reactions infrequent and minimal"; "undesirable reactions are seldom encountered or are minor in degree"; "lower incidence of severe side effects"; "virtually free from side reactions"; "side effects minor"; "side effects generally mild and can be overcome by adjustment in dosage"; "fewer side effects", et cetera.

I realize that these statements are out of context without the full ad, but are some of these statements the kind you, as a specialist, certainly would not endorse?

Dr. BEST. I would certainly agree; some of those statements I would consider very misleading. One of the problems in this whole business of studying the side effects of drugs is the question of confusing how frequently something occurs with how serious it is when it occurs, and—

Senator NELSON. And how unnecessary it is in those instances where it should not be used in the first place.

Dr. BEST. Yes.

Senator NELSON. Like the story of the fellow who, I think it was in the Philippine campaign where a soldier came back and everybody was saying, "Well, it was not a very big war," and he said, "No, but it was awfully big for those fellows that got killed." That is as big as it can get for the man.

Mr. GORDON. Doctor, on page 8 of your statement you refer to headlines like: "When it counts," "Among the most significant drugs in use today," and "A name you can count on when it counts."

Now, if I were to suggest that these slogans tend to play down the danger of the drug, would you accept that as a reasonably accurate statement?

Dr. BEST. Yes. I would consider these ads as being inadequately documented as to the dangers, and as I say, these were last summer. I do not know whether they still are putting these out anywhere or not but I looked through a pile of journals in the library and these I found.

Senator NELSON. Thank you very much, Doctor, for taking the time to come here and for your very useful contribution to these hearings. (The article by Dr. Best referred to previously, follows:)

[From the Journal of the American Medical Association, July 17, 1967, vol. 201, No. 3, pp. 181-188]

CHLORAMPHENICOL-ASSOCIATED BLOOD DYSCRASIAS—A REVIEW OF CASES SUBMITTED TO THE AMERICAN MEDICAL ASSOCIATION REGISTRY

(By William R. Best, M.D.)

From the Research Resources Laboratory, University of Illinois, College of Medicine, Chicago, and Biostatistics Research Support Center, Veterans Administration Hospital, Hines, Illinois. This report has been prepared at the request of the Panel on Hematology of the Section on Adverse Reactions of the AMA Department of Drugs. Reprint requests to Secretary, Council on Drugs, American Medical Association, 535 N. Dearborn St., Chicago 60610.

Chloramphenicol, an effective broad spectrum antibiotic, was introduced in 1948. Only after three years of extensive use did it become evident that this drug was capable of seriously depressing bone marrow activity in rare recipients. It was in response to the delay in recognizing the toxic potentialities of this drug

that the American Medical Association established the Registry of Blood Dyscrasias, hoping, among other things, to recognize such effects early when they occurred for other new drugs. The Registry and its study group have since accumulated data on a large number of drugs, have issued periodic tabulations and resumes of cases submitted, and have authored commentaries on various associated problems.¹⁻⁵ During this period, chloramphenicol has been implicated in more reports to the Registry than has any other single drug. It appeared that useful information could be obtained through a more thorough review of Registry reports.

Included in this study were 408 cases, reported to the Registry from 1953 through 1964, who were known to have received chloramphenicol during the year preceding a non-neoplastic depression of blood cell formation.

Generalizations from this experience would be most valuable if cases reported to the Registry represented an unbiased sample of the condition as it occurred throughout the world. However, there are unavoidable and, no doubt, unidentified biases in this collection of cases. For example, most cases have been voluntarily reported from selected sources, and the composition and attitudes of these sources have changed from year to year.

Some cases were abstracted from the medical literature. Nonetheless, this appears to be the best data available for study.

The Registry contains a total of 298 US reports, 25 known to be published, 273 not; plus 110 foreign reports, 70 known to be published, 40 not.

Yunis and Bloomberg reviewed much of the literature on this disorder, summarizing data on 94 cases.⁶ Twenty-one US and eight foreign literature cases are common to their review and to the Registry; their other cases are not in the Registry. The Registry contains 1 US and 65 foreign literature cases which were not covered in their review. There have been additional published case reports which appear neither in the review by Yunis and Bloomberg nor in the Registry.

METHODS OF ANALYSIS

During the years of existence of the Registry, the report form has gone through several different versions, more recent ones tending to call for more complete information. In general, no systematic attempt has been made to obtain more detailed clinical information or late follow-up of cases.

Reports were coded and punched on 80-column computer programming cards, using from 4 to 36 cards per patient, under the direction of Norman De Nosaquo, MD, and Mrs. Helene Weston of the AMA staff. Data transformation, reduction, tabulation, and analysis were performed by the author using computers and over 30 special computer programs.

GENERAL CHARACTERISTICS OF CASES

Age and Sex.—Females accounted for 62% of 407 cases. There was a wide distribution of cases by age with a rate of 0.5% to 1.5% of total cases per year of age from the teens through the 70's, occasional cases in older age groups, and a striking peak occurrence of about 5% per year of age in the 3- to 7-year age group. There was some difference in sex distribution at different ages: females accounted for 69% of 113 patients 0 to 9 years of age, 69 (73%) of 94 patients 10 to 39 years of age, but only 47% of 150 patients 40 years of age or older.

The percentage of females was essentially the same for cases reported from the United States as compared to reports from elsewhere; however, there is a much less striking peak of occurrence for the 3- to 7-year age group in the latter series (Fig 1).

¹ Motulsky, A. G.: Drug Reactions, Enzymes, and Biochemical Genetics, *JAMA* 165: 835-837 (Oct. 19), 1957.

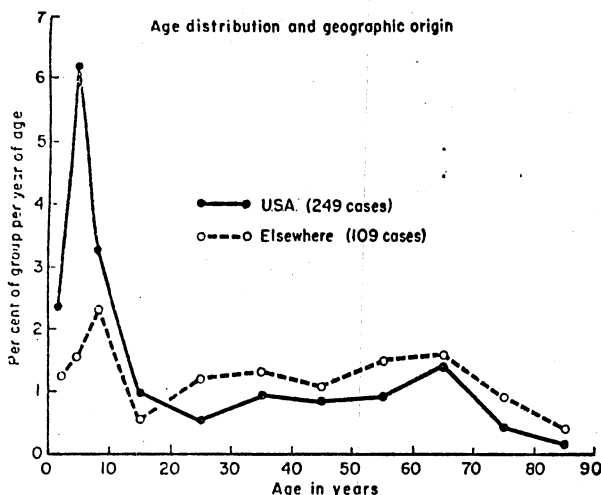
² De Nosaquo, N.: Development and Purpose of the Registry on Blood Dyscrasias, *JAMA* 170: 1925-1926 (Aug. 15), 1959.

³ Huguley, C. M., Jr., Erslev, A. J.; and Bergsagel, D. E.: Drug-Related Blood Dyscrasias, *JAMA* 177: 23-26 (July 8), 1961.

⁴ Erslev, A. J., and Wintrobe, M. M.: Detection and Prevention of Drug-Induced Blood Dyscrasias, *JAMA* 181: 114-119 (July 14), 1962.

⁵ Best, W. R.: Drug-Associated Blood Dyscrasias: Recent Additions to the Registry, *JAMA* 185: 286-290 (July 27), 1963.

⁶ Yunis, A. A. and Bloomberg, G. R.: Chloramphenicol Toxicity: Clinical Features and Pathogenesis, *Prog Hemat* 4: 138-159, 1964.



1. Age distribution of cases of chloramphenicol-associated blood dyscrasia as related to geographic origin.

The smaller 3- to 7-year age peak in the non-US cases might represent either different patterns by which this drug is prescribed for various age groups, different biases in the reporting of cases, or different hereditary patterns of age susceptibility to this complication as related to ethnic origin. The last of these possibilities seems unlikely, for 84% of the non-US cases are from Europe or European-colonized countries, and a similar background is claimed for most white patients from the United States. In addition, 14% of US patients are non-white whereas only 9% of foreign cases are nonwhite, and nonwhites had a lower peak of occurrence at ages 3 to 7 than did whites.

AGE, SEX, AND REASON FOR RECEIVING CHLORAMPHENICOL

Indication for chloramphenicol	Age group					
	0 to 9 years		20 to 39 years		60-plus years	
	Number of patients	Number of females	Number of patients	Number of females	Number of patients	Number of females
Upper respiratory tract or ear infections.....	29	19	4	2	7	4
Lower respiratory tract infections.....	7	6	6	5	21	7
Urogenital infections.....	10	10	11	9	21	5
Other indications.....	31	20	32	22	19	9
Total.....	77	55	53	38	68	25

The Table presents data on some of the more common indications for use of the drug in relation to age and sex. Upper respiratory tract or ear infections were the indications in 29 (almost 40%) of 77 patients, in the under 10-year age group but in only 7 (about 10%) of 68 patients in the older age groups; lower respiratory tract infections and urogenital infections, on the other hand, each accounted for almost a third of indications in the elderly, but only about a tenth of childhood indications. A comparison of US with other reports in this regard reveals similar patterns of indications for most age group except that there appears to be a slightly lower percentage of childhood cases corresponding to each of the three specific listed indications in the non-US group.

Race and Ethnic Origin.—Of the 346 patients whose race is known, 28 (8%) were Negro, 10 (3%) were Oriental, 3 were American Indian, and 2 were East Indian. Negroes accounted for 11% of the US group but were not present in the

non-US group. Only 18 (43%) of 43 nonwhite patients were female, whereas 191 (63%) of 303 white patients were female. Ethnic origin was indicated for 144 white patients. Of these, 79% were north European, 6% Jewish, 6% east Europeans, 5% Spanish-American, and 4% south European.

Other Genetic Information.—In a written communication to the Registry (March 1, 1960), D. J. Fernbach, MD, called attention to a set of identical twins, both of whom developed blood dyscrasias related to chloramphenicol; a published report of these cases appeared subsequently.⁷

These identical twins, who were white males 3 years of age, had been given seven- to ten-day courses of chloramphenicol on several occasions during the preceding two years for severe upper respiratory tract infections.

Twin A had six to ten such courses, the most recent being about a month before diagnosis, at which time trisulfapyrimidines was also given. Purpura developed characterized by thrombocytopenia and a hypoplastic marrow, which, over the course of about two months, developed into pancytopenia. Three marrow transplants were attempted from twin B during the next two years, but without apparent improvement. Hemoglobin returned to normal after 1½ years of corticosteroid and androgen therapy. The bone marrow became less hypocellular, but thrombocytopenia and modern leukopenia still persisted six years after onset.

Twin B had received only four courses of chloramphenicol, the most recent course (this drug only) being given two weeks prior to diagnosis, at about the same time that purpura appeared in twin A. Isolated thrombocytopenia associated with a hyperplastic marrow, including normal numbers of megakaryocytes, became evident when he was being worked up in preparation for the first marrow transplantation. He received no therapy and completely recovered within two weeks after chloramphenicol was discontinued.

BLOOD AND BONE MARROW

The reporting physician in each case indicated his diagnosis of the type of dyscrasia utilizing his usual criteria plus the admonition on the report form that leukopenia would consist of leukocyte counts of 3,000/cu mm or less. Further documentation was usually not present, and only rarely did members of the hematology panel find it necessary to change a diagnosis on the basis of such documentation when present.

All three major types of peripheral blood cells, erythrocytes, leukocytes, and platelets, were jointly depressed in 75% of 358 cases; two cell types were depressed in 6%; and a single cell type was depressed in 19% (leukocytes in 9%, erythrocytes in 6%, and platelets in 4%). Isolated erythroid cell depression was more common at ages 20 to 59 years (15% of 134 cases) than in younger (2% of 144 cases) or older (two [3%] of 80 cases) age groups, but no other age trends were apparent. Depression of granulocytes was the most striking component of leukopenia in most instances, but because the report forms did not always call for specific details in this regard, a more complete statistical breakdown is not given.

Bone marrow findings were available in 129 cases. In 3% of these, the marrow showed increased cellularity and in 7%, normal cellularity, often with other changes such as maturation arrest of the granulocytic series or vacuolation of erythrocytic precursors. Depression in number was noted for precursors of one of the major types of blood cell in 12% of cases; of two types in 5%; and of all three types (eg, hypoplastic or aplastic anemia) in 74%. Two marrows in the last category showed increased numbers of marrow lymphocytes, but on follow-up this apparently did not represent leukemia or lymphoma. Of 24 patients with only one or two cell types depressed in the blood, 2 (8%) showed a normal to hyperplastic marrow, 15 (62%) had one or two cell types depressed in the marrow, and 7 (29%) showed general marrow hypoplasia. Of 105 patients with all three cell types depressed in the blood, 10% showed a normal to hyperplastic marrow, 6% showed depression of one or two cell types in the marrow, and 84% showed general marrow hypoplasia.

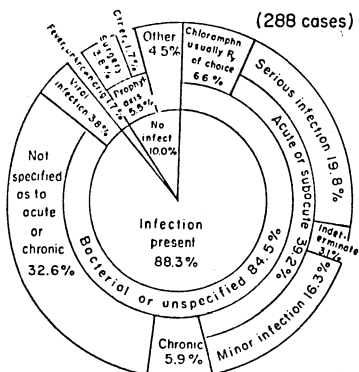
⁷ Fernbach, D. J., and Trentin, J. J.: "Isologous Bone Marrow Transplantation in an Identical Twin With Aplastic Anemia" in *Proceedings of the Eighth International Congress on Hematology*, Tokyo: Pan-Pacific Press, 1962, vol. 1, pp. 150-155.

Clinical manifestations were not reported in detail for most cases, but those which were given conformed with what one might expect: manifestations of anemia, propensity to hemorrhage, and increased susceptibility to infection.

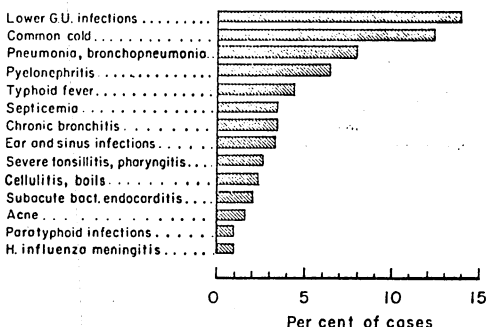
DETAILS OF DRUG ADMINISTRATION

General.—The reason that chloramphenicol had been given (for the most part infection or prophylaxis against infection) was cited in 71% of the 408 cases (Fig. 2).

Reasons drug was given



Some specific conditions for which chloramphenicol given

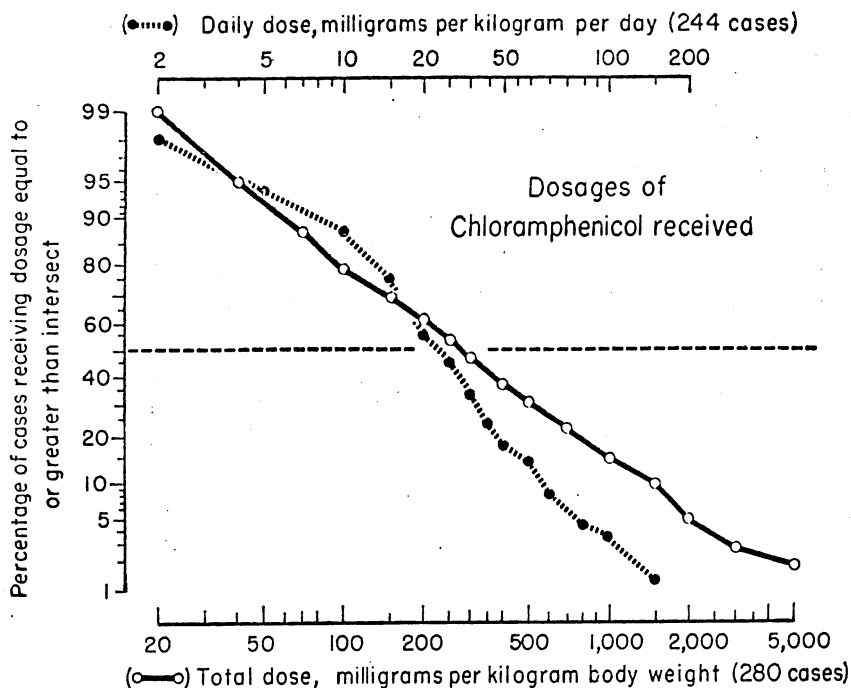


2. Reasons why chloramphenicol given. Left, General nature of indications. Right, Specific conditions; all those accounting for 3% or more of known indications plus selected conditions with lower percentages.

Chloramphenicol was the only known drug administered during the prior six months to 40% of patients. One other drug was mentioned for 19%, two for 13%, and three or more for 28%. In one case, 17 other drugs were listed. In 9% of all cases, the only other drugs mentioned were members of what the study group considers to be generally "innocent" drugs—*aspirin*, the *barbiturates*, *chloral hydrate*, *digitalis glycosides*, the *penicillins*, and the *tetracyclines*; in 37% of all cases, drugs other than "innocent" ones were administered, but no "toxic" drugs were given; in 9%, another toxic drug was administered, but suspicion was cast most strongly on chloramphenicol; and in 4% suspicion was cast most strongly on another toxic drug. Thus, in 96% of cases, there is strong suspicion that chloramphenicol was the causative agent, and in the remaining cases, this possibility cannot be ruled out. Since elimination of those patients receiving another toxic drug had virtually no effect on outcome of the dyscrasia, all cases were included in the analysis.

Duration and Dosage of Chloramphenicol.—It is known that 9% of patients received this drug at least once prior to the course in question.

The dashed line of Fig 3 presents a cumulative plot of average daily dose in milligrams per kilogram per day and a type of graph paper having logarithmic and probability scales. If the log-dose were distributed in gaussian fashion, such a plot should approximate a straight line. Central portions of such curves are generally more accurate than the extremes. In this case there is some deviation from a single straight line, but the fit is not bad. At any rate, interpolation will provide estimates of dosage levels defining selected percentiles. It is seen that 10% of patients received less than 8 mg/kg/day, 50% received less than 23 mg/kg/day, and 10% received greater than 60 mg/kg/day. This is to be contrasted with a manufacturer's recommendations for a starting dose of 50 mg/kg/day in adults and 50 to 100 mg per kilogram per day in children beyond infancy. Either smaller doses tend to be given to susceptible patient, or else the general trend in use of this drug is to administer smaller average amounts than recommended for initial therapy. The latter possibility seems more likely. There appears to be slight differences in patterns of daily dose administration for different age groups. Thus, the median doses were: 33 mg/kg/day for patients 0 to 9 years of age, 24 mg/kg/day for those 10 to 39 years of age, and 18 mg/kg/day for those 40 years of age and older.



3. Daily dose of chloramphenicol in milligrams per kilogram per day and total dose in milligrams per kilogram. Distribution of values for each curve is indicated cumulatively on log-normal coordinates.

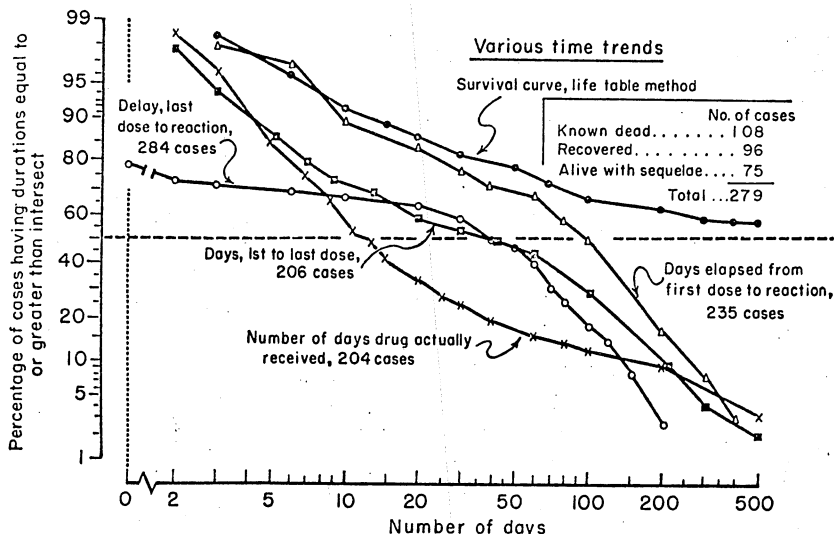
The number of days of therapy is similarly plotted as one of the curves in Fig 4. There is a concavity to the cumulative plot line. Although various interpretations are possible, a tendency of physicians to use either short courses or prolonged courses of therapy depending on the nature of the infection seems to be the most reasonable explanation for this nonlinearity. In 10% of cases, development of a blood dyscrasia was related to four days or less of therapy with chloramphenicol; in 50% it was related to 13 days or less; and in 10% to 150 days or more. In a few instances the drug was administered on only one occasion. Median duration of therapy by age group was: 11 days for patients 0 to 9 years, 13 days for those 10 to 39 years, and 15 days for those 40 years and over.

Time from first to last dose is similarly shown in Fig 4. This time amounted to four days or less in 10% of cases, 38 days or less in 50%, and 200 days or more in 10%. The main difference between these two curves, seen at their middle, is due to instances in which the drug was taken intermittently. Of the 329 patients on whom such information was available, 39% received the drug intermittently.

The small crossover of these two curves at their extremes reflects the fact that slightly different subsamples were suitable for each and that each curve is only an estimate rather than a precise indication of the curves which would be obtained from a much large population of similar cases.

The total dose of chloramphenicol received by various patients is plotted cumulatively in Fig. 3. The cumulative plot closely approaches a straight line using these coordinates. In 10% of cases the total dose amounted to 60 mg/kg or less, in 50% to 280 mg/kg or less, and in 10% to 1,300 mg/kg or more. One would expect the 50% intercept to agree fairly well with the product of 50% intercepts for average daily dose and number of days of therapy, and indeed the figure of 299 mg/kg obtained in this fashion is not far from the value of the other curve of Fig. 3, 280 mg/kg. There appears to be essentially no difference in total doses in milligrams per kilogram as related to age.

Time of Reaction as Related to Therapy.—One tends to think of adverse reactions as occurring during drug administration or shortly after discontinuation. Such a relationship proves to be the exception for chloramphenicol-associated blood dyscrasias. Among the 284 patients for which such information was available, only 22% showed manifestations of the dyscrasia while the drug was still being given as shown by the appropriate curve of Fig. 4. The median time from discontinuation of the drug until clinical evidence of the dyscrasia appeared was 38 days, and in 10% of cases this time was 130 days or longer. There is a definite downward bending of this curve, and one wonders whether time from first dose to reaction might not more nearly approach a log-normal distribution. This curve has also been charted in Fig. 4, and it shows an incomplete tendency to straightening. The reaction developed 10 days or less following initial dose in 10% of cases, in 95 days or less in 50%, and in 260 days or more in 10%.



4. Number of days chloramphenicol received; elapsed time of chloramphenicol course; time from first dose to reaction; time from last dose to reaction; and survival time. Distribution of values for each curve is indicated cumulatively on log-normal coordinates. The survival curve is based on life-table analysis.

None of the patients in this series are known to have been continued on or rechallenged with the drug after the dyscrasia was diagnosed, and we would not recommend that this be done.

SURVIVAL AND COURSE

Life Table Survival Curve.—Construction of a survival curve for a fatal disease on the basis of a series of patients, all of whom have not yet died at time of analysis, is best performed through the life table method.⁸ The present situation differs from that of a uniformly fatal disease in that, in addition to a trend towards mortality, there is also a trend towards recovery. Patients who have recovered are not known to have relapses unless the drug is administered further. In this instance, a satisfactory method of accounting for recoveries in life table analysis is to consider all patients who have recovered to be still alive at a relatively long period following onset of the dyscrasia, regardless of the actual length of follow-up. The top curve of Fig. 4 shows the results of this analysis. Because of recoveries, the curve approaches an asymptote rather than describing a straight line on a log-probability plot. The overall mortality approached is approximately 50%; 10% of the patients in the entire series have died within two weeks of onset of the dyscrasia. The 75% intercept (i.e., median survival for those with fatal outcome) is about 50 days. Rare cases may have a fatal outcome a year or more after diagnosis.

⁸ Merrell, M., and Schulman, L. E.: Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematosus, *J. Chronic Dis* 1: 12-32 (Jan.) 1955.

Course.—It was specifically reported in several instances that recovery followed withdrawal of the drug, and it was presumed that this occurred within a few weeks. Most of these instances were associated with depression of a single blood cell type. On the other hand, of the 75 patients known to be alive with persistent evidence of the dyscrasia despite cessation of the drug, 20 (27%) were alive 100 to 299 days after onset, and 11 (14%) were alive 300 or more days after onset. Recoveries have sometimes been noted after relatively long periods of disease.

Death is known to have occurred in 186 cases, 95% from complications of the dyscrasia. Performance of an autopsy was noted for 24% of these cases; however, details of this examination were not usually reported.

Therapeutic measures directed against the marrow depression were usually not reported, and no attempt was made to evaluate these.

PROGNOSIS

Detailed studies on prognosis have been submitted for publication elsewhere (W. R. Best). The most important clinical findings are that improved survival is associated with fewer cell-types depressed, shorter delays in onset, larger daily doses, and occurrence in Negroes.

COMMENT

Yunis and Bloomberg have reviewed various types of evidence bearing on the pathogenesis of those hematologic reactions to chloramphenicol which occur in rare cases at commonly employed dosage levels. They found no convincing evidence to support an autoimmune process, and the current data cannot be construed as adding such. Abnormal susceptibility due to some biochemical abnormality seems more likely, but the exact nature of such a disorder remains to be determined.

Yunis and Bloomberg suggest that a defect in localization, metabolism, or excretion of chloramphenicol, or an enzymatic or other biochemical deficiency involving a metabolic pathway that becomes essential in the presence of this drug, could account for these reactions. One suspects that there is an underlying hereditary difference between individuals who do and those who do not develop this reaction to chloramphenicol. The occurrence of dyscrasias in both members of a set of identical twins is one of the most interesting findings in the Registry relative to the genetic question. It is reasonable to suppose that many close relatives of Registry patients have received courses of chloramphenicol comparable to those of corresponding affected family members, and that a high percentage, if not all instances of multiple cases in a single family would have been called to the attention of the Registry. Yet, so far as we have been able to determine, the only instance in the Registry or the medical literature in which more than one member of a family has developed such a dyscrasia is this particular one involving the relatively rare sib combination of identical twins. One could reasonably expect several nontwin sibling pairs in the total experience to date if this susceptibility to chloramphenicol required a homozygous state relative to a single recessive gene. Simultaneous exposure to some unusual environmental factor or the fact that the only known sibling pair developing this defect share an identical genetic constitution strongly suggests that an unusual combination of genetic factors must be present in a homozygous form before this abnormal susceptibility becomes manifest.

Unusual racial or ethnic patterns of occurrence or course would be consistent with genetic disorders, but would not provide conclusive evidence thereof. Considering the racial composition and patterns of medical care of populations about whom the Registry is most likely to receive reports, one has no compelling reason to suspect that members of one race are more likely to develop this reaction, given a similar drug exposure, than are those of another. However, a striking difference in clinical course seems to be related to race in this series. Nonwhite patients tend to have a much more benign course than whites, a trend not previously noted.

Unusual patterns of occurrence relative to age or sex, if not otherwise explained, would tend to implicate developmental, degenerative, or hormonal factors as being of at least secondary importance. Females accounted for 54% of cases surveyed by Yunis and Bloomberg and 62% in the current report.

Some of the age-sex patterns noted can reasonably be assumed to reflect differences in occurrence rate for various diseases for which chloramphenicol is

often given (Table), but in addition, it seems likely from case data that there is an increased susceptibility to this complication in females prior to the menopause. A peak occurrence rate was noted at 6 to 10 years of age by Yunis and Bloomberg and at 3 to 7 years of age in the present series, the differences being in part due to different tabulation intervals. The marked difference between US and non-US reports in this regard suggests that there may be different national medical trends in the approach to use of chloramphenicol. Upper respiratory tract infections are frequent in this age group and account for a high proportion of uses. Thus, one can neither confirm nor refute at this time the possibility that children at this age may be more susceptible to chloramphenicol-induced marrow depression.

Clinical Characterization.—Yunis and Bloomberg interpret the data of their review as indicating that chloramphenicol produces two types of marrow toxicity. They state that the first of these usually occurs during therapy, is associated with a larger total dose, demonstrates a normocellular marrow, shows anemia with or without leukopenia or thrombocytopenia, and is reversible on withdrawal of the drug. The second type shows a delayed onset, is not necessarily dose-related, demonstrates an aplastic marrow with associated pancytopenia, and usually has a fatal outcome. A majority of cases in the current report conform in most respects to the second class, and there is another cluster which fits fairly well into the first class. However, a number of cases fall between or overlap these two groups. For example, nine of 60 patients in the present series who had at least two weeks delay between the last dose and development of the reaction showed a normocellular marrow or one with only isolated cellular depression, whereas Yunis and Bloomberg found no such cases. All combinations of blood cell depression were seen in association with nonaplastic marrows, and half of the current series showing pancytopenia in contrast to a more limited spectrum seen in the series reviewed by Yunis and Bloomberg. Patients with hypoplastic marrows tend to have received a smaller dose of drug, but there is an appreciable overlap. Thus, the 10%, 50%, and 90% intercepts of a cumulative dosage curve for 48 current cases with marrow hypoplasia were 5, 20, and 54 mg per kilogram per day, respectively; whereas for 28 cases with lesser degrees of marrow involvement the corresponding figures were 16, 31, and 88 mg per kilogram per day. These doses are well within usual recommendations. Curves for the duration of therapy were very similar for the two degrees of marrow involvement with a median of 11 to 12 days. The cases reviewed by Yunis and Bloomberg on the other hand, show a median duration of therapy of about 35 days for patients with hypoplastic marrows, and about 20 days for those with nonhypoplastic marrows. Unidentified biases in the reporting of cases may account for this difference between the two series.

The implication of these authors in dividing chloramphenicol-associated blood dyscrasias into two groups is that there may be two separate mechanisms involved. The current study would indicate that the cases as they occur are not always so sharply divisible, and that the possibility of a single pathogenic mechanism is by no means ruled out. Findings in the identical twins reported here would speak for a single mechanism, for the patient with the greater number of prior courses developed typical aplasia, whereas his twin showed a readily reversible, isolated cytopenia.

Preventive Aspects.—The best educated guess as to frequency of this complication, probably an underestimate of true occurrence, is that of Leikin et al.⁹ in which it would appear that less than one case of serious marrow toxicity occurs for every 100,000 courses of therapy. The data presently available are not appropriate for further speculation in this regard.

This study does, however, present a good deal of quantitative information relative to the types of drug course which have been associated with this complication. Marrow toxicity has been seen after low doses and high doses, chloramphenicol alone and in combination with other drugs, short courses and long courses, continuous therapy and intermittent therapy, and single courses and repeated courses. Most patients have received chloramphenicol in dosage and duration commensurate with best clinical practice. Unfortunately, however, it cannot be stated that indications for use always conformed to optimal standards.

Most experts would consider chloramphenicol the treatment of choice in

⁹ Leikin, S. L.; Welch, H.; and Guin, G. H.: Aplastic Anemia Due to Chloramphenicol, *Clin Pro Chil Hosp Wash* 17:171-181 (July) 1961.

typhoid and paratyphoid infections, and some would include *Haemophilus influenzae* meningitis. These three conditions accounted for 6.6% of indications in the current series, most of these being from non-US sources. Chloramphenicol is also indicated in certain other serious acute and chronic infections depending on in vitro sensitivities and particular features of a patient's course. The report forms did not request sufficient data for further evaluation in this regard. The drug is inactive against common viral and upper respiratory tract infections, but these conditions accounted for a significant percentage of stated indications in this series. Thus, the most powerful preventive tool available is the use of this agent only for serious infections in which the balance of risks of adverse reactions against the risks of inadequate therapy tend to favor use of this antibiotic over alternative methods of treatment. It should be recognized that the risk of occurrence in any case treated with chloramphenicol is quite slight, but the risk of a fatality in that patient who develops this reaction is great. Some physicians have belittled this complication because they have seen no hint of a blood dyscrasia in the many courses of chloramphenicol therapy which they have directed. One should not be surprised at such an experience, for it is a rare complication; however, this is little consolation to the future patient under such a physician's care who dies of aplasia because chloramphenicol was given when it need not have been.

Most patients develop manifestations of marrow depression after the drug has been stopped, often weeks or months later. It thus appears that monitoring blood counts during therapy would be of little or no value in preventing morbidity and mortality in the majority of cases. However, there is a minority of reactions, usually isolated cytopenias, which may become apparent during therapy and respond to withdrawal of the drug. It is for the recognition of such cases that we recommend the occasional performance of blood counts during chloramphenicol therapy. Under the assumption that an isolated cytopenia represents a basically different and less dangerous type of toxicity. Yunis and Bloomberg do not feel that therapy need be stopped in such cases. We do not agree. No cases in which chloramphenicol was continued after the development of a cytopenia have come to our attention, and one would seem ill advised to continue therapy on the basis of this unproven theory.

SUMMARY AND CONCLUSIONS

This review involves 408 cases of chloramphenicol-associated non-neoplastic depression of one of more blood cell types that were reported directly to the AMA Registry on Blood Dyscrasias or abstracted from the medical literature.

Various quantitative features of the occurrence of this dyscrasia and relationship to drug administration have been delineated.

The dyscrasias noted range from readily reversible, isolated cytopenias occurring during therapy to delayed, progressive aplastic anemia. This range is not considered as necessarily indicative of more than one fundamental type of drug reaction. It is apparent that blood dyscrasias may occur in relation to conventional and even brief courses of therapy, and that signs of such reaction may not be seen until long after the course has been completed. The best approach to prevention thus lies in a sound appraisal of possible benefits and dangers whenever use of this drug is contemplated. The occasional monitoring of blood counts may prove worthwhile in rare cases, but its expected value in the usual case is sufficiently small that one cannot substitute such a practice for good judgment in deciding when the drug should or should not be used.

A more complete bibliography indicating where previously published cases appear, together with other supplemental information, including rules and transformations used to estimate desired parameters from partial data, may be obtained by ordering Document No. 9515 from American Documentation Institute, Library of Congress, Washington, D.C. 20540, remitting \$2.50 for photoprints or \$1.75 for 35-mm microfilm.

GENERIC AND TRADE NAMES OF DRUG

Chloramphenicol—Chloromycetin, Cylphenicol, Tega-Cetin.

Senator NELSON. Our next witness is Dr. Mark H. Lepper.

Doctor, the committee appreciates your coming here today. Your

biographical material will be printed in full, so would you mind stating for the record a summary of your biographical and professional background.

STATEMENT OF DR. MARK H. LEPPER, VICE PRESIDENT, PROFESSIONAL AND ACADEMIC AFFAIRS, PRESBYTERIAN-ST. LUKE'S HOSPITAL, CHICAGO, ILL.

Dr. LEPPER. I would be happy to, Senator.

In connection with my background, I would also like to put in a disclaimer similar to that Dr. Dameshek used to point out that this is an attempt to be as objective as possible. It is quite clear that objectivity is something that none of us really achieves.

I do have a somewhat different point of view than the previous witnesses simply because my background was in infectious disease, probably as much responsible for my being here today as anything was in support of the drug industry throughout my career in the field of infectious disease research, particularly in therapy of infectious diseases. We have, therefore, been interested in the problems of the treatment of infection from the days of the sulfanomides.

Following this, I became professor of preventive medicine at the University of Illinois. Many people in infectious diseases—as control became the dominant activity—became more and more interested in preventive medicine. This is the gradually expanding interest in the biometric statistical approach to medicine, the so-called epidemiological approach, and finally, tied into medical care and medical care research.

I am vice president for professional and academic affairs at the Presbyterian-St. Luke's Hospital, which is an affiliate of the University of Illinois, and I continue to carry my title of professor of preventive medicine at the university.

I, too, am speaking as an individual. My opinion does not necessarily reflect the agencies which I have just mentioned.

(The biographical material submitted by Dr. Lepper follows:)

CURRICULUM VITAE—MARK HUMMER LEPPER, M.D.

Born : June 12, 1917—Washington, D.C.

Education

George Washington University, A.B.—1938, M.D.—1941.

Hospital Appointments

Intern, Sibley Memorial Hospital, 1941–1942.

Assistant Resident in Medicine, Gallinger Municipal Hospital, 1943–1944.

Consultant in Internal Medicine, Walter Reed General Hospital, 1948–1950.

Medical Superintendent, Municipal Contagious Disease Hospital, Chicago, Illinois, 1950–1952.

Attending Physician, Presbyterian-St. Luke's Hospital, 1952–1962.

Consulting Physician, Presbyterian-St. Luke's Hospital, 1962–

Executive Vice President, Prof. & Academic Affairs, Presbyterian-St. Luke's Hospital, 1966–

Following Appointments and Fellowships

Fellow in Medicine, George Washington University, 1942–1946.

Clinical Instructor in Medicine, George Washington University (part time), 1946–1948.

Clinical Instructor in Medicine, George Washington University (full time), 1948-1949.

Clinical Associate Professor of Preventive Medicine, University of Illinois, 1950-1952.

Associate Professor of Medicine in charge of Preventive Medicine, University of Illinois, 1952-1965.

Professor of Preventive Medicine and Head of the Department, University of Illinois, 1965-1966.

Professor of Preventive Medicine, 1966-

Military Service

U.S. Army Medical Corps, Platoon Leader to Station Hospital, Commander. Rank following discharge, Major, 1944-1946.

Certification by Specialty Board

American Board of Internal Medicine, 1950.

Membership in Professional Societies

American Society for Clinical Investigation.

Association of Teachers of Preventive Medicine, President, 1965-1966.

American Federation for Clinical Research.

Central Society for Clinical Research, Council, 1965-1968.

Central Clinical Research Club, President, 1965-1966.

Chicago Society of Internal Medicine.

Chicago Society of Allergy.

Fellow, American Public Health Association.

Fellow, American Medical Association.

Illinois Public Health Association.

Medical Society of the District of Columbia.

New York Academy of Science.

Fellow, American College of Physicians.

Sigma Xi, Scientific Society.

American Society of Microbiologists.

Infectious Disease Society of America, Council, 1964-1968.

Planning Committee Interscience Conference on Antimicrobial Agents and Chemotherapy, 1961-1963.

Membership in Honor Societies

Phi Beta Kappa.

Alpha Omega Alpha.

Membership in Community Societies

Board of Governors, American Heart Association.

Epidemiology Council, American Heart Association.

Study Section on Bacteriology and Mycology, National Institutes of Health, 1962-1964.

Surgeon General's Task Force on Tuberculosis, 1963.

Advisory Board to Director Communicable Disease Center, 1963-1967.

Advisory Board on Treatment Center Grants to National Foundation, N.Y.

Committee in Human Reproduction, A.M.A.

Advisory Committee, Mental Health Section, Board of Health, Chicago.

Poliomyelitis Technical Advisory Committee, State (Illinois) Health Department.

Board of Directors, Tuberculosis Institute of Chicago.

Medical Advisory Board, Suburban Cook County Tuberculosis Control.

Chairman, Community Service Council, Chicago Heart Association.

Board of Directors and Executive Committee, Chicago Heart Association.

Northeastern Illinois Air Pollution Technical Advisory Board.

Medical Board, Visiting Nurses Association, Chairman, 1960-1965.

Public Health Committee of Welfare Council.

Medical Advisory Council, Asthma and Allergy Foundation for Greater Chicago.

Advisory Committee, Heart Disease Control Program, Chairman.

Member, Editorial Board of Applied Microbiology.

Technical Committee on Infant Health Study of Welfare Council.

Medical Advisory Board, Chicago Committee on Alcoholism, Chairman.

Member, Board of Directors, Chicago Committee on Alcoholism.

Member of the Veterans Administration Research Program Advisory Board.

Food and Drug Committee on Veterinary Medicine and Non-medical Use of

Antibiotics, Chairman.

Advisory Board on Grants to National Arthritis Foundation.

Board of Trustees, Bishop Anderson Foundation, Vice Chairman, 1965.

Editorial Board, American Review of Respiratory Disease.

Research Committee, American Thoracic Society.

Editorial Board, Applied Microbiology.

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Dr. LEPPER. As one can see, I, too, have wrestled with the problem of the balance of good and harm which we always do in therapy. The problems of the use of chloramphenicol is one of the best examples of the many ramifications and difficulties inherent in establishing a clinical therapeutic index. I would emphasize there "clinical," because that is what we are talking about.

The concept of a therapeutic index, was originally stated by the father of chemotherapy, Ehrlich, early in this century, his concept was that the higher the ratio of therapeutic effective dose to toxic dose, the better the compound. This, however, was thought of primarily in terms of the experimental animal, and in them relatively easily handled on a statistical basis. Thus, it has become a routine to find the protective dose in an experimental infection and the lethal dose for toxicity in other animals of the same species.

The most common statistic used is the dose that is 50-percent effective on the one hand, and 50-percent lethal on the other. Thus, a drug that cures 50 percent of a group of animals at a dose level of 10 milligrams per kilogram and is lethal at a dose level of 500 milligrams per kilogram, in 50 percent of a group of similar, but uninfected, animals would have an index of 1/100. That is a very favorable therapeutic ratio, I might add.

If these doses were 10 and 20, respectively, however, the index would be one-half. That is not a very favorable ratio.

Certainly, this relatively simple laboratory guide has been quite a useful guide, but because of the many difficulties of going from a species, such as mice, with an artificially induced infection, to man with a naturally occurring infection, assures us that it is just a guide. The clinical investigator, therefore, is faced with the problem of developing a somewhat similar ratio for naturally occurring infections in a rather heterogeneous population from the toxicity point of view, as has been emphasized by the previous speaker.

Needless to say, the estimates of these ratios are much less precise and involve more than an arbitrary endpoint because we want 100-percent survival if we can get it, and obviously not a 50-percent lethal dose. However, there is a hierarchy of not necessarily mutually ex-

clusive effects that are, on the positive side: (1) the ability to prevent death; (2) the ability to maintain the permanent integrity of tissue, that is, the arrest of the process before irreversible and, therefore, crippling conditions have occurred, and this has to do with empiric use of drugs; and (3) the ability to shorten the duration of essentially reversible processes and limit morbidity.

Similarly, there are several endpoints for toxicity in their order of importance; (1) fatalities and the available countermeasures for their prevention; (2) permanent damage from the drug; and, (3) production of reversible disability and morbidity.

Now, obviously, in making these ratios, one tends to equate the categories and it is hard to equate a lethal toxicity with prevention of morbidity, for instance. It is a different order of magnitude in the equation.

Chloramphenicol is one of the early antibiotic discoveries, hence much information has accumulated for it. I think this is quite clear in the testimony and much of what we are talking about is the way the drug was developed, and in talking about relative indications, the way they came about, and whether they are still current.

Most of the information that reaches the profession really is about new agents. Once they are established, the amount of knowledge disseminated is relatively small. Hence, much of what is said about chloramphenicol indications come from the early years and are not well stated in terms of competitive new drugs.

Senator NELSON. I didn't understand that last statement.

Dr. LEPPER. Changes in indications have not been well emphasized in terms of competitive new drugs as we shall see later on when we come to the staphylococci. This was a lifesaving drug in the late fifties. It is no longer indicated as such, so that when you look at indications, you have to realize that this is a constantly changing field and the physician doesn't really get a reevaluation of old drugs and their relative role nearly as thoroughly as he gets an evaluation of the new drugs and their potential toxicities in relative roles.

Chloramphenicol has wide antibacterial activities and, therefore, may be considered for use in many infections. This has already been indicated. As a matter of fact, from the package insert, one can pick out 17 groups of infections which are mentioned or listed, and some of these groups, such as salmonellosis, which includes typhoid fever, have hundreds of organisms of different species involved. Most of the indications have more than one species of organism involved. Hence, the range of potential specific indications is quite great.

Second, because of this, the empirical use has often been ordered without prior diagnosis, either because of urgency, which may be considered an indication or a feeling that the condition is not serious enough to warrant the expense of the work-up. In this situation they are used because potentially you can treat a lot of things, hence you do not need do a work-up. This is not a valid indication for chloramphenicol, although it is one that undoubtedly is the heart of the use in minor respiratory illnesses which is still going on.

Moreover, we have to consider the prophylactic use because this is one of the big uses of antibiotics.

Senator NELSON. In what kind of situation is a prophylactic use of chloramphenicol indicated?

Dr. LEPPER. I discuss this a little later. It might be more appropriate there. But, for instance, to prevent postoperative infections in persons who have had, say, a ruptured appendix. This is a use that some people would recommend because the enteric organisms are involved. And we know people who have had a ruptured appendix are most apt to get a postoperative infection. This is not a valid indication in our opinion.

There are better prophylactics and, as a matter of fact, the whole area of prophylaxis is a debatable one, but it is the kind of situation in which chloramphenicol is quite frequently used.

Senator NELSON. That is what I was getting at. What kind of clearly specified instances are there in which chloramphenicol is indicated for prophylactic use?

Dr. LEPPER. In my opinion, there is no justifiable prophylactic use for chloramphenicol, but there are other opinions. It is used extensively in this way more in some hospitals than in others.

Another area, for instance, might be in prevention of infection after an indwelling urinary catheter. I think, (a) prophylaxis here is not well proven, and (b) if it is done at all, there are probably equally good agents which are less toxic which meet the criterion of the warning on the package insert.

On the other hand, it is still used by some in this area because of the early emphasis on the breadth of the spectrum. The fact that you could treat so many different things, makes it logical that, if you are trying to prevent a wide variety of things, you use the agent that will prevent the widest variety and hence the emphasis on chloramphenicol in this regard.

Now, as I say, I do not believe these are justifiable indications but they are indications and I would suspect in Dr. Best's gray zone. They are indications which some people have used and have recommended its use, and it is still being used in these situations in very many hospitals. In fact, I would be quite surprised if you went in a major hospital and did not find that some people were still using the drug in this respect because I know of none that I have looked at in which it is not being done.

Senator NELSON. Your judgment is that it is not indicated in most of these cases.

Dr. LEPPER. It is not indicated prophylactically at all. I think in the first place the whole area of prophylaxis of this kind is difficult to document. In general, when it is documented, it is documented for a few months and then the propagation of resistant organisms in the hospital, is such that it loses whatever effectiveness it had originally, and hence, there is considerable debate over the whole concept in the first place.

Now, when you add to that the fact that chloramphenicol is more toxic than many of the other drugs which can be used similarly, including tetracyclines and some of the newer penicillins, it becomes clear that chloramphenicol really has no such indication at the present time.

Mr. GORDON. Dr. Lepper, in the package inserts, under "Respiratory Tract Infections," we have the following statement:

Chloramphenicol may be employed for severe infections of the respiratory tract due to susceptible microorganisms and in the presence of contraindications or lack of response to other agents.

Does that tell you very much?

Dr. LEPPER. No. That is a typical ambiguous statement which tends to foster overuse. In the first place, the vast majority of the respiratory infections are due to viruses and in contrast, I think, Dr. Best's statement chloramphenicol is not active against viruses. Early, it was thought to be useful for some viruses, because we misclassified certain organisms such as the psittacosis agent as a virus but is now recognized to be a very small intracellular bacteria.

Also, a condition known as primary atypical pneumonia which was thought to be a virus infection at the time of the introduction of these agents turns out to be a small free-living bacteria, the mycoplasma. Thus, the initially reported antiviral activity has turned out to be a specific kind of antibacterial activity. We can say quite clearly now there are none of these antibacterials and antibiotics which are effective against known virus, meaning things like polio, common cold virus, influenza virus, the mumps virus, and measles virus, and so forth.

Now, the vast majority of respiratory infections are a virus. Among those which are bacterial, the vast majority, meaning over 95 percent, are bacteria such as the pneumococci and the streptococci. These respond better to penicillin than they do to chloramphenicol. Chloramphenicol is not as good a therapeutic agent in these and the one organism that causes infections in which chloramphenicol is as good or better than penicillin is *Hemophilis influenza*, which is a bacteria that was once thought to cause the disease we now recognize as virus influenza.

This was a mistake and the bacteria, therefore, got its name and has confused everybody since. *Hemophilis influenza* causes ear infections in children, makes up less than 10 percent of all bacterial infections which make up less than 5 percent of all respiratory infections. We are down to 0.5 percent or less that you are talking about.

Except for the possibility, as we mention later, of *Hemophilis influenza* infections in the central nervous system being somewhat better treated by chloramphenicol, there is no evidence that the tetracyclines are not as good as chloramphenicol in the treatment of *Hemophilis* infections and they are less toxic.

Therefore, again, there is no particular respiratory indication. In addition, Ampicillin, which is the newest of the penicillins, and Cephalothin, which is a penicillin-like drug, both have excellent anti-*Hemophilis* activity and also are less toxic.

Hence, in the area of the respiratory infections of the primary type one sees in the community, there is no indication for chloramphenicol. In the hospital we have, because of the use of rather dirty aerosol equipment, engendered a fair number of infections of the lungs due to delivery of the gastrointestinal bacteria to the susceptible lungs. This is known as aerosol-induced pneumonia and is caused by gram negative rods. These are very difficult to treat. They are often in the kind of patients Dr. Best was talking about, severely ill patients, the patient who has otherwise fatal or very severely damaging underlying diseases.

These pneumonias are difficult to treat and you have your choice, often, between a drug like Kanamycin and a drug like chloramphenicol, both of which have considerable toxicity. This choice usually is re-

solved at the laboratory level and somewhat by the age level because, when I mention gray sickness, you will see that in infants, where this was a problem because these infants had humidifiers on their incubators, Kanamycin is a less toxic drug than chloramphenicol and replaced chloramphenicol in the newborn nursery.

In the older age group where renal function is naturally deteriorating, chloramphenicol may be a better drug. So in this very restricted area of the gram negative rod pneumonias acquired in the hospital, and which is usually preventable, chloramphenicol may be indicated.

That, as far as I see, is the only respiratory tract use for the chloramphenicol.

In contrast to this potentially favorable effects are some serious side effects. First and foremost, the drug can produce a fatal aplastic anemia, the frequency of which appears to be dose dependent, although not in the sense that Dr. Dameshek used dose effect in the metabolic effect. In other words, there is a susceptible subgroup, but this subgroup can be disclosed to a larger and larger extent by increasing the dose, so it is dose dependent. It is the most frequent aplastic anemia, not associated with a malignancy of a known cause.

This reaction probably is not in exaggeration of the dose related response which is the almost uniform interference by high doses, with blood cell formation due to blocking of protein synthesis, but is more of an idiosyncratic reaction probably of some metabolic origin and is not predictable.

The most recent definitive study in California, which was done at the request of their Legislature, of all deaths from aplastic anemia in the State suggests that aplastic anemia occurs once in about half a million people other than those taking chloramphenicol. Among those taking chloramphenicol the rate for those taking a 5-gram total dose was about 1 in 40,000; a 7½-gram total dose, 1 in 25,000.

While these rates were low, it should be noted that the doses were also quite low. As a matter of fact, the package insert recommends 50 to 100 milligrams per kilogram per day. Most adults weigh 50 to 70 kilograms, so the recommended dose is from 3 to 6 grams. This obviously means that most of the patients in the California study were treated with ineffectual drug levels.

There is no good evidence in the literature that bacterial diseases will respond to doses lower than those recommended, although the rickettsial diseases will respond to as low as 25 milligrams per kilogram in short courses. So they will respond to a total dose of something like 10 grams, 2 grams a day for 5 days, in a medium-sized adult.

However, typhoid fever was shown not to respond to less than 50 milligrams per kilo per day, or a 3-to-4-gram-a-day dose. These are the only diseases in which they are a really good study on a dose effect curve for a disease.

Mr. GORDON. I note in the publication from California, the report to the California State Assembly, dated January 1, 1967, in table 16 in the back, it says that the estimated mean grams of chloramphenicol received per patient is 9.55, 1965 to 1966. What is the significance of that particular dosage?

Dr. LEPPER. This indicates that the vast majority of patients receiving chloramphenicol get an inadequate dose for the purposes for

which it is being prescribed, and the reason this happens is clearly that the vast majority is being used in such things as the respiratory diseases, in which the condition is self-limited, or being used in the prophylactic situations which I have outlined, where the results cannot be evaluated.

In our University Research Hospital I happened to have had the opportunity to study the use of antibiotics of all kinds, several years ago. At that time, well over 50 percent of all patients receiving chloramphenicol, received 1 gram a day. One gram a day in adults should not be able to treat anything either by pharmacologic principles nor in any well substantiated study.

Now, you say, why it is used in this dosage? It is used in this dosage, I believe, because—and I agree with Dr. Best—the message has gotten across in the university hospitals that it is a dangerous drug. For some reason the message hasn't gotten across that it doesn't do any good to give a dangerous drug in small doses if it doesn't do any good for the patient.

MR. GORDON. Dr. Dameshek, although I don't recall in what connection, talked about 6 grams. Now, is that an average daily dosage?

DR. LEPPER. Six grams a day is the initial starting dose recommended for the treatment of typhoid fever. In other words, a concept of a loading dose followed by 3 to 4 grams a day, depending on the patient's size.

The dose of 100 milligrams per kilo recommended in hemophilus meningitis translated to an adult is about 7 grams a day. The child is getting a standard dose equivalent to 7 grams a day, and because he is getting it intravenously, there is less wastage as oral drug has wastage.

Consequently, he is getting a full 7 grams a day at the recommended dose and, as a matter of fact, if you use much less than this in hemophilus meningitis, you begin to lose effectiveness. So I think it is clear from the California study, that the vast majority of the patients are getting a drug at a level you can't expect to work and in spite of that you are still getting aplastic anemia.

SENATOR NELSON. Even at that low a level, it does expose the patient to the risk of aplastic anemia?

DR. LEPPER. Yes. At a rate of 1 in 20,000 to 1 in 40,000 as specified from the quote.

In fact, the most definitive evidence from the treatment of typhoid fever and hemophilus meningitis is that the dose cannot be compromised. Yet it is.

Now, there are several other blood dyscrasias that I have mentioned which are less serious, but at times fatal, and many more reversible such as agranulocytosis, thrombocytopenia, and so forth, which also occur.

Other reactions which are more related to prolonged use include neuritides causing disability such as blindness, but fortunately usually reversible. Morbidity, such as gastrointestinal upset is more common than any of these, of course.

One other serious, often fatal, reaction that is dose related is "gray sickness." This occurs only with an overdose in adults and children, but in young infants, particularly those born prematurely, in whom there is an underdeveloped detoxifying mechanism, it can occur with a standard dose. Hence, the dose must be reduced in such instances.

Other patients with diseases which damage these mechanisms, such as liver disease, also may be easily overdosed. The symptoms are those of abdominal distention, cyanosis collapse and often death in a few hours.

This has an interesting history. Its use stemmed from the broad spectrum concept and in the midfifties because of the staphylococcal outbreaks in newborn nurseries and because of the frequency of the gram negative rod gastrointestinal organisms. Mother frequently infected the infant with such organisms in different ways, like premature rupture of the membranes. Thus, many infants had infections caused by organisms which are susceptible to chloramphenicol as a general rule, and for this reason many nurseries began using chloramphenicol prophylactically in the newborn nurseries. It was finally discovered in some controlled studies, one in Los Angeles County Hospital, that there were more deaths in the chloramphenicol group than there were in the control group, and out of this, gray sickness was discovered. Thus, in fact, we were poisoning the infants in the newborn nurseries all over the country at that time with an otherwise unrecognized syndrome.

This use grew out of the concept of the broad spectrum and its prophylactic potential.

For this reason chloramphenicol by and large is not used in the newborn. Almost all the recent papers on the treatment of newborn infections with gastrointestinal organisms transmitted from the mother to the child, emphasize Kanamycin as the choice. This is a direct outgrowth of this unfavorable experience in the late fifties.

This is a drug that has great therapeutic potential, but several serious toxicities which can and continue to give much difficulty. Essentially it has an unfavorable clinical therapeutic index.

On the toxicity side, the fact that the aplastic anemia can start even after the drug has been stopped and is almost completely nonpredictable and irreversible, makes the therapeutic ratio based on death, one much less favorable than with several competitive agents, even including Kanamycin, which is a relatively toxic drug.

For example, we have summarized for teaching purposes the 25 major diseases which antibiotics have helped control in the United States, and while chloramphenicol is potentially useful in at least half of these, we listed it as the drug of choice in only three—typhoid fever, other salmonellosis, certain gram negative rod infections in well-studied situations.

This is best summarized, perhaps, by the 1966 edition of "New Drugs Evaluated by the Council on Drugs or the AMA" which says:

This drug should be used only for the treatment of typhoid fever, other salmonellosis, and infections that do not respond to less potentially dangerous agents.

That implies a trial of less potentially dangerous agents or a considerable knowledge of the ability to predict where a bacteria sensitive to chloramphenicol only is going to occur. The package insert itself has a strong similar warning, as has just been mentioned.

I might point out one thing about typhoid fever. Interestingly enough, while chloramphenicol works very well in acute typhoid fever in shortening the duration and preventing gastrointestinal hemor-

rhage and perforation, which are the two complications besides toxicity that kill, it does nothing to prevent the carrier state. The chronic typhoid carrier, which is the public health menace, is not benefited by the use of chloramphenicol. One of the big errors in the use of chloramphenicol in typhoid fever is to begin to treat a patient because he is a carrier after he has recovered from the acute illness. This will not work.

Ampicillin, probably does not work as well, as Dr. Dameshek pointed out, in acute typhoid fever works better for the carrier state, so that here we have a crossover of the drugs. So we are talking about a highly specific indication even in the typhoid area.

Senator NELSON. Do I understand you to be saying that chloramphenicol is not indicated in the carrier?

Dr. LEPPER. That is correct.

Senator NELSON. But is prescribed.

Dr. LEPPER. It is often prescribed.

Mr. GORDON. Wouldn't that qualification make Ampicillin really a drug of choice for typhoid fever?

Dr. LEPPER. I think it is quite likely that Ampicillin will be the drug of choice for the milder cases of typhoid fever. I think there is the problem. We do not understand why chloramphenicol works as well in typhoid as it does because—and we make a clear differential here—the tetracyclines are equally active in the laboratory, but they do not work as well.

This has been known, essentially, since 1949. We have never had a good explanation, as a matter of fact, still don't, because the mechanisms of action are similar and their body distributions are similar.

Mr. GORDON. In typhoid.

Dr. LEPPER. In typhoid fever. Streptomycin was very active against typhoid organisms in the laboratory. It never worked well at all. Even penicillin itself, in large doses, did not work as well as one would think from the laboratory data. There is some problem in typhoid about the intracellular parasitism of the organism that apparently chloramphenicol overcomes better than the other agents.

In a highly toxic, severely ill typhoid, it is quite likely that one would still use chloramphenicol.

Its use in the other Salmonellosis is not as well proven. It has been used as Dr. Best pointed out—when he said paratyphoid fever, he was talking about some of the other salmonellosis. In the other Salmonella, the actual documentation of chloramphenicol effectiveness is not clear because without drugs the diseases are so variable and infrequent. There are no good studies documenting the dose-effect curve similar to those that we have for typhoid fever.

There is only one condition in which its activity seems sufficiently unrivaled to use without extensive prior laboratory study. That is typhoid fever. Here even the new and less toxic penicillin derivations do not seem as effective. Hemophilus influenza meningitis is another disease for which some will make a case, and this is particularly true of the pediatricians, and stems from the fact that at the time chloramphenicol was introduced it was studied mainly in pediatric clinics and tetracyclines were being studied concurrently in adult clinics.

However, Ampicillin has come on the scene and this is as effective in the hands, at least, of the group working in the Los Angeles County

Hospital, and it does seem to be an equal alternative. Therefore using the criteria of the package inserts would be the drug in choice.

I might say parenthetically, in our own study of about 800 of these patients over a period of about 10 years at the contagious diseases hospital in Chicago, tetracycline appropriately used was also equally good in an alternate case series, 400 chloramphenicol patients and 400 tetracycline patients, with less than 2 percent death rate in each group. As a matter of fact, we went one period with 180 consecutive cases treated with tetracycline without a death.

We feel tetracycline is a competitive drug in this area and also less toxic. The vast majority of the pediatric community do not feel this way.

Senator NELSON. The vast majority of the pediatricians do not feel that way? On what do they base their opinion?

Dr. LEPPER. Mainly, I think, the historic—what happened was that hemophilus influenza meningitis in the late forties was being treated with a combination of antiserums, sulfanomides, and streptomycin.

The death rate with these procedures was between 25 and 50 percent. Both tetracycline and chloramphenicol lowered the death rate to less than 5 percent, practically overnight.

This was so dramatic that, depending on which drug you used, you went on the stump for it. It so happens that the leading individual, a very fine person who worked with meningitis all her life, studied chloramphenicol and saturated the pediatric community that this was the drug of choice, and indeed this was very important because people were still using the streptomycin, the sulfanomides and antiserum.

This message had to get across. It has continued to plague us because it has never been really challenged except by our tetracycline data and the Ampicillin data available from the group in California. This is a problem of how do you get communication to change prior teaching.

In many of the infections in which it is potentially effective, such as pneumococcic, streptococcic, and so forth, it has never been shown to be as good as other less toxic agents.

This failure to demonstrate it in part is perhaps because there has been a reluctance to use it by investigators because of the known toxicity. Failure has been observed by us frequently enough to feel that it is actually inferior.

In rheumatic fever prophylaxis the tetracyclines are clearly inferior to penicillin and there is no reason to think that chloramphenicol will not be equally inferior.

One of the major reasons for treating respiratory infections in children is that they may have streptococcal infections and they may therefore get rheumatic fever. Prevention of rheumatic fever is one of the major reasons for using antibiotics, going all the way back to the sulfanomides which did not work well.

It is quite likely from the tetracycline data, that chloramphenicol does not work well in this regard, so if there is any justification for giving antibiotics to children with respiratory diseases fairly indiscriminately, this one specific indication, most important reason for using them, doesn't hold for chloramphenicol.

For an ad like the one Dr. Best referred to, "use certain respiratory infections," undoubtedly if you challenge the basis for this it is these

peculiar hospital infections we talked about caused by the gram negative rods. It implies perhaps certain very seriously ill people with pneumonia should get this. Most of these are caused by pneumococci. If you give chloramphenicol plus penicillin, which is a very common thing to do, it is quite likely that you may antagonize the activity of the penicillin, so you really get less effect in these patients than you would with penicillin alone.

There is a very small group of *Klebsiella* infections which are enteric organisms that occur particularly among the alcoholic patients as a primary pneumonia acquired outside the hospital. These we can usually pick out and they are picked out regularly by an initial smear examination of the sputum, on the basis of the staining characteristics of the organism. The relative merits of tetracycline and chloramphenicol is not settled in these cases. Unfortunately, neither works very well. Thus, chloramphenicol rarely, if ever, is indicated in respiratory infections.

In staphylococcal disease, during the late 1950's, there was a time when it was competitive drug. The major drugs, penicillin, tetracycline, and to a certain extent erythromycin, lost their effectiveness essential due to overuse and inbreeding of the resistant organisms. They were not chloramphenicol because its use had been somewhat restrained by aplastic anemia reports in the midfifties, had a marked resurgence in the late fifties because of the staphylococcal problem. I already indicated this led to its use in newborn nurseries, and the discovery of gray sickness.

It also was used extensively in the 1957 influenza epidemic. Here, the real deficit of the drug as a competitive drug with really good antistaphylococcal antibiotics was shown by fairly high failure rates in postinfluenza staphylococcal pneumonia. It is just not as active a drug as the new penicillins.

So, I think this is a historic use, that it is no longer a current indication.

There are many gram negative rod infections in which the drug probably is as good as others, but there are few in which there is not a better alternative, and this gets back to this statement that we should only use it when we know it is better than the others. And there are very few such situations.

Because of its broad range of activity, it is often turned to in seriously ill persons before the organism is known. And Dr. Best did refer to this use. This, in my opinion, is a mistake since one can usually make a reasonable diagnosis and often another drug is clearly preferable when you make that reasonable diagnosis.

For instance, it is difficult in the leukemia patient to differentiate between staphylococcal disease on the one hand and these gram negative rods on the other. Usually one can get enough information from microscopic examinations of smears, medical history and examination, and the nature of the portal of entry to get some idea of what is going on.

If you can't do that, and this is particularly true in persons who seem to have "septic" shock, that is, shock associated with an infection, and these are often caused by gram negative rods, you have to pick empirically. Some very good people have studied this syndrome and

recommend this drug. It is, however, bacteriostatic or less rapidly active than Kanamycin.

The latter is also toxic, but is easier to control if careful attention is given to urine output and total dose. If one were clearly to enforce and follow the requirements of the package insert, that it be shown to be the only active agent, it would not be possible to use it this way because it requires much more study of the patient than can be given in these shock situations.

Now, this is one area in which I am sure one can find a good counter-argument about whether chloramphenicol should be used or whether Kanamycin should be used.

I happen to belong to the school of thought that Kanamycin is the preferable drug because it is even a little broader than chloramphenicol in its activity, that only about 85 percent of the organisms in this kind of patient will respond to chloramphenicol, and 95 percent will respond to Kanamycin in the laboratory. At the clinical level, because they are critically ill patients, only a handful actually recover, regardless of what you use, but this is still a difference based on laboratory criteria that favors Kanamycin when one has to make an empiric choice.

Unfortunately, the advertising engendered aura about the broad spectrum concept, and this has come about from a wide variety of these not only for chloramphenicol but for the tetracyclines. All these ads essentially say is if a drug kills a wide enough variety of organisms you don't really have to worry about what you have. This is the broad spectrum concept, and it has led to a wholesale use of a wide variety of these drugs, including chloramphenicol, in a variety of minor respiratory infections, in which none of these should be used.

The package insert clearly states that chloramphenicol should not be used this way, yet, because of this miseducation of earlier years, this use is still extensive. In fact, since there are few, if any, indications for this drug outside of the hospital, if the AMA recommendations are followed, it might be wise to restrict it only to hospital use.

I might dilate a little.

I would favor this method of control for several reasons. Granted, there is overuse in the hospital, and I have already documented, I believe, a considerable amount of overuse in the hospital. On the other hand, the overuse in the hospital can be studied. It can be answered progressively as many of our other problems in the hospital because the physician group in the hospital by the nature of hospital accreditation is a self-disciplining organization and it has many of the characteristics, many of the learned professions have for internal self-discipline.

Actually, we control, for instance, the frequency of cesarean sections this way, in which if a hospital upon accreditation examination is found to have twice the usual number, questions are really asked. What are the indications? What is the control in your hospital? If you don't have adequate control, you lose your accreditation.

It is an intraprofessional discipline. Now, I am sure if we restricted the use of chloramphenicol to the hospital, while it will increase paperwork, and as a hospital administrator I have always felt that some day I will be crushed in a paper avalanche, I think the paperwork in this case is worth it. I believe the paperwork would lead the Joint Com-

mission teams to ask, "How much chloramphenicol is used in your hospital?"

If it seems excessive, what kind of control is the staff exerting on the use of this? What is the average dose of chloramphenicol? Are the vast majority of the patients getting one gram a day, for instance? A totally inadequate level?

So I think restricting to the hospital would, by taking out of the community, do away with a lot of the repeated use that Dr. Dameshek has emphasized, and which I agree is an important factor. It would also allow a sequential control of its overuse and a more precise definition of unagreed upon recommendations like septic shock and a better evaluation of where, precisely, this drug should be used.

Senator NELSON. Are all the cases where chloramphenicol would be indicated cases of patients which ought to be hospitalized anyway?

Dr. LEPPER. Yes. I know of no real indication—you might say, well, how about some of the urinary tract infections? Now, urinary tract infections come in two groups, those acquired in the hospital which are often due to a multitude of organisms resistant to antibiotics because they are acquired in the hospital where the antibiotics are being used extensively, and chloramphenicol may be what looks like the best drug for some of these.

A very small percentage, I might add, because there are more agents for treatment of urinary tract infections because in the nature of the concentrating mechanism of the kidney, than there are for treatment in systemic infections. The second group, the vast majority, are acquired in the community. Over 90 percent of the ones acquired in the community respond to a drug like the sulfanomides, as Dr. Kass has clearly shown in his studies of urinary infections of the young pregnant female.

Of the remainder, almost all of them will respond to nitrofurantoin—furadantine—so it is certainly less than 1 percent of the community-acquired infections which may need chloramphenicol. When it is used for a recurring bladder infection, it is just totally unacceptable by any standards. These infections are not serious enough to warrant it.

So I know of no definite indication for out-of-hospital use.

When you talk about serious pneumonias, such as those following surgical procedures and inhalation therapy, we have mentioned, clearly they should be in the hospital. Bloodstream infections should, also.

When you talk of typhoid fever, they should go into the hospital.

So, certainly meningitis should be in the hospital.

When you look at the cases that are mentioned by the AMA specifically, and which we teach the medical students specifically, there are essentially no home indications for this drug.

Finally, another statement fostered by the advertisements of several years ago was that resistance was not a problem. We have concrete evidence that resistance in gram negative rods and staphylococci appear almost immediately in patients receiving this drug and spread to others on the ward within 36 hours of giving the agent to as few as 15 percent of the patients on a ward. This, of course, is the big problem with prophylactic therapy.

The recent description of extrachromosomal mechanisms of resistance, that is, the most recent mechanisms which explain how or-

ganisms get resistant—they have standard genes and extra parts of genetic material which are easily transmitted between organisms that allow the build-up of these populations of resistant organisms. These studies show that chloramphenicol resistance is commonly mediated by this mechanism. And this means, of course, chloramphenicol resistance is potentially a serious problem, and indeed has been so documented recently.

In short, it is likely that this is one of the most overused and poorly used drugs in the antibacterial armamentarium, in spite of the warnings by the AMA council and the package insert.

My reaction, then, is that if you ask whether warnings have been adequate, I would say they, by all criteria, looking at what has happened, have not been adequate.

Senator NELSON. Both Dr. Best and Dr. Dameshek made what they said was a guess about the percentage of patients who receive chloramphenicol in cases in which it was clearly indicated out of the total number of patients who are given the drug? Do you have a guess of your own about that?

Dr. LEPPER. Yes. My guess, of course, gets back to this idea of absolute indications and relative indications. I would think if we stuck to the absolute indications, if we take the AMA council's absolute indications, salmonella infections that are serious enough to treat, which is mainly typhoid fever, acute typhoid fever, even if we throw in hemophilus meningitis because this is so controversial and we can call it a definite area, and then we put in septic shock, which, for instance—there were perhaps 100 in a city like Chicago in the last 5 years—and we put in some of the urinary tract infections, perhaps 1 to 5 percent, you cannot come up with a figure that is much greater than 10,000 to 50,000 people.

Senator NELSON. You come up with a figure of what?

Dr. LEPPER. Between 10,000 and 50,000 people, and this is a relatively generous estimate in my opinion. I think if you ask me if I were doing all of the ordering, how many would you use it in, I would probably use it in less than 10,000 people a year.

Now, I will grant that statements such as using evidence of failure of other drugs, less toxic drugs, and you get into the problem of kanamycin toxicity versus chloramphenicol toxicity, you could increase this, but I don't believe you would get it over 100,000, no matter how you tried to increase it.

Senator NELSON. Well, if the figure is even roughly correct that the drug is being prescribed for somewhere around 3½ million people, this is certainly a fantastic overprescription of chloromycetin, isn't it?

Dr. LEPPER. I think—I certainly concur in this. This has been a great source of concern to some of us, at least. One must realize, however, that we may be talking about two kinds of overuse. It is quite likely that the antibiotic overuse is greater than 50 percent for all antibiotics. In fact, because of the respiratory problem and the relatively few indications in the respiratory diseases, it is quite likely that we are talking about a four- or five-fold overuse for the entire antibiotic field, and then you talk about misuse within that remaining, you obviously have a very big overuse factor.

Senator NELSON. You heard the testimony of Dr. Dameshek in which he expressed his concern about the need to find some method to control the use of the drug, or at least of assuring that this drug wouldn't continue to be overprescribed.

Is it your view that the situation is so serious that some method ought to be developed?

Dr. LEPPER. Yes, I think it clearly is, as I made recommendation to restrict it to hospitals because when we have introduced some new drugs in recent years they have been originally restricted to hospitals. It has been fairly easy to prevent them, then, from becoming used for any more than some specific indications. We have never, to my knowledge, gone the other direction to restrict an old drug back to the use in the hospital.

However, this would certainly get around the massive overuse in respiratory infections in the community and the massive overuse in urinary tract infections in the community, which happen to be the two most common infections in the community.

It would also then allow us, as I say, to develop control mechanisms within the hospital as to what is a reasonable level of utilization such as we have for caesarian sections or therapeutic abortions, or other kinds of controversial procedures. In these the hospitals have very similar rates, and if some hospital has excessive use, it becomes quite apparent to the accreditators that there is something different going on here.

Senator NELSON. You mentioned that some drugs have been restricted to hospital use. Which drugs were you referring to?

Dr. LEPPER. Well, I think vancomycin was one such drug that was introduced for the staphylococcal problem, which was marketed only to the hospital pharmacists. It was not put on the general market.

Senator NELSON. Was that a result of a regulation by FDA or was that a self-imposed restriction on the part of the manufacturer?

Dr. LEPPER. I believe this was an era, sir—I am not awfully sure of the legal aspects—I believe there was an era in which new drugs were released sequentially by FDA for hospital use, followed by general community use, and some of the drug got as far as hospital use and were never released further for several reasons.

Vancomycin specifically could only be given intravenously, and therefore was not a very competitive drug in the community, and I don't believe it then got past being released for use outside the hospital.

I believe, however, FDA did have that legal authority of approving drugs for use at one point along the way. I do know there has been a tremendous body of literature, talking about restricting drugs to hospitals on a voluntary basis, and this was done successfully in Australia with erythromycin when the staphylococcal problem was so bad and they wanted to try to keep an overuse of this drug from occurring. That is, try to limit it to staphylococcal diseases so you wouldn't lose its effectiveness.

This was somewhat successful in Australia for a period of about 2 years in the midfifties. In this country there was some talk about doing the same thing with erythromycin. It never happened on a voluntary basis.

Senator NELSON. Thank you very much for your very valuable contribution to the hearings, Doctor. We appreciate your taking the time to come here today.

Dr. LEPPER. My pleasure.

Senator NELSON. That will conclude the hearings until 10 o'clock on Thursday morning. I might ask, before you go, did either you, Dr. Dameshek, or you, Dr. Best, have any observations you wanted to add to anybody else's testimony?

Dr. BEST. No, thank you.

Dr. DAMESHEK. No.

Senator NELSON. Thank you very much.

(Whereupon, at 1:25 p.m., the subcommittee adjourned, to reconvene at 10 a.m., on Thursday, February 8, 1968.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, FEBRUARY 8, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Our first witness this morning is Dr. James Weston, Utah State medical examiner.

Dr. Weston, the committee appreciates very much your taking the time to come here today.

I have studied your testimony and know that it will be a very valuable contribution to the record we are compiling with respect to a number of subjects involving the drug industry. You may proceed to present your statement in any way you wish.

At such places in your statement where you would wish to elaborate in a way that would be helpful to understanding in the record, we would be glad to have you do so. I realize that if you wrote all the detail that you knew about any particular subject you would have a much longer statement than you might be willing to spend the time to prepare.

But some elaboration would be helpful for the record in those cases where you would like to extemporize and explain in more detail any aspect of your statement. I assume you would have no objection if we should interrupt from time to time with a question?

Dr. WESTON. No, sir.

Senator NELSON. Thank you very much, Doctor.

STATEMENT OF DR. JAMES T. WESTON, STATE MEDICAL EXAMINER, UTAH STATE DIVISION OF HEALTH, SALT LAKE CITY, UTAH

Dr. WESTON. Do you desire that I read the entire statement into the record?

Senator NELSON. That is probably the best way to proceed, unless you would prefer otherwise.

Dr. WESTON. No; this is fine.

Senator NELSON. Then when you arrive at some point in your statement where you would like to elaborate, feel perfectly free to do so.

Did you submit a biography for the committee?

Dr. WESTON. Yes; I believe it is attached.

Senator NELSON. Your biographical data will be printed in full in the record preceding your statement, but if you wanted to make a brief summary of what your credentials are and what your present position is, go ahead.

(The biographical sketch of Dr. Weston follows:)

CURRICULUM VITAE—JAMES T. WESTON, M.D.

Born : Newark, New Jersey, 1924.

Family : Wife, Deon James Weston, and 2 children, Debra Deon, nee 1956, and Christopher James, nee 1959.

Education :

Premedical Education : Cornell University 1942-44.

Medical Education : Cornell University Medical College, M.D., 1948.

Postgraduate Training :

Internship : Children's Hospital, Boston, Mass., 1948-49.

Residency : U.S. Naval Hospital, San Diego, Calif., 1951-52.

Fellowship : Memorial Center for Cancer and Allied Diseases, New York City, New York, 1953-54.

Military Experience :

Lieutenant, Medical Corps, U.S. Naval Reserve, 1949-52.

Pathologist, U.S. Naval Hospital, Key West, Fla., 1949-50.

Field Duty, Korean Theatre, 1950-51.

Lieutenant Commander, Medical Corps, U.S. Naval Reserve, currently.

Professional Experience :

Chief of Medical Division, San Diego, Calif., Coroner's Office, 1954-61.

Associate Pathologist, San Diego County General Hospital, 1956-61.

Associate Pathologist, Chula Vista Community Hospital, Chula Vista, California, 1959-61.

Assistant Medical Examiner, City of Philadelphia, Pa., 1961 to 1967.

Chief Medical Examiner, State of Utah, July 1967 to date.

Certification : American Board of Pathology—Anatomic Pathology, 1967.

Licensure : Physician and Surgeon :

California, September 3, 1952.

Pennsylvania, December 14, 1961.

Utah, September 1, 1967.

Membership :

Fellow : American Academy of Forensic Sciences.

Member : Utah Pathologists Association. Salt Lake County, Utah State and American Medical Associations.

Teaching Appointments :

Visiting Lecturer in Legal Medicine, Jefferson Medical College, 1962 to 1967.

Assistant Professor of Pathology, University of Utah Medical College, 1 July 1967 to date.

Current Research Interests :

Child Abuse, with a sociopathologic correlation and analysis of the pathologic findings. Currently preparing the pathology section of the comprehensive volume on the subject to be published in early 1967 by University of Chicago Press.

Single auto vehicular accidents, their cause.

Special Interests : Data Retrieval Systems and their special application in Forensic Medicine.

Community Activities :

Youth Fellowship Advisor, Wasatch Presbyterian Church.

Member-at-Large, National Council, Boy Scouts of America.

References:

G. D. Carlyle Thompson, M.D., Director of Health, State of Utah, Division of Health, 44 Medical Drive, Salt Lake City, Utah.

William H. Carnes, M.D., Professor of Pathology, University of Utah Medical College, Medical Drive, Salt Lake City, Utah.

Joseph Edward Campbell, M.D., Assistant Medical Examiner, City of Philadelphia, 13th and Wood Sts., Philadelphia, Pennsylvania.

PUBLICATIONS

Author(s)	Title	Journal reference
Britton, R. C., Weston, J. T., and Landing, B. H.	Plastic Injection Techniques in Pediatric Pathology with particular reference to Roentgenographic Study of Injected Specimens.	Am. J. Med. Museums: 31: 124-166. 1950.
Weston, J. T., and Guin, G. H.	Epithelial Atypias with Chemotherapy in 100 Acute Childhood Leukemias.	Cancer: 18: 179-186, 1955.
Weston, J. T.	Cardiac Arrest in Surgery	Proceedings of National Coroner's Association, 1959.
Do	Airway Foreign Body Fatalities in Children.	Annals of Otolaryngology, 74: 1144-1148, 1965.
Do	Forensic Pathology Slide Seminar.	Journal of Forensic Sciences (in preparation).
Do	The Pathology of Child Abuse	Chapter in book edited by Kempe, C. H., and Helfer, R. E., University of Chicago Press, 1967 (submitted for publication).

Dr. WESTON. Briefly, I am the chief medical examiner for the State of Utah, having served in the last 6 years as the assistant medical examiner in the city of Philadelphia. My education includes undergraduate and the doctor of medicine degree from Cornell University, following which I had my training in pathology at Children's Hospital in Boston, in part in the naval service, and Memorial Hospital in New York City.

My military experience includes V-12 training during the Second World War, and the Korean conflict shortly thereafter. I have served in California as the chief pathologist in the coroner's office in San Diego, and in Philadelphia, and finally where I am now in Utah. Having taught at Jefferson Medical College, and now assistant professor of pathology at the University of Utah Medical Center, I am certified by the American Medical Board of Pathology as a diplomate.

Senator NELSON. What do your duties as Utah State medical examiner involve?

Dr. WESTON. To direct the investigation and examination of all persons who are referred to us having died of suspectedly unnatural death in any form. This would include drug toxicity, which I haven't encountered in Utah yet, but saw in Philadelphia prior to going to Utah.

Senator NELSON. Thank you. Go ahead, Doctor.

Dr. WESTON. Much of, or a good part of, my statement has already been covered by Dr. Dameshek and Dr. Best. I summarized much of what they have in the literature but I will read the entire statement.

Senator NELSON. Go ahead.

Dr. WESTON. In 1948 Chloromycetin—chloramphenicol—was first put on the market by Parke, Davis & Co., as a broad-spectrum antibiotic capable of controlling infections by a large number of organisms with a very low incident of immediate side effects, such as nausea

and vomiting, and yeast or other intercurrent infections. Chloromycetin soon became a very popular, widely used drug. From 1948 to 1952 its sales rose markedly, and it has been stated by the company that over 8 million patients were treated with the drug during this period. However, reports began to come in which noted that blood dyscrasias were associated with its use. Of these blood dyscrasias, aplastic anemia was the most common. The Federal Food and Drug Administration requested that the National Research Council make an investigation into the problem and submit a report of their findings. The Council, recognizing the potential and serious toxicity of the drug recommended that the following warning be placed on the packages and in the circulars distributed with Chloromycetin.

The Federal Food and Drug Administration concurred: Warning to be placed at the top of the circular was as follows:

Certain blood dyscrasias (aplastic anemia, thrombocytopenia purpura, granulocytopenia and pancytopenia have been associated with the administration of Chloromycetin. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloromycetin should not be used indiscriminately or for minor infections.

To appear on immediate container label:

Warning: Blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made.

These warnings were subsequently placed by Parke, Davis on the appropriate packages and in the circulars enclosed with the parenteral forms of Chloromycetin, but no circulars were included in the packages containing the oral preparations.

Senator NELSON. You state that the circulars with the printed warnings were enclosed in the package forms; is that correct?

Dr. WESTON. With the form for parenteral administration, that is injected.

Senator NELSON. That is an injectible?

Dr. WESTON. Yes, sir. It was not included in the material that was distributed for oral consumption initially.

Senator NELSON. That meant that the injectibles that went directly to the doctor did have the warnings; is that correct?

Dr. WESTON. Yes, sir.

Senator NELSON. And that the packages containing the tablet form of Chloromycetin which went to the pharmacist did not, is that correct?

Dr. WESTON. That is correct.

The injectibles, of course, may have been handled by the pharmacists as an intermediary.

Senator NELSON. But even the warnings that went to the pharmacist weren't seen by the doctor anyway, is that correct?

Dr. WESTON. Not necessarily.

The ones that were packaged, some of them were put on the label proper. There are two types of warnings, one was put on the label proper, and one was put in the literature that the instructions included.

Senator NELSON. If it were an injectible, of course, it ended up in the doctor's hands for his administration, is that correct?

Dr. WESTON. Yes, sir.

Senator NELSON. If it were in tablet form, the usual procedure would be that the prescription would be written by the doctor and dispensed by the pharmacist, so the doctor does not see the package, is that not correct?

Dr. WESTON. It could well happen. I don't know how many times—he could well have not seen the warning. I have seen or have heard the statement of several doctors who said they weren't aware there was a warning put into the drug at this particular period in its chronology.

Senator NELSON. But in the ordinary procedure of prescribing, the doctor writes the prescription and, unless it is in a hospital, the patient takes it to the pharmacist. The package containing tablets now contains a warning but the doctor ordinarily does not see the drug or the package at all, unless it is administered in his office, does he?

Dr. WESTON. That is correct, yes.

Immediately following this announcement by the Federal Food and Drug Administration, Parke, Davis & Co. issued "President's Letter No. 4" on August 12, 1952. Despite the obvious limitations placed on the use of the drug by the warning, the statement was made in this letter, over the signature of the president of Parke, Davis & Co., that Chloromycetin had been "officially cleared by the Federal Food and Drug Administration and the National Research Council with no restrictions" on its use. In an open letter, published in the Journal of the American Medical Association, in August of 1952, Parke, Davis & Co. stated that the above warning would be included in all their Chloromycetin literature in the future. However, from 1952 to 1961, the advertising for Chloromycetin contained only the following words: I will comment on these after I read the warning:

Chloromycetin is a potent therapeutic agent, and because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections.

Furthermore—

And it is stated right in its warning—

as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

Senator NELSON. When it says adequate blood studies should be made if a patient requires prolonged or intermittent therapy, what is your judgment as to what blood studies should be made? That is, should they always be made when chloroamphenicol is administered or only under certain circumstances?

Dr. WESTON. Well, let me bring into text the chronology of this thing.

At this particular time they were not aware of the fact that a single, as little as 1 gram of chloromycetin would have caused the dyscrasias. This pretty much became apparent later on in the history. Of course, now we know that with 1 gram of Chloromycetin there may not be an alteration in the bone marrow. On the other hand, there may well be an alteration in the bone marrow and actually, practically speaking, there is no way of detecting this if you want to be strictly honest about it. However, with prolonged therapy you may see a morphological alteration in the bone marrow. I am sure Dr. Dameshek testified to this,

and a certain percentage of the cases will go on to develop aplastic anemia or other dyscrasia.

Senator NELSON. Regardless of the fact that you may not be able to discover any bone marrow problem from blood studies, should blood studies always be made when chloroamphenicol is administered?

Dr. WESTON. Always be made.

Senator NELSON. Always be made.

Dr. WESTON. Yes, sir.

Senator NELSON. Regardless of whether one dose or several doses are given?

Dr. WESTON. That is correct.

This warning did not begin with words of caution but with a glowing tribute to the efficacy of the drug. Also the types of bone marrow dyscrasias involved were not enumerated as they were by the Federal Food and Drug Administration. Further, the words "it is essential" were deleted, detracting from the emphasis on the requirement for blood tests and the expression "as with certain other drugs" was added, thereby equilibrating the toxicity of Chloromycetin to that of other, unnamed medications. The Parke, Davis warning was not, at this time, placed at the top or beginning of this literature but was placed well down in the writing and often in small print. Witnesses in at least one malpractice action have testified that the Parke, Davis warning was no different from the warnings on many other drugs which led them to use Chloromycetin freely and without reservation.¹ This refers to the *Incollingo v. Ewing, Parke, Davis and Cucinotta* trial in which I appeared in the Philadelphia court, in which Dr. McGehee was present as a hematologist expert and he not only testified to the fact that this had quite a contrary effect on the warning, it was equated with what one might anticipate with the sulfonimides, aspirin and a variety of common household medications which were used quite commonly, and to see it put in that same wastebasket was, in effect, saying that you are dealing with a drug which only very occasionally will give you an untoward reaction.

I will cover more of Dr. McGehee's other testimony as we get on in the statement.

Following the issuance of the FDA warning, the sales of Chloromycetin dropped precipitously. However, by 1960, sales of the drug reached a level even greater than that of its peak years in the early 1950's. This resurgence was due in large part to the promotional efforts put forth by Parke, Davis & Co. through its advertising and detail men. This vigorous overpromotion was made despite the well-documented toxicity of the drug, by this time. Chloromycetin, it was urged, was still the most effective antibiotic in a wide variety of infections, with minimal side effects. The Parke, Davis campaign to bring Chloromycetin back into widespread use for a multiplicity of clinical conditions was evidenced very early. In November of 1952, just 4 months after the FDA warning requirement was issued, a letter was sent from the sales department of Parke, Davis to its professional sales staff. Included with the letter were "suggested details" and "ideas and suggestions" for promoting the use of Chloromycetin to physicians.

¹ *Incollingo v. Ewing, Parke Davis and Cucinotta*, Philadelphia Court of Common Pleas No. 6, December Term, 1961, No. 3248.

The statements which follow were made under the heading "approaches to be used in detailing the drug."

These are not taken as they might appear out of text. They are actually quotes of entire paragraphs within the text of these suggested details.

Intensive investigation by the Food and Drug Administration, carried on with the assistance of a special committee of eminent specialists appointed by the National Research Council, resulted in unqualified sanction of continued use of Chloromycetin for all conditions in which it had previously been used.

Senator NELSON. That, of course, is not an accurate statement, is it?

Dr. WESTON. Absolutely not.

Senator NELSON. Because the sanction for continued use given by the Council was very qualified.

Dr. WESTON. It was very qualified and the warning was elaborated on even more in the second warning.

A sensible caution against indiscriminate use, which we have incorporated into our advertising and labeling, is a welcome addition to our literature and to the label on Chloromycetin products, and in our opinion, would be appropriate in those on any potent chemotherapeutic agent. Actually, such caution is an assurance that the full benefits of well-tolerated Chloromycetin will be available and free from misuse.

Here again, it implies that Parke-Davis themselves were responsible for putting this on, and again it equates the toxicity of Chloromycetin with some of the other antibiotics.

Quote No. 3:

Are the broad-spectrum antibiotics important factors in the incidence of blood dyscrasias? Of course, it is logical to use Chloromycetin as an example, because it has been the subject of intensive and thorough investigation.

This is quite a while after first reports of some blood dyscrasias with some of the other antibiotics which had not been investigated as intensively, but in which the incidence was of a much smaller magnitude than this drug.

We ask for open-mindedness in approaching this subject (of drug induced blood dyscrasias). We assure you that Parke-Davis will take every means possible and exhaust every possibility in attempting to get at the solution of this baffling problem of modern therapeutics, involving, obviously, not only Chloromycetin, but many other potent chemotherapeutic agents as well.

Again an equation with other antibiotics.

Before terminating this interview may I re-emphasize a fact which has not changed with the developments of the past year? Chloromycetin continues to be the outstanding wide-spectrum antibiotic because of its well-tolerated nature and its high degree of effectiveness.

Your efforts (those of sales representatives) should all be directed in a positive direction designed to provide facts which will induce physicians to use Chloromycetin in the wide range of infections in which it is effective.

Senator NELSON. As I understand it, it is effective in a wide range of infections, is it fair to say that?

Dr. WESTON. Yes; I think it is fair to say that Chloromycetin is probably as or more effective in a wider spectrum of infectious diseases than any other antibiotic available at this time.

Senator NELSON. So the apparent intent here is to persuade doctors to use it in a wide variety of infections including conditions for which, in fact, it should not be used at all, or when there is a substitute drug that may be as effective but less toxic as this one?

Dr. WESTON. That is correct.

The mechanics of this, I am sure, have probably been pointed out by some of the other experts, but in testing a patient and an organism to determine its sensitivity, one has to take from the person a culture, which is really a growth of the organism outside of the body, transplant this into an artificial media, and then attempt to grow this organism in this artificial media in the presence of the antibiotics that are available. There is an element of time entailed in this. You first have to take it out and grow it with the antibiotics and without the antibiotics, and if in its artificial media it is shown not to grow with the antibiotic, then, of course, this would be the antibiotic choice. But this does require a matter of hours, days before you can determine this. By giving an agent which is effective in virtually every infection you preclude the necessity of doing this.

Senator NELSON. Am I correct in my interpretation of the expert testimony that we have had thus far that although chloramphenicol is effective in a wide range of infections, there are a number of those infections for which, in fact, it should not be used despite the fact that it may be effective, is that correct?

Dr. WESTON. That, sir, this is true of most of them. I will come to that later on, in the vast majority of them.

Senator NELSON. In the vast majority of areas where it is effective it still should not be used, is that correct?

Dr. WESTON. That is correct.

This is quoted:

A new full-color blotter, portraying all the product forms, will be supplied to you (sales representatives) very shortly, as will a desk-top product information card. A deluxe product booklet is being made ready for the press at this time. Other promotional material is in process of preparation and will be released as soon as possible.

It should be kept in mind that the incidence of aplastic anemia is not known because statistics on this affection are incomplete and inadequate. In the survey, among those who received the estimated 8,000,000 courses of therapy of Chloromycetin, aplastic anemia is known to have appeared in 193 patients. The ratio 193: 8,000,000 gives a rate of 1.74 per 100,000 which probably is not much greater incidence than would be expected in a population of sick persons who had not received any Chloromycetin.

Senator NELSON. Considering the present knowledge available about the risk, that is not a correct statement?

Dr. WESTON. That is correct. The California study just completed establishes the most reliable statistics of what the anticipated incidence of fatal aplastic anemia would be, again taking into consideration not only registered cases but a survey of death certificates which was occasionally followed up by follow-up investigation.

Now, I should point out in all deference to my colleagues that if I were prescribing Chloromycetin for a minor respiratory infection and a year from now it became apparent that this patient developed aplastic anemia, I would be somewhat reluctant to sign a death certificate on such a case as aplastic anemia having seen at least two malpractice cases that approached \$200,000 awarded in the country in the last several years. Not only do you lose money in your insurance, but you lose patients this way. So, I think you have to view any reporting of the incidence of any untoward reaction to a drug with a rather jaundiced eye, so to speak, and realize that it really touches only a small

segment of what may actually be happening. I would not want to sensationalize it. On the other hand, I do not think saying you can see one in a thousand or one in 10,000 is a true picture. I do not think anybody really knows, but I am sure we are seeing that there is a great deal more blood dyscrasia from Chloromycetin than is reported in a voluntary register of any kind.

Mr. GORDON. Dr. Weston, the figures given in the California report, if I am not mistaken, indicate that the risk of aplastic anemia is one in 524,600 per year in California for those who have not received chloramphenicol; is that correct?

Dr. WESTON. Yes, sir.

Mr. GORDON. But the Parke, Davis instructions to the detailed men said one in, 1.74 per 100,000?

Dr. WESTON. Yes, sir.

Mr. GORDON. You have no idea where they go that figure?

Dr. WESTON. No; I do not.

Mr. GORDON. Thank you very much.

Dr. WESTON. The recent California survey reveals an incidence in 71½-gram doses of one fatal aplastic anemia in approximately 21,000.

Mr. GORDON. That is for those who take Chloromycetin?

Dr. WESTON. That is for those who take it; yes, sir.

Thus Parke, Davis & Co. sought to convince the medical profession by its advertising and detailing that Chloromycetin was the broad-spectrum antibiotic of choice, that its uses were in no way curtailed by the FDA announcement, and that the drug's toxicity was akin to that of many other drugs. The increase in sales speak for the widespread use of Chloromycetin from the late 1950's to a total sales volume within the United States in 1962 of \$37,499,733. Experts in malpractice trials have testified that the detail men of Parke, Davis were loath to discuss the bone-marrow toxicity of the drug and emphasized its effectiveness in a wide variety of clinical conditions, this includes again Dr. McGehee in *Incollingo v. Parke, Davis and Associates*. Dr. McGehee at that time was a practicing clinician, practicing internal medicine as well as hematology and was aware by virtue of his hematology experience of the untoward effects as well as in constant contact with the detail men as is any practicing physician.

Parke, Davis was highly successful in the period from 1952 to 1960 in setting the standard of care for the medical profession. However, in the late 1950's, reports of blood dyscrasias associated with Chloromycetin therapy began to multiply; and in 1961, the National Research Council was again asked to submit a report with recommendations to the Federal Food and Drug Administration. The Council, at this time, recommended that the following warning, more forceful and explicit be placed on the Chloromycetin packages and circulars:

(Immediate container label): "WARNING: Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made (see enclosed warnings and precautions.)"

And then the drug enclosure:

WARNING: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug.

This is the first instance of blood dyscrasias after short-term administration made reference to in the warning.

Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective or in treatment of trivial infections.

And I call your attention to colds

"such as colds, influenza, viral infections of the throat, or as a prophylactic agent."

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Senator NELSON. The warning says Chloromycetin should not be used for "viral infections of the throat." What about other viral upper respiratory tract infections?

Dr. WESTON. I don't believe that it has ever been indicated in any viral upper respiratory infection.

Senator NELSON. Why would this warning specify viral infections of the throat and neglect to mention all viral upper respiratory infections?

Dr. WESTON. Because it was used quite widely almost from its inception in preventing secondary infection which is a common complication of any viral infections in the upper respiratory system. In other words, the common cold, as you are probably aware, starts out probably as a virus infection. The virus attenuates the mucosa of the respiratory tree, produces an excess secretion. This, in turn, opens it up to infections by bacteria which take over in the virulent stage when your discharge changes from water into a yellowish type of discharge. Then the antibiotic could be used to prevent the secondary stage of this infection, the bacterial stage.

Senator NELSON. Has it been used prophylactically for rheumatic fever, for example?

Dr. WESTON. Oh, I think it has; yes, sir.

Not with recognition by any organized program of any kind, to my knowledge.

Senator NELSON. That is why I was curious not as to why they simply said viral infections of the throat rather than all upper respiratory infections.

Mr. GORDON. Dr. Weston, coming back to the warnings about when it shouldn't be used, Dr. Best, who testified here on Tuesday, said that this caution is not observed by all members of the medical profession.

Do you have any idea why this is so?

Dr. WESTON. I cover that later on in my statement, but I can elaborate on it right here. There are probably—if I say it now it would just be recanting what I will say later on.

Mr. GORDON. All right, we will come to it.

Dr. WESTON. Since 1962, these warnings had been on the Chloromycetin packages, in the circulars placed in both the oral and parenteral use Chloromycetin packages and in the Chloromycetin promotional literature put forth by Parke, Davis & Co. This warning has

also been boxed and placed at the head of the listing within the PDR, the Physicians' Desk Reference, and I included a sample page for illustration.² This has been consistent since this time. The type of warning which they have is exactly the same from year to year.

It is placed at the head of the listing.

Senator NELSON. What is the date of the warning on the Thermofax page of the Physicians' Desk Reference you have submitted?

Dr. WESTON. This is 1963. I checked with the latest edition and it is exactly the same.

Senator NELSON. Thank you.

Dr. WESTON. The causal relationship between Chloromycetin and blood dyscrasias, especially aplastic anemia, was clearly set out in the literature in the 1950's and 1960's. And here I make reference to Dr. Best's statement which I have included for evidence,³ which indicates that between the period 1953 and 1964 there were 408 recorded cases who were known to have received chloramphenicol during the year preceding a non-neoplastic depression of blood cell formation; of these 298 were U.S. reports, 25 were published in the literature and 273 were not, plus 110 foreign reports of which 70 were published and 40 were not. The registry also contains one United States and 65 foreign literature cases which were not covered in their review and notes that there have been additional published case reports which do not appear in any review or in the registry. I already indicated, of course, that a voluntary registry of any kind cannot be statistically considered to be of very much significance.

The accuracy of information in the registry is dependent upon the initiative of the physician in reporting such cases, evaluation of the validity of such cases and upon thorough search for such cases within the literature. This may be augmented by search within accurate statistical reporting, including review of death certificates. This was done in the California statistical report. However, as was indicated by testimony in the California Senate proceedings published in January of 1963,⁴ (1) with the Senate of the California Legislature proposing the exclusion of Chloromycetin from the therapeutic regime of physicians within their State initially, and subsequently proposing its use only in hospital admitted cases, a thorough followup of a relatively large number of cases by at least one physician has indicated that deaths subsequent to Chloromycetin therapy, which clinically and pathologically may have been due to blood dyscrasia, were masked within the statistics either intentionally or unintentionally as related blood conditions such as leukemia, spontaneous cerebral hemorrhage, or gastrointestinal hemorrhage, and, while this states unequivocally that chloramphenicol has been implicated in more reports to the registry than has any other single drug, this cannot, therefore, be quantitated to represent the total incidence of untoward reaction.

The estimated risk from exposure to Chloromycetin is statistically outlined in the following table taken from a comprehensive study of the drug by the California Department of Public Health requested

² See attachment No. 1, p. 2496, *infra*.

³ See attachment No. 2, p. 2497, *infra*.

⁴ "Particularly Chloromycetin, a Study of Antibiotic Drugs." Report of California Senate Fact-Finding Committee on Public Health and Safety, January 1963.

after their Senate investigation that I referred to before,⁵ and here in the table you can see that with an assumed average dose of 4½ grams the risk of death is one in 36,118, varying upwards to an assumed dose in grams at 7½ with a risk of death of one in 21,671.

Senator NELSON. These statistics don't indicate the length of the course of treatment; that is, how many times 4.5 grams was administered to get these results?

Dr. WESTON. No, sir; it would be impossible in this report; it is all within the complete volume. It is the most accurate statistical tabulation that I have encountered.

Senator NELSON. I see.

So these dosages may have been for a course of treatment for 10 dosages or five or any variety of number of dosages; is that correct?

Dr. WESTON. Yes, sir.

(The table referred to follows:)

ESTIMATED RISK OF DEATH FROM APLASTIC ANEMIA FOLLOWING EXPOSURE TO CHLORAMPHENICOL—
CALIFORNIA, JAN. 1, 1963, TO JUNE 30, 1964

Assumed average dose (in grams)	Risk of death		
	Within 1 year from exposure	More than 1 year from exposure	Combined
4.5.....	1 per 40,769.....	1 per 316,634.....	1 per 36,118.
5.0.....	1 per 36,692.....	1 per 284,971.....	1 per 32,507.
5.5.....	1 per 33,356.....	1 per 259,065.....	1 per 29,551.
6.0.....	1 per 30,578.....	1 per 237,476.....	1 per 27,090.
6.5.....	1 per 28,224.....	1 per 219,208.....	1 per 25,004.
7.0.....	1 per 26,206.....	1 per 203,551.....	1 per 23,219.
7.5.....	1 per 24,461.....	1 per 189,981.....	1 per 21,671.

Dr. WESTON. In addition to the damaging effect upon the bone marrow, Chloromycetin has also been implicated in producing optic neuritis, an inflammation of the optic nerve in both children and adults with resulting extensive loss of vision.⁶ This untoward effect is apparently protected by use of high doses of other agents, namely pyridoxine and cyanocobalamin, in a small series of cases.⁸

The widespread use of Chloromycetin continued to grow from 1962, when its gross sales, as enumerated above, were approximately \$39.5 million, to 1966, when the U.S. gross sales slightly exceeded \$45.5 million and sales throughout the world during the same year were slightly in excess of \$70.5 million. During this period, of which 3 years are subsequent to the widely publicized California State Senate investigation, it is apparent that physicians are continuing to prescribe this agent in spite of the warnings to the contrary which are displayed quite prominently in Parke, Davis' literature. Some responsibility for such misuse may still rest with Parke, Davis as represented by the attached reproductions, and these are taken from JAMA advertisements⁹ within the last 3 months in which, in a double-page spread, as you can see, in large print for the physician who doesn't care to read

⁵ "Fatal Aplastic Anemia and Chloramphenicol." Report to the California State Assembly and Senate by the California Medical Association and State Department of Public Health, with cooperation and assistance of the California Pharmaceutical Association, Jan. 1, 1967.

⁶ Cocke, J. G. F. L.: *Journal of Pediatrics*, vol. 68, No. 1, pp. 27-31, January 1966.

⁷ Huang, N. N. F. L.: *Journal of Pediatrics*, vol. 68, p. 27, January 1966.

⁸ Cocke, J. G.: *Amer. J. Dis. Child.* 114: 424-426, October 1967.

⁹ See attachment No. 3, p. 2506, *infra*.

the fine print, you see it indicated "When it counts Chloromycetin (chloramphenicol) can be useful in urinary tract infections." And then you have a whole page of fine print.

The same thing is true, and these are incidentally in their original advertisements, partly in color "may be indicated in certain severe respiratory infections." They carried the same list of indications and warnings within the advertisement that is published elsewhere.

Senator NELSON. In which type of severe respiratory infection is chloramphenicol indicated?

Dr. WESTON. Well, categorically I would say chloramphenicol is not indicated in any respiratory infection in which any other antibiotic which is less toxic is effective, and this is true of any infection in the body for that matter. Now, the only exception to that might be in a patient in which another antibiotic is effective, but the patient is so sensitive to the drug that you might endanger his life by administering it to him.

Senator NELSON. Well, the headings says "May be indicated in certain severe respiratory infections." There are, of course, a wide range of respiratory infections. Is there any respiratory infection itself, in addition to the one circumstance you just named, in which chloramphenicol is the drug of choice?

Dr. WESTON. Yes, sir.

Senator NELSON. There is none in which it is the drug of choice?

Dr. WESTON. No, not taking other antibiotics into consideration. They say this; I don't mean to imply that in the scope of the two-page advertisement they don't say exactly what I have said, because they do. It is in fine print, it says "Because of its wide antibacterial spectrum and its ability to diffuse into effective forms Chloromycetin may be of value in the treatment of selected severe respiratory tract infections due to susceptible microorganisms. However, as with any antibacterial agent, the administration of Chloromycetin must be adjunctive to the overall therapeutic approach to this family of diseases. Appropriately treated good results can be expected." Then they go on to say "The decision to choose Chloromycetin from a group of antibiotics suggested by in vitro studies to be potentially effective against specific and respiratory tract pathogen should be guided" by various, "by severity of infection, relative susceptibility pathogenically to the various antibacterial drugs, relative efficacy of the various drugs in this family of infections and the important additional concepts contained in the warning box." They say everything that I just said. If there is no other drug that is less toxic which can be used then use Chloromycetin, but they have put it, couched it in, quite different language than I think I expressed here. They have again equated it with the toxicity of other antibiotic drugs.

Now, I have asked myself the question many times, why has this occurred? Referring back to the continuing widespread use. I believe the reason is twofold. Chloromycetin is a very effective antibiotic which may be used to control virtually the entire spectra of infections ranging from Rickettsial diseases, which include Scrub Typhus, Murine and Epidemic Typhus, Rickettsiapox and Rocky Mountain Spotted Fever, and most of the gram negative and gram positive diseases in between. But as I indicated previously most of these infections, and

all of them at the present time, can be controlled by other antibiotics which do not have this toxic effect. It is also as effective in treating gram negative and gram positive organisms, including *Hemophilis influenza*, an organism responsible for an extremely dangerous, previously quite uniformly fatal meningitis in the newborn and neonatal age group. Until quite recently, within the last two and a half, to 3 years there is no question but that if you suspected *Hemophilis influenza* meningitis in the newborn age group, Chloromycetin was the drug of choice and it was used quite commonly in a triple-shot type of treatment where it was combined with streptomycin and other antibiotics to treat this disease. This was done in infants who were severely ill, quite often even without the benefit of cultures of any kind because you had little time to treat them in this state of their illness.

Senator NELSON. Is there now another drug as effective?

Dr. WESTON. Yes, I believe, Ampicillin which has been on market two and a half to three years, somewhat in that period of time, has now been demonstrated to be as effective, if not more effective, in treating *Hemophilis influenza* infections. Ampicillin is being combined usually in a triple medication form remembering there is not the opportunity for a culture, and consequently, you might be treating *Hemophilis influenza*, you might be treating some other type of meningitis, you are not sure, but they don't wait ordinarily to determine what the organism is.

Senator NELSON. Well, the fact that it is known to be effective in a wide spectrum of infections may account for its being very frequently prescribed. But it seems to me that some other factor accounts for the fact that it is used prophylactically for the trivial infections. Testimony before this committee has been that it should never be used prophylactically. The fact is that it has been used for treating acne, minor infections of the gum; it has been used for head colds. In fact, Doctor, one of the doctors testifying yesterday pointed out a case of a lady who was, given cholarmphenicol and was told that whenever she had a head cold to take some. She developed aplastic anemia. Well, the fact that it is effective against this wide range of conditions doesn't account for this kind of indiscriminate prescribing, it seems to me.

Dr. WESTON. No, sir.

Senator NELSON. It just has to be that the doctors who are prescribing Chloromycetin in this way, it seems to me, can't be aware of what they are really doing.

Dr. WESTON. No, sir.

Let me give you a little personal experience. The day the telegram came in from the FDA recalling the 30-odd different products which had been shown to be absorbed and excreted at a slightly slower rate than the Parke-Davis preparation, I called attention to my secretary and said "Well, it looks like they might be starting to control the use of Chloromycetin; I sure hope they do." And she said "What do you mean?" And I said, "Well, I wouldn't want to give Chloromycetin to my child and I don't know any doctor who would give Chloromycetin to his child." She said, "Well, my son just got through taking it for 3 days," and I said, "Your son, for what?" "For flu," she said, and I said, "You mean your son just got through taking this?" And she said, "Yes, positively." And I went to the druggist that evening, unan-

nounced, without telling anybody who I was and said "Have you had an increase in the sales of antibiotics including Chloromycetin in the last 3 weeks," because in Utah we have had continued publicity about flu although we haven't documented it in any of our laboratories accurately yet, and he said, "Yes, we have had a marked increase in all antibiotics and we have this usually, seasonally, including Chloromycetin."

So there is no question; there never has been any question in my mind, but that it has been used indiscriminately, and this is an example of a lay person working in a medical center, who had no idea of the degree of toxicity.

I have read quite a bit in the California proceeding, I am sure you have already considered putting something on the prescription package which actually ultimately wound up in the hands of the patient telling them that they were taking a drug which might cause serious reaction, and I feel perhaps, as most of the doctors do, that this is unwise because there may be a patient, possibly one in a million, I don't know how many it would be, who may have to have this drug who is allergic to tetracycline, Ampicillin, or one of the other drugs and is in a life-threatening situation and if she were to receive this particular drug with a warning "This might kill you, it may depress your bone marrow, or it may do something else," I am sure I wouldn't want to take the drug and perhaps she wouldn't want to and yet it might, in that particular instance, be the agent of choice. So I am inclined to agree with the physicians, if there is going to be a warning, or if there is going to be restriction on its use, the restriction should lie with the person who prescribes it, not with the advertisement on the material to the patient themselves, although this was considered at some length in the California hearings which you probably are aware of.

Senator NELSON. Well, I am still puzzled about the explanation for the widespread prescribing of this drug for minor infections. It seems to me, since it is perfectly clear from the law suits that have already been tried, that the doctors are liable for prescribing it for a minor infection. The only logical conclusion, it would seem is that the doctor prescribing it really isn't aware of the caution that should be used with this drug. I can't come to any other conclusion.

Dr. WESTON. Well, in my field I deal a great deal with human behavior, working with things other than drugs, motivations, reason for automobile accidents and related accidents, and I would say that there is a widespread feeling, not only in physicians, but people in general that this won't happen to me, and this is really, in my estimation, the crux of the thing.

I can't believe there are enough physicians uninformed about Chloromycetin today with what has been in the literature, including at least three editorial comments from the council on drugs in the JAMA, which have covered a full page. The Senate hearings in California were quite widely publicized and I can't believe that the doctor is that uninformed. He may well be, but I think that—I would have to conclude that part of the responsibility at this point rests with the doctor. I can't blame it all on Parke-Davis, because he has to open the PDR, he has undoubtedly received samples from Parke-Davis, and warnings in the literature with the material. When a doctor gets up in a malprac-

tice trial today and states he has never heard of a warning on Chloromycetin then I would have to say I didn't believe him.

You will find the same thing true with alcohol in motor vehicle accidents. I am sure that you will find most experts will tell you that alcohol is present in 50 percent or greater of people who are killed in motor vehicle accidents if they are drivers, but this doesn't stop people from drinking and driving. This can't happen to me. This is a concept basically ingrained in human motivation. And I think it is one that has to be considered when we are talking about something which occurs 1 in 24,000 times.

Mr. GORDON. But, Dr. Weston, a doctor can't say "This can't happen to me." He is prescribing it for somebody else.

Dr. WESTON. No, this is interesting. I went to 12 doctors in the University of Utah before I left and I said "Do you prescribe Chloromycetin for your children?" And I didn't find one who said yes, they do. On the other hand, in that medical center complex I didn't find any that prescribed Chloromycetin for anybody.

Senator NELSON. You didn't find any physician who prescribed it for anybody?

Dr. WESTON. For anybody for anything at this point, no, sir. This is, of course, in a university setting which is different from what you find in a physician on the street corner, but I couldn't find anyone who thought it was indicated for any condition.

Senator NELSON. Well, that is why it seems to me your explanation isn't really very satisfactory because here are doctors at a university teaching hospital who really know apparently what chloramphenicol is all about, and they don't say "Well, it can't happen to me." So if the doctors who in that setting don't prescribe it, then how do you explain why doctors outside that setting will say "I know what it is all about, but it can't happen to me."

Dr. WESTON. Well, I think you have to understand the spectrum of medical knowledge. At one extreme you have the university setting and at the opposite extreme you have the physician who hardly reads the Journal from one year to the next, practicing medicine, seeing 40 or 50 patients a day in his office and this physician is not going to read much more than the big print in this ad. This is the drug of choice, that is it. He hardly will get to the small print on the second page and I am sure he won't get very far in two paragraphs or a full page in small print like that in an advertisement.

I think this is the crux of the thing. They don't understand what the toxic potentiality is.

Senator NELSON. That is what I was getting at. It is more out of ignorance, then, that it is prescribed, at least in minor infections where it is clearly not indicated and in cases where there is clearly an effective alternative. It must be ignorance rather than feeling, "Well, it only happens 1 in 24,000 times, and therefore, it is not much of a risk," don't you think?

Dr. WESTON. Yes, but this type of ignorance is inexcusable. When I say the doctor can't be held blameless, I mean that I think this type of ignorance today in medical practice is inexcusable. I think a physician has a certain obligation to overcome this degree of ignorance. If he is going to prescribe a drug he has an obligation to his patients

to insure himself that this drug does not have a risk beyond a certain potential. This is the drug of choice, so to speak. I don't think you can excuse him by saying he is ignorant today.

Senator NELSON. I don't say there is any excuse for that, but I say that ignorance on the part of the physician would appear to me to be the best explanation thus far. We had testimony recently, as you are aware, from three distinguished doctors on chloromycetin. I asked them to estimate what percentage of the patients who receive chloramphenicol should actually receive it. All three said it would be a guess on their part, but they were in agreement that the drug was way overprescribed, and their guess would be that around 90 percent of the people who received it should not have received it at all.

Dr. WESTON. Yes, I think it is higher than that. I don't think that even 90 percent of the people should have received it. I think it is probably indicated today in less than 1 percent of the people that received it.

Senator NELSON. In other words, in less than 1 percent of the cases in which chloramphenicol was prescribed it was in fact indicated?

Dr. WESTON. Yes, sir. Now, you have got to take it almost year for year, remembering that during certain periods there is no question but that it was the drug of choice in certain conditions. Then other antibiotics came onto the scene. That is why any legislation or any attempt to control it has to take into consideration what is going on with all the antibiotics at any one time.

Senator NELSON. Obviously, then, there is a vast amount of overprescription of this drug. Three recent witnesses thought that not more than 10 percent of those who receive the drug should receive it and you think not more than 1 percent. On balance, then, what is your judgment as to how much good this drug has done versus how much harm it has done?

Dr. WESTON. Well, there are several ways of equating this. If you take as positive indications what was a positive indication, there are some things you will have to say you do not know, but if you take on the positive side of the ledger those things for which it was positively indicated until the advent of tetracycline and Ampicillin, you would be dealing pretty much with *Salmonella* infections, rickettsial infections, and other infections in which the patient is either sensitive or in which the micro-organism is resistant to the antibiotic, this is the thing. You cannot throw in any type of formula because they did not run a culture to begin with, so you do not know whether the organism would have been sensitive to penicillin or streptomycin or sulfanamide or in the wider spectrum one of the other antibiotics at that time.

On the other hand, if you want to take 300-some-odd cases of typhoid that occur in a year, between 100 and 200 cases of rickettsial diseases, and figure that every one of those would be fatal if it had not been treated, then figured out on the basis of that, and take Parke, Davis' own figures in terms of grams and divide them up into five-gram doses, using California statistics which I firmly believe are the most accurate as far as the incidence of fatal blood dyscrasia, you would wind up with somewhere in the neighborhood of 2,250 people on a four and a half gram dosage who would have an untoward—a fatal blood dyscrasia in a year from Chloromycetin as contrasted with 500

or 600 who would die from rickettsial or Salmonella infection. So, I do not think there is any question but what they have done more harm than they have good with Chloromycetin just in this country, and, of course, you get outside of this country and you have an entirely different situation.

Senator NELSON. Thank you.

So, if I understand you correctly, you feel that because of the overprescription of this drug, on balance it has done more damage than it has good. Is that what you are saying?

Dr. WESTON. Well, this is a hard question to answer for this reason. If you have a real bad meningitis and a choice of giving tetracycline or Chloromycetin and you give Chloromycetin, the Chloromycetin will clear that meningitis but the tetracycline would have, too, the chances are.

Now, for me to say categorically that Chloromycetin has done more harm than good would be to eliminate the fact that in the vast majority of cases where Chloromycetin was used, it was used and it cleared up the infection, but another antibiotic could have cleared up the infection without this incidence of untoward effect, so you cannot really answer that question.

Senator NELSON. You are counting the cases where Chloromycetin, chloramphenicol, was used and did effectively clear up the infection without any untoward result.

Dr. WESTON. Yes, sir.

Senator NELSON. But in the same case, tetracycline or Ampicillin could have done as effective a job without the risks. So in the case where you end up with a serious blood dyscrasia, aplastic anemia, that is a negative effect of the use of chloramphenicol, correct?

Dr. WESTON. If you are going to answer that question affirmatively, yes, that would have to be considered a negative effect of chloramphenicol.

Mr. GORDON. So, on balance, considering the way it is being prescribed today, the conclusion, I think, was that it has done more harm than good; is that correct?

Dr. WESTON. It has done more harm, taking into consideration the fact that another antibiotic may have been used other than chloramphenicol and used as effectively, if not more effectively, than it has good. You cannot rule out the fact that Chloromycetin has cured thousands of cases of meningitis and thousands of strep throats and done it effectively. But, so would have a dozen other drugs.

The California legislation, in its attempt to curb the use of this drug, met with opposition from all segments of the medical community, and this, I think, is important, including public health authorities who indicated that such legislation was only seeking to control medical practice and that such a decision of judgment rested with the physician who could be controlled effectively through means already at their disposal if injudicious medical practice was established.

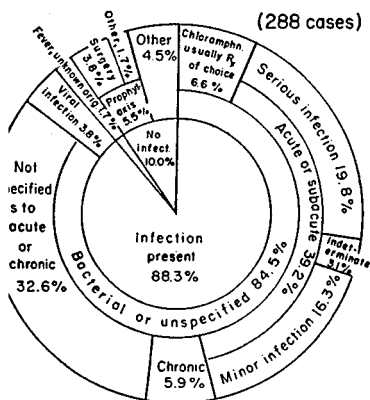
Now, California has probably one of the most sophisticated systems for doing this.

Such measures are resorted to only when willful gross negligence is evident, and in many States, the only means of doing this is the criminal court, I should say in most States. However, it would appear

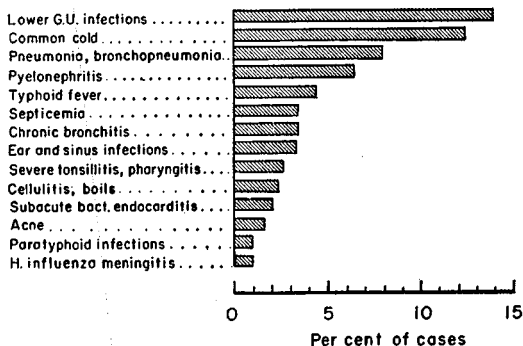
from this table from the previously referred to Council on Drugs report of July 1967, depicting the reasons the drug was given in 288 cases, that the physician has not assumed responsibility to inform himself of modern therapeutic practices or has chosen to disregard these warnings. And as Dr. Best testified to, the common cold is the disease treated in 12 percent of the cases.

(The table referred to follows:)

Reasons drug was given



Some specific conditions for which chloramphenicol given



2. Reasons why chloramphenicol given. Left, General nature of indications. Right, Specific conditions; all those accounting for 3% or more of known indications plus selected conditions with lower percentages.

Senator NELSON. Now, it is never indicated for the common cold, is it?

Dr. WESTON. No, sir. In fact, if you look at that circular graph, you will see that most of them fit into the category of minor or unspecified infections in which it also is never indicated. Acne, of course, runs about 2½ percent, which is unbelievable, in university medical practice.

My interest in chloramphenicol and its untoward effects is derived from experience in conducting postmortem examinations on two children who died at intervals of 12 to 36 months following exposure to chloromycetin, prescribed injudiciously for minor respiratory ailments. Numerous similar reports are in the literature. I would say categorically, that if you look at the reports of untoward reactions to chloromycetin, in virtually every instance the drug is not indicated, whereas if you go back and look at your typhoid, and this has been done by several people, look at your typhoid that was treated during the period when it was indicated, you will find conversely no untoward reaction to chloromycetin. I am sure this varies—it is just a matter of chance. I do not see why there would be any reason for this particular person to be sensitive to it and this one not, but in most of the surveys that have to date been made, where it has been indicated there has not been an untoward reaction to it, this is very strange.

Senator NELSON. Well, would one explanation obviously be that it is used in typhoid cases 300 or 400 times a year, whereas it is given to over 3½ million individuals for other cases?

Dr. WESTON. Yes.

Senator NELSON. Would that statistically be the answer?

Dr. WESTON. Statistically, I am sure it would, yes.

I do not want to become sensational in this presentation but I would just like to tell you a little bit about the last case that I examined. The father had a myocardial infarction shortly after the daughter died. The daughter had been sick for about 3 years. It is a case of a youngster who had a bad cold and sore throat, tonsillitis. The mother was given a prescription by a physician, took it to the drugstore and got it filled. This particular prescription was for chloromycetin. It worked very effectively against the youngster's tonsillitis.

The youngster got sick about 3 weeks later and the mother went down to the druggist and got the prescription refilled, took it home and gave it to her daughter again.

The third time she went down to the druggist the druggist asked if she was sure she wanted this refilled? And the woman said, "Yes, I do." "Well," he said, "I can't do it without calling the doctor." So, he thereupon called the doctor and the doctor was not in. So she said, "Well, isn't there anything that you can do?" he said, "Yes, I have another physician that I can call." So, he called this other physician and said, "I have a little girl with real bad tonsillitis. She has had chloromycetin before. Can I give her a prescription?" He said, "Yes." So, therefore, upon telephone communication with the second doctor, never even having seen the patient, he gave the little girl a third prescription.

Well, all in all, she had some five different courses of chloromycetin. She came into the hospital and was treated for about $3\frac{1}{3}$ years with hormones. The mother is now in a psychiatric institution because she has all the guilt reaction which goes with her having talked the druggist into prescribing this drug. The father is incapable of working any longer.

This is not an unusual case. When chloromycetin is prescribed neither the druggist or doctors seem to realize the potential toxicity. On the other hand, if you talk to this doctor, after he had this type of drug reaction, and ask him whether he would give chloromycetin to this or any other patient for just about any condition, he would say: "No, I would not give it. I just will not give it, period."

So, I have had the occasion to talk to three different doctors who have had this type of reaction. Dr. Wintrobe in our department, of course, has dealt with families going almost into the hundreds that have had this type of reaction since he is such a well-qualified hematologist. He tells you uncategorically, he would not give chloromycetin and he does not see how they give chloromycetin. It is an entirely different situation than if you have a youngster who is coming in with typhoid fever. You have got a kid with a cold, that is what it amounts to, a runny nose, and you are giving him something that could take his life away anywhere from 3 months to 3 years later.

There just does not seem to be any way of equating the thing, as far as most university physicians are concerned at this time. It is really very sad; it is impossible.

Now, to go on in the statement, Parke, Davis has, from its outset equated the untoward reaction to chloromycetin to that with other drugs and, I am sure you will find in the literature if you look for it,

references to granulocytopenia, treated with sulfonamides, and a substantial array of medical literature now on anaphylactic reactions, many of them due to penicillin, but you cannot equate the amount of penicillin which has been given to the amount of chloromycetin given and quantitatively put it down on anaphylactic reactions even if they were all uniformly fatal which they are not any longer. They are treated and suspected and watched for in quite a large percentage of the patients. So that you cannot equate them.

Aspirin is another thing which in two malpractice trials I have seen introduced as something which causes untoward reactions. If you stop to think of how many aspirin are administered or taken in this country in a year, this is a rather ridiculous argument. Certainly there are a smaller number of cases but my own personal search of the literature reveals that more children die from taking aspirin accidentally in a home in 1 year than have been reported from untoward reactions to aspirin in 10 years. So that again, you cannot equate aspirin.

And if you are going to go into dicumarol, which is another thing I have seen in malpractice testimony, this is ridiculous, because here you have a man who is on the borderline of life and death. You are offering him the opportunity to keep his coronary arteries open at the cost of introducing an agent which has a very definite calculated risk and you cannot equate this any more than you could with a variety of anti-neoplastic agents that we are using which are known to be toxic, which are known to cause bone marrow damage. You are dealing with fatal conditions and potentially fatal conditions and we cannot put the two of them in the same sentence even in court testimony.

Chloromycetin is indicated in any infectious disease in which another antibiotic with less toxic effect is not efficacious, or cannot be tolerated by the patient. Present indication, again depending on the method of administration, the sensitivity of the patient, could be construed to include at the very most typhoid fever, certain rickettsial infections such as epidemic, murine and scrub typhus, rickettsiapox and Rocky Mountain spot fever.

It may be indicated in overwhelming infections where positive identification in the organism and sensitivity to antibiotic would only serve to delay the value of effective chemotherapy and hasten death.

Senator NELSON. May we back up a moment?

Dr. WESTON. Yes, sir.

Senator NELSON. Maybe I do not read this sentence correctly. You say: "Chloromycetin, (chloramphenicol) is indicated in any infectious disease in which another antibiotic with less toxic effect is not efficacious."

Dr. WESTON. Well, you have to take into consideration the method of administration. Tetracycline administered orally has frequently sufficient side effects to it that it causes the patient such gastrointestinal disturbance that he is incapable of keeping it within his system, and if you are going to talk about treating a patient with tetracycline, you have to consider that the patient will be capable of keeping the drug within his stomach and his intestine long enough for it to be absorbed, or you are going to have to administer it parenterally or by injection. Now, if you can do this, that is fine, but if you cannot do this, then you have got to use chloromycetin, is what I am saying.

Senator NELSON. I guess it is that sentence standing alone which bothers me. You are saying it is indicated in any infectious disease in which another antibiotic with less toxic effect is not efficacious, I assume you mean in any disease which is very serious and in which no other antibiotic is effective. Is that what you are saying?

Dr. WESTON. Yes. Any infectious disease which is capable of causing death in which no other antibiotic as—I really would assume we are talking about serious infectious diseases.

Senator NELSON. I knew you were, but standing alone, I thought that the sentence required clarification.

Dr. WESTON. And here again, I think you have to be fair to Chloromycetin and say that some of the drugs that we are using today perhaps have not undergone the therapeutic trial that Chloromycetin has with respect to toxicity. Now, tests were made from 1948 to 1950 with Chloromycetin before we had enough to hold a hearing. Dr. Wintrobe and his associate really met with the council and discussed toxicity of Chloromycetin and some of these agents we are talking about using, especially for hemophilus influenza infections, have barely been on the market much longer than that. So while we are not aware of any toxicity, this does not mean that you can equate the drug at this time with something like Chloromycetin and I would be the first to say that if Ampicillin 5 years from now was showing changes in the body which were toxic, it should be given the same sort of study that Chloromycetin has, but I do not think it has been on the market long enough yet to say beyond a doubt that it is nontoxic.

The use of Chloromycetin should be accompanied by studies of peripheral blood and if necessary the bone marrow at frequent intervals in order that toxicity may be detected as soon as possible. I do not think the physician should be misled into the concept—I question this—into the concept that this is going to detect every fatal bone marrow reaction.

Conversely, the use of Chloromycetin, is positively contraindicated, in minor infections in any location in the body.

In practice, there is no question but that limiting the use of Chloromycetin to hospital practice would result in danger in certain severe fulminating infections and consequently any measure designed to control the use of Chloromycetin should make provision for the emergency dispensing of the drug by physician in such conditions. This may change. In fact, it already appears to be changing as practically the only infection which you can put into that category are these near fatal, early childhood infections of which the most serious is hemophilus influenza and if this triple medication including Ampicillin instead of Chloromycetin proves to be nontoxic over the next couple of months, I would say categorically that you could limit the use of Chloromycetin to hospital practice without endangering any person's life because you can get a patient into a hospital to treat typhoid fever and *Salamonella* infections or you can treat these with another antibiotic on an outpatient basis. If the risk that is involved in this cannot be sufficiently transferred to the physician by way of communication I certainly would think that admission to the hospital is indicated.

However, the evidence presented indicates that the misuse of the drug continues in spite of numerous warnings to the contrary and

previous attempts at legislation controlling its use in at least one State. With the numerous agencies available for reporting use of the drug in outpatient and hospital practice, it would appear at this time that a legislative attempt should be made to limit the use of this toxic antibiotic to those conditions in which it is indicated. However distasteful such measures may be to physicians, my personal experience in dealing with physicians who have been associated with severe untoward reactions to the drug has revealed considerably more displeasure on their part at this time.

Senator NELSON. You mean more displeasure about what?

Dr. WESTON. About their untoward reactions, about their aplastic anemias. Whenever anyone has a reaction, they stop using Chloromycetin, has been my experience. Of course, it is too late.

Senator NELSON. In the cases you have recited, are you talking about doctors who prescribed it for a case in which it was not indicated?

Dr. WESTON. Yes, sir.

Senator NELSON. They should not have prescribed it.

Dr. WESTON. That is correct.

Senator NELSON. And, in all of those cases the doctor would have been happier if there had been some restriction on his freedom of prescription, is that right?

Dr. WESTON. Yes, sir.

Senator NELSON. We had testimony to that effect on Tuesday. Dr. Lepper testified that there ought to be some limitation upon prescription of this drug. He was not prepared to say what kind of formula or what kind of a method should be used. One of the witnesses suggested that we follow the same procedure used in the prescription of morphine: That chloramphenicol be identified in a certain way and a record filed, and so forth. But, in any event, I understand your testimony to be that there should be some attempt, legislative or otherwise, to control the use of this drug.

Dr. WESTON. Yes, sir. I would not limit it to this drug. I think that there are now and there will be, perhaps not nearly as toxic as Chloromycetin, but I am sure that experimentally the time will come when there may be another drug which may have untoward effects and any machinery which is set in motion to control these drugs, I think should take into consideration the fact that we are using drugs in different ranges of effectiveness and in different ranges of risk. Dicumarol certainly has a well accepted risk. We know a certain number of people are going to take Dicumarol to the point where they will bleed internally and subsequently die from this. On the other hand, to equate this with the effect it has in preventing perhaps thrombosis within a coronary artery, this is not a bad risk. The same is true of agents which are used for prevention of cancer or treatment of cancer. We have watched the antileukemic agents for a number of years and have seen the bone marrow of these patients sometimes go down to nothing, and then tried to build them up. We knew this was an accepted risk.

These were experimental drugs and I think any doctor that gives an experimental drug to a patient has an obligation to the patient or to the family to explain that this is an experimental drug. So, I think the legislation—and I am sure, as Dr. Lepper testified, that the

machinery is there. We have public health laws that require reporting of certain diseases and we have very definite controls on narcotics which have been very effective over a long span of years now, so that there is machinery there that we can utilize, but I think a study like this should not be directed at just one drug. I think we ought to look at the whole spectrum of drugs and separate the experimental drugs from the drugs which are proven therapeutically and have no toxic effects and then put ones like Chloromycetin in the center and control its use this way. I would not want to discriminate against Chloromycetin.

Senator NELSON. I was not suggesting that. I take it that you would suggest that some kind of a mechanism be established to control the drug. For example, a distinguished panel of experts from the medical profession would be formed to study the problem, and would make a recommendation to the FDA or some other appropriate place, that this drug should be in a special category to limit its administration in one fashion or another. Is that the kind of thing you are talking about?

Dr. WESTON. Yes, sir. Positively.

Senator NELSON. Thank you.

Dr. WESTON. It is recognized that considerable pressure may be brought to bear by numerous economics groups, including not only the manufacturer, but the dispenser, when a commodity with gross national sales of the magnitude of this agent is curbed to this degree. It should also be recognized in any legislation that extensive research is currently being conducted within the facilities of the manufacturer, Parke, Davis, to develop an agent capable of protecting the body against deleterious effects of this drug such as has been shown to occur in protecting the eye from untoward effects in a limited number of cases. With virtually every State in the Nation requiring reporting of certain diseases and conditions to public health or other authorities and such stringent control carefully exercised on the use of addicting and now dangerous drugs, it would appear that the machinery is available for effective control of other toxic drugs such as Chloromycetin. It remains to devise the legislation necessary and the method of implementation within these agencies.

Senator NELSON. The day before yesterday, in the testimony of some of the witnesses, the question was raised as to the reporting of side effects from this or any other drug. Would you think it would be valuable to the profession and to the public if hospitals, for example, were required to report to some central place—the FDA might be one or the AMA might be another—the information they accumulate each year about side effects of drugs used in that hospital? I am not saying that you would report all side effects, but side effects that were of significance and information about which would contribute to the body of medical knowledge. Would you consider that a useful, valuable thing to do?

Dr. WESTON. No, sir.

Senator NELSON. You would not?

Dr. WESTON. No, sir. It is much the same as the battered-child legislation. We went to a great deal of trouble to get battered-child

legislation passed in—I believe it is present in all but two, maybe it is in all the States now.

Senator NELSON. Which legislation is that?

Dr. WESTON. This requires the reporting by a physician when he suspects that a child has been abused by its parents, and it just has not proven to be of the value that it was anticipated to be because even with an immunity clause in it, in that particular instance, providing immunity to the physician in case he did make a false accusation, you have other factors to consider. You have the factor that this family is treated by the doctor in this particular instance and the doctor reports this family, so he loses all the patients in the block as soon as word gets around.

Senator NELSON. Maybe you did not understand my question. Maybe I did not make it clear.

Dr. WESTON. Well, you have exactly——

Senator NELSON. I am saying hospitals, only hospitals, would report the medically significant statistical information on drug side effects. They have the patient there. The patient's records are there. They have qualified physicians in the hospital. For example, say that you have found a blood dyscrasia as a consequence of chloramphenicol. At the end of the year the significant statistics which you have accumulated would be reported to a central place. That is my question. I was not referring to known side effects of a drug like penicillin that has been used over a period of many, many years.

Dr. WESTON. Well, you have two cases now, one in excess of \$200,000 and one approaching \$200,000 in which awards have been made to families on the basis of Chloromycetin. Do you suppose a doctor is going to be naive enough if he treats a patient with an upper respiratory infection with Chloromycetin to admit this patient into the hospital and write down at the end of the hospital chart, if there is any way to mask it, the fact that he has used this drug and that this patient has ultimately died from the untoward reaction? I do not believe so. You cannot get the information either by voluntary or—the accurate information either by voluntary or compulsory reporting systems.

Senator NELSON. I am not talking about getting information for purposes of prosecuting doctors, but we have heard you and some other distinguished doctors testify and nobody can give us any idea really of how many cases of serious blood dyscrasias occur from this drug or apparently from any other drug. All I am saying, for the benefit of educating the medical profession about the drugs, if you have a number of cases of a certain side effect from a particular drug, would not it be valuable to the researchers in the profession to know that the drug is causing it? This is what the medical profession hopes to learn as fast as it can about every drug and I am suggesting that they might learn it faster if the information accumulated in the hospitals around the country was furnished to FDA and the American Medical Association. That is my question.

Dr. WESTON. Oh, I agree with your point. Do not get me wrong. I agree wholeheartedly with your point, but somewhere along the line,

in order for that to get reported by the hospital to the FDA, it has to appear in the hospital chart.

Senator NELSON. Yes.

Dr. WESTON. Well, have you ever seen lawyers go through hospital charts? I mean, what you are doing in effect is you are asking the doctor to invite upon himself a malpractice case. And they just do not do it. They are getting more and more cautious about malpractice and to put down anything that is equivocal in any way on a hospital chart is to invite its inspection by an attorney, and that is why I say in theory it sounds wonderful but it just—I have worked so much with malpractice cases, not only drug reactions but where doctors have had surgical misadventures, and as a matter of fact, in Philadelphia we had a very elaborate system whereby every patient that died in surgery, everyone who died after surgery, or everyone who died as a course of treatment, either immediately or delayed, as this would ordinarily be, had to be reported to the medical examiner. They were referred down to the medical examiner's office for examination. In the course of that examination the hospital chart was subpoenaed, a privilege allowed the medical examiner in that city. It is in many. The chart was brought in and summarized.

Now, if in the course of the entire workup, including the hospital chart summary, post mortem examination, chemical studies, and everything else, it could be shown that the doctor was negligent, derelict in his duty, this case was anonymously presented to a committee of the medical society. It was quite effective in bringing the hospital, the physician, and his peers together and pointing out that they are doing something which is not being done by most of the physicians or, as a matter of fact, in some cases you are committing a gross error bordering on criminal neglect. That is in my experience the most sophisticated type of system we have in the United States today. This is similar to California which has set up their board of examiners and they can at will call for a hearing but if you were to go into most communities today, there actually is no agency that functions in this way; the result is that the physician is not protected to the degree that he should be and he protects himself. And that is why they are so conscious of malpractice today that it really has started to be felt in the way they practice medicine.

Senator NELSON. I realize there are tiny 25-bed, 10-bed hospitals that may follow a different procedure, but is it not correct that you could go into any major hospital and the patient's record will show the case history, the diagnosis, the treatment, and so forth, if the patient is in there as a consequence of some dramatic reaction to a drug that has been administered, the record will show that, will it not?

Dr. WESTON. If the diagnosis is established.

Senator NELSON. Yes. You do not mean to tell me that in major hospitals in this country if a patient comes in who has a dramatic reaction to a drug, and it is known what the drug is, it is known that this is a side effect, and they are treating this patient, the hospital would fail to disclose in the record what the patient's condition is? Is that happening? The hospitals are hiding from the record the patient's diagnosis?

Dr. WESTON. The record is made by the doctor. The record is not made by the hospital.

Senator NELSON. Well, the patient goes into a hospital and is being treated there.

Dr. WESTON. The hospital supplies the paper. The doctor makes the record. The nurse writes her notes. But the record is made by the doctor.

Senator NELSON. Is it common in the medical profession for a doctor who has made a diagnosis but is afraid he has made a mistake, to keep his patient in the hospital and be treating him covertly and not putting in the record what it is all about?

Dr. WESTON. I would not say it is common, but I have encountered it more times than I can count on my fingers and toes in the course of my reasonably limited career, so it is not so completely uncommon, and you have in the California proceedings the statements of at least one other physician who says that he saw blood dyscrasia misdiagnosed as leukemia, spontaneous cerebral hemorrhage, spontaneous GI hemorrhage.

Now, I do not think there is any question but what some of the doctors in our medical community would be prone to cover up this sort of reaction if they had used the drug injudiciously and it had caused a bone marrow dyscrasia. I do not think there is any question about it. And, I think any doctor who came in here and said otherwise would be naive.

Senator NELSON. It would not be possible, would it, for a doctor to fail to disclose all the details of a case if he had some kind of a clinical practice in which more persons than one were seeing the patient? If a person came in with a serious blood dyscrasia, I would assume he would then call upon other specialists in the hospital to evaluate the patient.

Dr. WESTON. Well, that is the assumption that I am not making.

Senator NELSON. I see. You scare me. I had assumed that.

Dr. WESTON. If you do not take a bone marrow biopsy on one of these patients, you really sometimes are not going to know exactly what is going on in their bone marrow. I do not mean to frighten you, but I just know that it does occur. It is not in a very large segment of our profession fortunately, but it does occur in a small segment, small percentage.

Mr. GORDON. I have just one question. In the cases in which you were the medical expert, what were the issues involved?

Dr. WESTON. Well, in the cases that I was the medical expert in, the issues revolved around three things, the first of which was the dicta I have already enumerated, the watering down, so to speak, of the warning which was initially directed to be put on the product by Parke, Davis, and in this one I have already stated that at least two other physicians besides myself, felt that the tenor of the warning had been altered significantly in the form that it was presented to the physicians, and the impact of it was altered considerably by the promotion that occurred in addition to this.

Now, the other issues concerned indications and contraindications for the drug and whether in fact a condition had been diagnosed at all in this particular circumstance.

Mr. GORDON. Thank you very much.

Senator NELSON. Dr. Weston, we appreciate very much your very valuable and useful testimony and I appreciate your taking the time from your busy schedule to come here and appear before the committee. Thank you very much.

Dr. WESTON. Thank you, sir.

(The supplemental information submitted by Dr. Weston follows:)

ATTACHMENT No. 1

WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia.

INDICATIONS

Oral and Parenteral. Chloromycetin (chloramphenicol) is a broad-spectrum antibiotic having specified therapeutic activity against a wide variety of organisms.

Chloromycetin (chloramphenicol) is indicated in the treatment of patients with rickettsial infections, including epidemic and murine typhus fevers, scrub typhus fever, Rocky Mountain spotted fever, and rickettsialpox; typhoid fever and certain other salmonella infections; urinary tract infections due to susceptible organisms; surgical infections such as postoperative wound infections, cellulitis, infected sinus tract, and peritonitis or intra-abdominal abscess from ruptured intestine, diverticula, or appendix, usually due to microorganisms sensitive to chloramphenicol; severe respiratory tract infections due to susceptible organisms, in those instances when contraindications to other drugs exist or when there is lack of response to other agents; meningeal infections due to susceptible organisms; and certain other miscellaneous infections, wherein other therapeutic agents have been found ineffective.

The antibiotic is supplied in a number of product forms, of which the palmitic ester and the sodium salt of the succinic acid ester of chloramphenicol require conversion to free chloramphenicol before exhibiting marked antimicrobial activity. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in the liver and kidney; lowest concentrations are found in the brain and cerebrospinal fluid.

Parenteral. Parenteral therapy with Chloromycetin (chloramphenicol) is recommended for patients too severely ill to take therapy orally. After symptoms subside, treatment may be continued with the oral preparation of choice for the individual.

Topical (dermal, ophthalmic, otic). Chloramphenicol ophthalmic preparations without steroids have given good therapeutic results in bacterial conjunctivitis caused by *Esch. coli*, *H. influenzae*, *Staph. aureus* (*Micrococcus pyogenes*), *Strep. hemolyticus*, and *Morax-axenfeld*.

Chloramphenicol ophthalmic preparations with steroids have given good results in nonpurulent conjunctivitis. Hydrocortisone is intended to suppress inflammatory reaction when desirable.

Chloramphenicol when used topically may be supplemented by appropriate systemic medication when necessary.

ATTACHMENT No. 2

[From the Journal of the American Medical Association, vol. 201, No. 3, July 17, 1967]

CHLORAMPHENICOL-ASSOCIATED BLOOD DYSCRASIAS

A REVIEW OF CASES SUBMITTED TO THE AMERICAN MEDICAL ASSOCIATION REGISTRY

(By William R. Best, M.D.)

Chloramphenicol, an effective broad spectrum antibiotic, was introduced in 1948. Only after three years of extensive use did it become evident that this drug was capable of seriously depressing bone marrow activity in rare recipients. It was in response to the delay in recognizing the toxic potentialities of this drug that the American Medical Association established the Registry on Blood Dyscrasias, hoping, among other things, to recognize such effects early when they occurred for other new drugs. The Registry and its study group have since accumulated data on a large number of drugs have issued periodic tabulations and résumé of cases submitted, and have authored commentaries on various associated problems.¹⁻⁶ During this period, chloramphenicol has been implicated in more reports to the Registry than has any other single drug. It appeared that useful information could be obtained through a more thorough review of Registry reports.

Included in this study were 408 cases, reported to the Registry from 1953 through 1964, who were known to have received chloramphenicol during the year preceding a non-neoplastic depression of blood cell formation.

Generalizations from this experience would be most valuable if cases reported to the Registry represented an unbiased sample of the condition as it occurred throughout the world. However, there are unavoidable and, no doubt, unidentifiable biases in this collection of cases. For example, most cases have been voluntarily reported from selected sources, and the composition and attitudes of these sources have changed from year to year.

Some cases were abstracted from the medical literature. Nonetheless, this appears to be the best data available for study.

The Registry contains a total of 298 US reports. 25 known to be published, 273 not; plus 110 foreign reports, 70 known to be published, 40 not.

Yunis and Bloomberg reviewed much of the literature on this disorder, summarizing data on 94 cases.⁶ Twenty-one US and eight foreign literature cases are common to their review and to the Registry; their other cases are not in the Registry. The Registry contains 1 US and 65 foreign literature cases which were not covered in their review. There have been additional published case reports which appear neither in the review by Yunis and Bloomberg nor in the Registry.

METHODS OF ANALYSIS

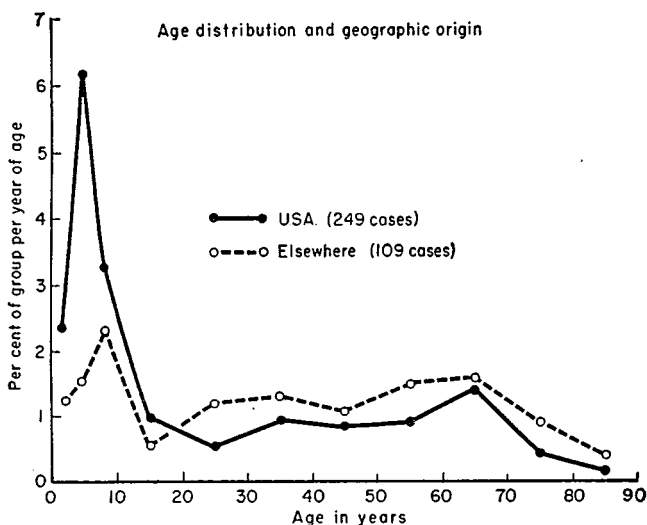
During the years of existence of the Registry, the report form has gone through several different versions, more recent ones tending to call for more complete information. In general, no systematic attempt has been made to obtain more detailed clinical information or late follow-up of cases.

Reports were coded and punched on 80-column computer programming cards, using from 4 to 36 cards per patient, under the direction of Norman De Nosaquo, MD, and Mrs. Helene Weston of the AMA staff. Data transformation, reduction, tabulation, and analysis were performed by the author using computers and over 30 special computer programs.

GENERAL CHARACTERISTICS OF CASES

Age and Sex.—Females accounted for 62% of 407 cases. There was a wide distribution of cases by age with a rate of 0.5% to 1.5% of total cases per year of age from the teens through the 70's, occasional cases in older age groups, and a striking peak occurrence of about 5% per year of age in the 3- to 7-year age group. There was some difference in sex distribution at different ages: females accounted for 69% of 113 patients 0 to 9 years of age, 69 (73%) of 94 patients 10 to 39 years of age, but only 47% of 150 patients 40 years of age or older.

The percentage of females was essentially the same for cases reported from the United States as compared to reports from elsewhere; however, there is a much less striking peak of occurrence for the 3- to 7-year age group in the latter series (Fig.1).



1. Age distribution of cases of chloramphenicol-associated blood dyscrasia as related to geographic origin.

The smaller 3- to 7-year age peak in the non-U.S. cases might represent either different patterns by which this drug is prescribed for various age groups, different biases in the reporting of cases, or different hereditary patterns of age susceptibility to this complication as related to ethnic origin. The last of these possibilities seems unlikely, for 84% of the non-U.S. cases are from Europe or European-colonized countries, and a similar background is claimed for most white patients from the United States. In addition, 14% of US patients are nonwhite whereas only 9% of foreign cases are nonwhite, and nonwhites had a lower peak of occurrence at ages 3 to 7 than did whites.

The Table presents data on some of the more common indications for use of the drug in relation to age and sex. Upper respiratory tract or ear infection were the indications in 29 (almost 40%) of 77 patients, in the under 10-year age group but in only 7 (about 10%) of 68 patients in the older age groups; lower respiratory tract infections and urogenital infections, on the other hand, each accounted for almost a third of indications in the elderly, but only about a tenth of childhood indications. A comparison of US with other reports in this regard reveals similar patterns of indications for most age groups except that there appears to be a slightly lower percentage of childhood cases corresponding to each of the three specific listed indications in the non-U.S. group.

AGE, SEX, AND REASON FOR RECEIVING CHLORAMPHENICOL

Indication for chloramphenicol	Age group					
	0-9 years		20-39 years		60-plus years	
	Number of patients	Number of females	Number of patients	Number of females	Number of patients	Number of females
Upper respiratory tract or ear infections.....	29	19	4	2	7	4
Lower respiratory tract infections.....	7	6	6	5	21	7
Urogenital infections.....	10	10	11	9	21	5
Other indications.....	31	20	32	22	19	9
Total.....	77	55	53	38	68	25

Race and Ethnic Origin.—Of the 346 patients whose race is known, 28 (8%) were Negro, 10 (3%) were Oriental, 3 were American Indian, and 2 were East

Indian. Negroes accounted for 11% of the U.S. group but were not present in the non-U.S. group. Only 18 (43%) of 43 nonwhite patients were female, whereas 191 (63%) of 303 white patients were female. Ethnic origin was indicated for 144 white patients. Of these, 79% were north European, 6% Jewish, 6% east Europeans, 5% Spanish-American, and 4% south European.

Other Genetic Information.—In a written communication to the Registry (March 1, 1960), D. J. Fernbach, MD, called attention to a set of identical twins, both of whom developed blood dyscrasias related to chloramphenicol; a published report of these cases appeared subsequently.⁷

These identical twins, who were white males 3 years of age, had been given seven- to ten-day courses of chloramphenicol on several occasions during the preceding two years for severe upper respiratory tract infections.

Twin A had six to ten such courses, the most recent being about a month before diagnosis, at which time trisulfapyrimidines was also given. Purpura developed characterized by thrombocytopenia and a hypoplastic marrow, which, over the course of about two months, developed into pancytopenia. Three marrow transplants were attempted from twin B during the next two years, but without apparent improvement. Hemoglobin returned to normal after 1½ years of corticosteroid and androgen therapy. The bone marrow became less hypocellular, but thrombocytopenia and moderate leukopenia still persisted six years after onset.

Twin B had received only four courses of chloramphenicol, the most recent course (this drug only) being given two weeks prior to diagnosis, at about the same time that purpura appeared in twin A. Isolated thrombocytopenia associated with a hyperplastic marrow, including normal numbers of megakaryocytes, became evident when he was being worked up in preparation for the first marrow transplantation. He received no therapy and completely recovered within two weeks after chloramphenicol was discontinued.

BLOOD AND BONE MARROW

The reporting physician in each case indicated his diagnosis of the type of dyscrasia utilizing his usual criteria plus the admonition on the report form that leukopenia would consist of leukocyte counts of 3,000/cu mm or less. Further documentation was usually not present, and only rarely did members of the hematology panel find it necessary to change a diagnosis on the basis of such documentation when present.

All three major types of peripheral blood cells, erythrocytes, leukocytes, and platelets, were jointly depressed in 75% of 358 cases; two cell types were depressed in 6%; and a single cell type was depressed in 19% (leukocytes in 9%, erythrocytes in 6%, and platelets in 4%). Isolated erythroid cell depression was more common at ages 20 to 59 years (15% of 134 cases) than in younger (2% of 144 cases) or older (two [3%] of 80 cases) age groups, but no other age trends were apparent. Depression of granulocytes was the most striking component of leukopenia in most instances, but because the report forms did not always call for specific details in this regard, a more complete statistical breakdown is not given.

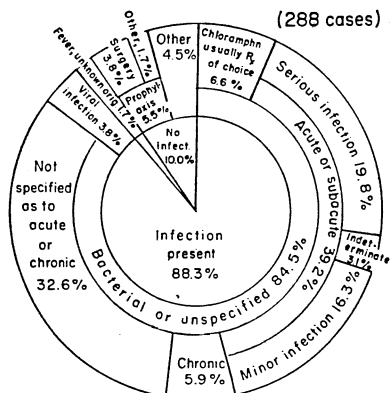
Bone marrow findings were available in 129 cases. In 3% of these, the marrow showed increased cellularity and in 7%, normal cellularity, often with other changes such as maturation arrest of the granulocytic series of vacuolation of erythrocytic precursors. Depression in number was noted for precursors of one of the major types of blood cell in 12% of cases; of two types in 5%; and of all three types (e.g., hypoplastic or aplastic anemia) in 74%. Two marrows in the last category showed increased numbers of marrow lymphocytes, but on follow-up this apparently did not represent leukemia or lymphoma. Of 24 patients with only one or two cell types depressed in the blood 2 (8%) showed a normal to hyperplastic marrow, 15 (62%) had one or two cell types depressed in the marrow, and 7 (29%) showed general marrow hypoplasia. Of 105 patients with all three cell types depressed in the blood, 10% showed a normal to hyperplastic marrow, 6% showed depression of one or two cell types in the marrow, and 84% showed general marrow hypoplasia.

Clinical manifestations were not reported in detail for most cases, but those which were given conformed with what one might expect: manifestations of anemia, propensity to hemorrhage, and increased susceptibility to infection.

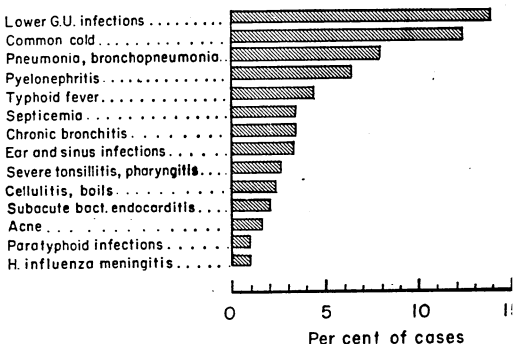
DETAILS OF DRUG ADMINISTRATION

General.—The reason that chloramphenicol had been given (for the most part infection or prophylaxis against infection) was cited in 71% of the 408 cases (Fig 2).

Reasons drug was given



Some specific conditions for which chloramphenicol give

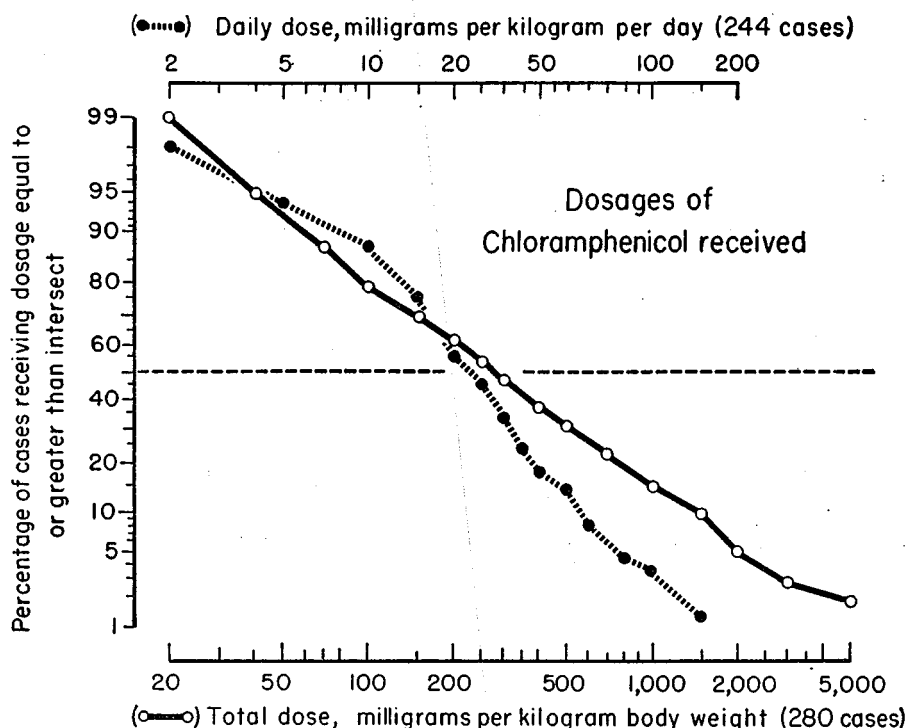


2. Reasons why chloramphenicol given. Left, General nature of indications. Right, Specific conditions; all those accounting for 3% or more of known indications plus selected conditions with lower percentages.

Chloramphenicol was the only known drug administered during the prior six months to 40% of patients. One other drug was mentioned for 19%, two for 13%, and three or more for 28%. In one case, 17 other drugs were listed. In 9% of all cases, the only other drugs mentioned were members of what the study group considers to be generally "innocent" drugs—aspirin, the barbiturates, chloral hydrate, digitalis glycosides, the penicillins, and the tetracyclines; in 37% of all cases, drugs other than "innocent" ones were administered, but no "toxic" drugs were given; in 9%, another toxic drug was administered, but suspicion was cast most strongly on chloramphenicol; and 4% suspicion was cast most strongly on another toxic drug. Thus, in 96% of cases, there is strong suspicion that chloramphenicol was the causative agent, and in the remaining cases, this possibility cannot be ruled out. Since elimination of those patients receiving another toxic drug had virtually no effect on outcome of the dyscrasia, all cases were included in the analysis.

Duration and Dosage of Chloramphenicol.—It is known that 9% of patients received this drug at least once prior to the course in question.

The dashed line of Fig 3 presents a cumulative plot of average daily dose in milligrams per kilogram per day on a type of graph paper having logarithmic and probability scales. If the log-dose were distributed in gaussian fashion, such a plot should approximate a straight line. Central portions of such curves are generally more accurate than the extremes. In this case there is some deviation from a single straight line, but the fit is not bad. At any rate, interpolation will provide estimates of dosage levels defining selected percentiles. It is seen that 10% of patients received less than 8 mg/kg/day, 50% received less than 23 mg/kg/day, and 10% received greater than 60 mg/kg/day. This is to be contrasted with a manufacturer's recommendation for a starting dose of 50 mg/kg/day in adults and 50 to 100 mg per kilogram per day in children beyond infancy. Either smaller doses tend to be given to susceptible patients, or else the general trend in use of this drug is to administer smaller average amounts than recommended for initial therapy. The latter possibility seems more likely. There appears to be slight differences in patterns of daily dose administration for different age groups. Thus, the median doses were: 33 mg/kg/day for patients 0 to 9 years of age, 24 mg/kg/day for those 10 to 39 years of age; and 18 mg/kg/day for those 40 years of age and older.



3. Daily dose of chloramphenicol in milligrams per kilogram per day and total dose in milligrams per kilogram. Distribution of values for each curve is indicated cumulatively on log-normal coordinates.

The number of days of therapy is similarly plotted as one of the curves in Fig. 4. There is a concavity to the cumulative plot line. Although various interpretations are possible, a tendency of physicians to use either short courses or prolonged courses of therapy depending on the nature of the infection seems to be the most reasonable explanation for this nonlinearity. In 10% of cases, development of a blood dyscrasia was related to four days or less of therapy with chloramphenicol; in 50% it was related to 13 days or less; and in 10% to 150 days or more. In a few instances the drug was administered on only one occasion. Median duration of therapy by age group was: 11 days for patients 0 to 9 years, 13 days for those 10 to 39 years, and 15 days for those 40 years and over.

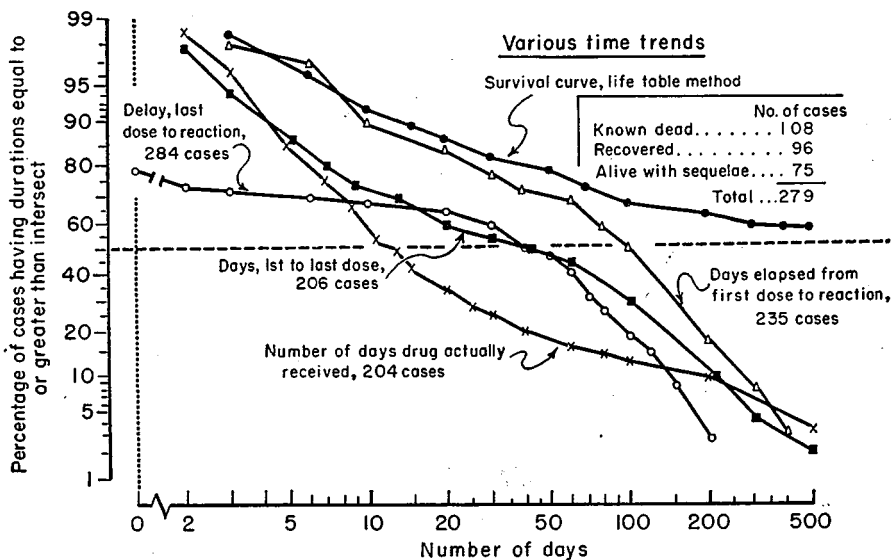
Time from first to last dose is similarly shown in Fig. 4. This time amounted to four days or less in 10% of the cases, 38 days or less in 50%, and 200 days or more in 10%. The main difference between these two curves, seen at their middle, is due to instances in which the drug was taken intermittently. Of the 329 patients on whom such information was available, 39% received the drug intermittently.

The small crossover of these two curves at their extremes reflects the fact that slightly different subsamples were suitable for each and that each curve is only an estimate rather than a precise indication of the curves which would be obtained from a much larger population of similar cases.

The total dose of chloramphenicol received by various patients is plotted cumulatively in Fig. 3. The cumulative plot closely approaches a straight line using these coordinates. In 10% of cases the total dose amounted to 60 mg/kg or less, in 50% to 280 mg/kg or less, and in 10% to 1,300 mg/kg or more. One would expect the 50% intercept to agree fairly well with the product of 50% intercepts for average daily dose and number of days of therapy, and indeed the figure of 299 mg/kg obtained in this fashion is not far from the value of the other curve of Fig. 3, 280 mg/kg. There appears to be essentially no difference in total doses in milligrams per kilogram as related to age.

Time of Reaction as Related to Therapy.—One tends to think of adverse reactions as occurring during drug administration or shortly after discontinuation. Such a relationship proves to be the exception for chloramphenicol-associated blood dyscrasias. Among the 284 patients for which such information was available, only 22% showed manifestations of the dyscrasia while the drug was still being given as shown by the appropriate curve of Fig. 4. The median time from discontinuation of the drug until clinical evidence of the dyscrasia appeared was 38 days, and in 10% of cases this time was 130 days or longer. There is a definite downward bending of this curve, and one wonders whether time from first dose to reaction might not more nearly approach a log-normal distribution. This curve has also been charted to Fig. 4, and it shows an incomplete tendency to straightening. The reaction developed 10 days or less following initial dose in 10% of cases, in 95 days or less in 50%, and in 260 days or more in 10%.

None of the patients in this series are known to have been continued on or re-challenged with the drug after the dyscrasia was diagnosed, and we would not recommend that this be done.



4. Number of days chloramphenicol received; elapsed time of chloramphenicol course; time from first dose to reaction; time from last dose to reaction; and survival time. Distribution of values for each curve is indicated cumulatively on log-normal coordinates. The survival curve is based on life-table analysis.

SURVIVAL AND COURSE

Life Table Survival Curve.—Construction of a survival curve for a fatal disease on the basis of a series of patients, all of whom have not yet died at time of analysis, is best performed through the life table method.⁸ The present situation differs from that of a uniformly fatal disease in that, in addition to a trend towards mortality, there is also a trend towards recovery. Patients who have recovered are not known to have relapses unless the drug is administered further. In this instance, a satisfactory method of accounting for recoveries in life table analysis is to consider all patients who have recovered to be still alive at a relatively long period following onset of the dyscrasia, regardless of the actual length of follow-up. The top curve of Fig. 4 shows the results of this analysis. Because of recoveries, the curve approaches an asymptote rather than describing a straight line on a log-probability plot. The overall mortality approached is approximately 50%; 10% of the patients in the entire series have died within two weeks of onset of the dyscrasia. The 75% intercept (i.e., median survival for those with fatal outcome) is about 50 days. Rare cases may have a fatal outcome a year or more after diagnosis.

Course.—It was specifically reported in several instances that recovery followed withdrawal of the drug, and it is presumed that this occurred within a

few weeks. Most of these instances were associated with depression of a single blood cell type. On the other hand, of the 75 patients known to be alive with persistent evidence of the dyscrasia despite cessation of the drug, 20 (27%) were alive 100 to 299 days after onset, and 11 (14%) were alive 300 or more days after onset. Recoveries have sometimes been noted after relatively long periods of disease.

Death is known to have occurred in 186 cases, 95% from complications of the dyscrasia. Performance of an autopsy was noted for 24% of these cases; however, details of this examination were not usually reported.

Therapeutic measures directed against the marrow depression were usually not reported, and no attempt was made to evaluate these.

PROGNOSIS

Detailed studies on prognosis have been submitted for publication elsewhere (W. R. Best). The most important clinical findings are that improved survival is associated with fewer cell-types depressed, shorter delays in onset, larger daily doses, and occurrence in Negroes.

COMMENT

Yunis and Bloomberg⁶ have reviewed various types of evidence bearing on the pathogenesis of those hematologic reactions to chloramphenicol which occur in rare cases at commonly employed dosage levels. They found no convincing evidence to support an autoimmune process, and the current data cannot be construed as adding such. Abnormal susceptibility due to some biochemical abnormality seems more likely, but the exact nature of such a disorder remains to be determined. Yunis and Bloomberg suggest that a defect in localization, metabolism, or excretion of chloramphenicol, or an enzymatic or other biochemical deficiency involving a metabolic pathway that becomes essential in the presence of this drug, could account for these reactions. One suspects that there is an underlying hereditary difference between individuals who do and those who do not develop this reaction to chloramphenicol. The occurrence of dyscrasias in both members of a set of identical twins is one of the most interesting findings in the Registry relative to the genetic question. It is reasonable to suppose that many close relatives of Registry patients have received courses of chloramphenicol comparable to those of corresponding affected family members, and that a high percentage, if not all instances of multiple cases in a single family would have been called to the attention of the Registry. Yet, so far as we have been able to determine, the only instance in the Registry or the medical literature in which more than one member of a family has developed such a dyscrasia is this particular one involving the relatively rare sib combination of identical twins. One could reasonably expect several nontwin sibling pairs in the total experience to date if this susceptibility to chloramphenicol required a homozygous state relative to a single recessive gene. Simultaneous exposure to some unusual environmental factor or the fact that the only known sibling pair developing this defect share an identical genetic constitution strongly suggests that an unusual combination of genetic factors must be present in a homozygous form before this abnormal susceptibility becomes manifest.

Unusual racial or ethnic patterns of occurrence or course would be consistent with genetic disorders, but would not provide conclusive evidence thereof. Considering the racial composition and patterns of medical care of populations about whom the Registry is most likely to receive reports, one has no compelling reason to suspect that members of one race are more likely to develop this reaction, given a similar drug exposure, than are those of another. However, a striking difference in clinical course seems to be related to race in this series. Nonwhite patients tend to have a much more benign course than whites, a trend not previously noted.

Unusual patterns of occurrence relative to age or sex, if not otherwise explained, would tend to implicate developmental, degenerative, or hormonal factors as being of at least secondary importance. Females accounted for 54% of cases surveyed by Yunis and Bloomberg⁶ and 62% in the current report.

Some of the age-sex patterns noted can reasonably be assumed to reflect differences in occurrence rates for various diseases for which chloramphenicol is

often given (Table), but in addition, it seems likely from case data that there is an increased susceptibility to this complication in females prior to the menopause. A peak occurrence rate was noted at 6 to 10 years of age by Yunis and Bloomberg⁶ and at 3 to 7 years of age in the present series, the differences being in part due to different tabulation intervals. The marked difference between US and non-US reports in this regard suggests that there may be different national medical trends in the approach to use of chloramphenicol. Upper respiratory tract infections are frequent in this age group and account for a high proportion of uses. Thus, one can neither confirm nor refute at this time the possibility that children at this age may be more susceptible to chloramphenicol-induced marrow depression.

Clinical Characterization.—Yunis and Bloomberg⁶ interpret the data of their review as indicating that chloramphenicol produces two types of marrow toxicity. They state that the first of these usually occurs during therapy, is associated with a larger total dose, demonstrates a normocellular marrow, shows anemia with or without leukopenia or thrombocytopenia, and is reversible on withdrawal of the drug. The second type shows a delayed onset, is not necessarily dose-related, demonstrates an aplastic marrow with associated pancytopenia, and usually has a fatal outcome. A majority of cases in the current report conform in most respects to the second class, and there is another cluster which fits fairly well into the first class. However, a number of cases fall between or overlap these two groups. For example, nine of 60 patients in the present series who had at least two weeks delay between the last dose and development of the reaction showed a normocellular marrow or one with only isolated cellular depression, whereas Yunis and Bloomberg found no such cases. All combinations of blood cell depression were seen in association with nonaplastic marrows, and half of the current series showing pancytopenia in contrast to a more limited spectrum seen in the series reviewed by Yunis and Bloomberg. Patients with hypoplastic marrows tend to have received a smaller dose of drug, but there is an appreciable overlap. Thus, the 10%, 50%, and 90% intercepts of a cumulative dosage curve for 48 current cases with marrow hypoplasia were 5, 20, and 54 mg per kilogram per day, respectively; whereas for 28 cases with lesser degrees of marrow involvement the corresponding figures were 16, 31, and 88 mg per kilogram per day. These doses are well within usual recommendations. Curves for the duration of therapy were very similar for the two degrees of marrow involvement with a median of 11 to 12 days. The cases reviewed by Yunis and Bloomberg on the other hand, show a median duration of therapy of about 35 days for patients with hypoplastic marrows, and about 20 days for those with nonhypoplastic marrows. Unidentified biases in the reporting of cases may account for this difference between the two series.

The implication of these authors in dividing chloramphenicol-associated blood dyscrasias into two groups is that there may be two separate mechanisms involved. The current study would indicate that the cases as they occur are not always so sharply divisible, and that the possibility of a single pathogenetic mechanism is by no means ruled out. Findings in the identical twins reported here would speak for a single mechanism, for the patient with the greater number of prior courses developed typical aplasia, whereas his twin showed a readily reversible, isolated cytopenia.

Preventive Aspects.—The best educated guess as frequency of this complication, probably an underestimate of true occurrence, is that of Leikin et al.⁹ in which it would appear that less than one case of serious marrow toxicity occurs for every 100,000 courses of therapy. The data presently available are not appropriate for further speculation in this regard.

This study does, however, present a good deal of quantitative information relative to the types of drug course which have been associated with this complication. Marrow toxicity has been seen after low doses and high doses, chloramphenicol alone and in combination with other drugs, short courses and long courses, continuous therapy and intermittent therapy, and single courses and repeated courses. Most patients have received chloramphenicol in dosage and duration commensurate with best clinical practice. Unfortunately, however, it cannot be stated that indications for use always conformed to optimal standards.

Most experts would consider chloramphenicol the treatment of choice in typhoid and paratyphoid infections, and some would include *Haemophilus influenzae* meningitis. These three conditions accounted for 6.6% of indications in the current series, most of these being from non-U.S. sources. Chloramphenicol is

also indicated in certain other serious acute and chronic infections depending on in vitro sensitivities and particular features of a patient's course. The report forms did not request sufficient data for further evaluation in the regard.

The drug is inactive against common viral and upper respiratory tract infections, but these conditions accounted for a significant percentage of stated indications in this series. Thus, the most powerful preventive tool available is the use of this agent only for serious infections in which the balance of risks of adverse reactions against the risks of inadequate therapy tend to favor use of this antibiotic over alternative methods of treatment. It should be recognized that the risk of occurrence in any case treated with chloramphenicol is quite slight, but the risk of a fatality in that patient who develops this reaction is great. Some physicians have belittled this complication because they have seen no hint of a blood dyscrasia in the many courses of chloramphenicol therapy which they have directed. One should not be surprised at such an experience, for it is a rare complication; however, this is little consolation to the future patient under such a physician's care who dies of aplasia because chloramphenicol was given when it need not have been.

Most patients develop manifestation of marrow depression after the drug has been stopped, often weeks or months later. It thus appears that monitoring blood counts during therapy would be of little or no value in preventing morbidity and mortality in the majority of cases. However, there is a minority of reactions usually isolated cytopenias, which may become apparent during therapy and respond to withdrawal of the drug. It is for the recognition of such cases that we recommend the occasional performance of blood counts during chloramphenicol therapy. Under the assumption that an isolated cytopenia represents a basically different and less dangerous type of toxicity, Yunis and Bloomberg⁶ do not feel that therapy need be stopped in such cases. We do not agree. No cases in which chloramphenicol was continued after the development of a cytopenia have come to our attention, and one would seem ill advised to continue therapy on the basis of this unproven theory.

SUMMARY AND CONCLUSIONS

This review involves 408 cases of chloramphenicol-associated non-neoplastic depression of one or more blood cell types that were reported directly to the AMA Registry on Blood Dyscrasias or abstracted from the medical literature.

Various quantitative features of the occurrence of this dyscrasia and relationship to drug administration have been delineated.

The dyscrasias noted range from readily reversible, isolated cytopenias occurring during therapy to delayed, progressive aplastic anemia. This range is not considered as necessarily indicative of more than one fundamental type of drug reaction. It is apparent that blood dyscrasias may occur in relation to conventional and even brief courses of therapy, and that signs of such reaction may not be seen until long after the course has been completed. The best approach to prevention thus lies in a sound appraisal of possible benefits and dangers whenever use of this drug is contemplated. The occasional monitoring of blood counts may prove worthwhile in rare cases, but its expected value in the usual case is sufficiently small that one cannot substitute such a practice for good judgment in deciding when the drug should or should not be used.

A more complete bibliography indicating where previously published cases appear, together with other supplemental information, including rules and transformations used to estimate desired parameters from partial data, may be obtained by ordering Document No. 9515 from American Documentation Institute, Library of Congress, Washington, DC 20540, remitting \$2.50 for photoprints or \$1.75 for 35-mm microfilm.

GENERIC AND TRADE NAMES OF DRUG

Chloramphenicol—*Chloromycetin*, *Cylphenicol*, *Tega-Cetin*.

NOTE.—From the Research Resources Laboratory, University of Illinois, College of Medicine, Chicago, and Biostatistics Research Support Center, Veterans Administration Hospital, Hines, Illinois.

This report has been prepared at the request of the Panel on Hematology of the Section on Adverse Reactions of the AMA Department of Drugs.

Reprint requests to Secretary, Council on Drugs, American Medical Association, 535 N Dearborn St, Chicago 60610.

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ATTACHMENT NO. 3

[From the Journal of the American Medical Association]

WHEN IT COUNTS . . . CHLOROMYCETIN (CHLORAMPHENICOL)

MAY BE INDICATED IN CERTAIN SEVERE RESPIRATORY INFECTIONS

Because of its wide antibacterial spectrum and its ability to diffuse into infective foci, Chloromycetin may be of value in the treatment of selected severe respiratory tract infections due to susceptible microorganisms. However, as with any antibacterial agent, the administration of Chloromycetin must be adjunctive to the overall therapeutic approach to this family of diseases. Appropriately treated, good results can be expected in bacterial pneumonia and empyema; in bacterial complications of bronchiectasis and bronchitis; all of which are severe disorders often chronic and difficult to eradicate.

The decision to choose Chloromycetin from among a group of antibiotics suggested by *in vitro* studies to be potentially effective against a specific respiratory tract pathogen(s) should be guided by severity of infection, relative susceptibility of the pathogen(s) to the various antibacterial drugs, relative efficacy of the various drugs in this family of infections, and the important additional concepts contained in the "warning box."

Patients with respiratory tract infections usually become afebrile in 18 to 72 hours on recommended doses; roentgenographic clearing may be slower.

Neoplastic, fungal, and mycobacterial disease as a cause of persisting respiratory disease should be ruled out by appropriate means.

CHLOROMYCETIN

Detailed information, including indications and dosage, appears in the package inserts of Chloromycetin products for systemic use. Consult the appropriate package insert.

"Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections.

"Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

Chloromycetin, an antibiotic having therapeutic activity against a wide variety of organisms, must, in accordance with the concepts in the "warning box" above, be used only in certain severe infections.

Contraindications: Chloramphenicol is contraindicated in individuals with a history of previous sensitivity reaction to it.

It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions and Side Effects: Untoward reactions in man are infrequent; however, they have been reported with both short-term and prolonged administration of the drug. Among the reactions reported are blood dyscrasias as mentioned in the warning. When, during the course of therapy, blood counts show unusual deviations which may be attributable to the drug such as reticulocytopenia, leukopenia, or thrombocytopenia, therapy with chloramphenicol should be discontinued. Also reported are certain gastrointestinal reactions resulting in glossitis and stomatitis, which are indications to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported. Pseudomembranous enterocolitis has been reported in a few patients. Hypersensitivity reactions manifested by angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in chloramphenicol-sensitive patients. Urticaria and vesicular lesions have been observed. They are usually mild in character and ordinarily subside promptly upon cessation of treatment.

Febrile reactions have been reported.

A reaction of the Jarisch-Herxheimer type has been reported following therapy in syphilis, brucellosis, and typhoid fever. Typhoid fever patients have exhibited a "shock-type reaction" characterized by circulatory collapse attributed to sudden release of endotoxin. Neurotoxic reactions, including optic and peripheral neuritis, headache, mild depression, "dazed feelings," internal ophthalmoplegia, mental confusion, and delirium have been reported. Symptoms of peripheral neuritis or decreased visual acuity call for prompt withdrawal of the antibiotic and the possible use of large doses of oral or parenteral vitamin B complex. When prolonged high dosage is necessary, toxic side effects may occur which call for dosage reduction or discontinuance of chloramphenicol therapy. Adults and children with impaired liver or kidney function, or both, may retain excessive amounts of the drug. In such instances, dosages should be adjusted accordingly.

Toxic reactions, the signs and symptoms of which have been referred to as the "gray syndrome," with some fatalities, have resulted from high concentrations of the drug in the premature and newborn age groups. One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. The following summarizes the clinical and laboratory studies that have been made on these patients: (1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life. (2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. (3) The symptoms appeared in the following order: (a) abdominal distention with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. (4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules. (5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses. (6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Precautions: See "warning box" for precautions.

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, the drug should be discontinued and appropriate measures should be taken.

Monitoring of liver and kidney function should be accomplished during therapy in patients with existing liver or kidney disease.

Supplied: Chloromycetin is available in a variety of forms including Kap-seals of 250 mg.

WHEN IT COUNTS . . . CHLOROMYCETIN (CHLORAPHENICOL)

CAN BE USEFUL IN URINARY TRACT INFECTIONS

Urinary tract infections, often recurrent and resistant to treatment, are among the most frequent and most troublesome types of infections seen in clinical practice. Successful therapy is largely dependent on identification and susceptibility testing of invading organisms, administration of appropriate antibacterial agents, and correction of obstruction or other underlying pathology.

Chloromycetin has proved to have a wide and effective range of activity against pathogenic invaders of the urinary tract, including the coliform group, certain proteus and aerogenes species, micrococci and enterococci. Clinical response usually parallels *in vitro* susceptibility. Relief of symptoms and repeated bacteriologic studies should be depended upon to indicate duration of treatment. Chloromycetin continues to be a most valuable drug in the management of urinary tract infections.

The decision to choose Chloromycetin from among a group of antibiotics suggested by *in vitro* studies to be potentially effective against a specific pathogen should be guided by the severity of infection, the relative susceptibility of the pathogen to the various drugs, the efficacy of the various drugs in urinary tract infections, and the important additional concepts contained in the "warning box."

CHLOROMYCETIN

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"Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

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It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions and Side Effects: Untoward reactions in man are infrequent; however, they have been reported with both short-term and prolonged administration of the drug. Among the reactions reported are blood dyscrasias as mentioned in the warning. When, during the course of therapy, blood counts show unusual deviations which may be attributable to the drug such as reticulocytopenia, leukopenia, or thrombocytopenia, therapy with chloramphenicol should be discontinued. Also reported are certain gastrointestinal reactions resulting in glossitis and stomatitis, which are indications to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported. Pseudomembranous enterocolitis has been reported in a few patients. Hypersensitivity reactions manifested by angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in chloramphenicol-sensitive patients. Urticaria and vesicular lesions have been observed. They are usually mild in character and ordinarily subside promptly upon cessation of treatment.

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Toxic reactions, the signs and symptoms of which have been referred to as the "gray syndrome," with some fatalities, have resulted from high concentrations of the drug in the premature and newborn age groups. One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. The following summarizes the clinical and laboratory studies that have been made on these patients: (1) in most cases therapy with chloramphenicol had been instituted within the first 48 hours of life. (2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. (3) The symptoms appeared in the following order: (a) abdominal distention with or without emesis; (b) progressive palad cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. (4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules. (5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses. (6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Precautions: See "warning box" for precautions.

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, the drug should be discontinued and appropriate measures should be taken.

Monitoring of liver and kidney function should be accomplished during therapy in patients with existing liver or kidney disease.

Supplied: Chloromycetin is available in a variety of forms including Kapseals® of 250 mg.

Senator NELSON. Our next witness is Dr. Paul D. Hoeprich. Doctor, we appreciate very much your patience in waiting to appear. We appreciate your taking the time to come here today.

STATEMENT OF DR. PAUL D. HOEPRICH, DIRECTOR, SECTION OF CLINICAL MICROBIOLOGY AND IMMUNOLOGY, DEPARTMENT OF INTERNAL MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA, DAVIS, CALIF.

Senator NELSON. Have you submitted a biography?

Dr. HOEPRICH. No; I did not.

Senator NELSON. Would you, then, for the record, summarize your professional background?

Dr. HOEPRICH. Surely. At present, I am professor of medicine in the School of Medicine at the University of California at Davis. I have been in this position since September 1, 1967. Prior to that time I was on the faculty of the Department of Medicine, University of Utah College of Medicine, where I was for 10½ years, coming there from the medical faculty of Johns Hopkins. I got my degree in medicine at Harvard Medical School and had postgraduate training in bac-

teriology and immunology at Harvard and in teaching hospitals in Boston, New Haven, and in Cleveland.

I am certified by the American Board of Internal Medicine and by the American Board of Microbiology. My particular interest is infectious diseases.

In my academic capacities I have headed, and do now head, sections within the department of medicine that are concerned with infectious diseases.

Senator NELSON. Thank you very much. You may proceed to present your statement and at any time you may elaborate on any part of your statement if you think it will be helpful for the record.

Dr. HOEPRICH. Thank you, Senator Nelson.

Discovered in 1947, chloramphenicol is an antibiotic substance that is elaborated by the fungus *streptomyces venezuelae*. In concentrations that are readily attained in the blood and body fluids of humans given ordinary doses, chloramphenicol halts the growth of many kinds of micro-organisms that cause infectious diseases in man. These include:

1. Bacteria—both Gram positive, for example, pneumococcus, and Gram negative, for example, typhoid bacilli.
2. Rickettsiae—minute micro-organisms, smaller than bacteria, that cause diseases such as Rocky Mountain spotted fever.
3. Bedsoniae—smaller, even, than rickettsiae but larger in size than the true viruses, these micro-organisms cause infections such as psittacosis.
4. Mycoplasma—remarkably pleomorphic micro-organisms that frequently cause respiratory tract infections in man.

INDICATIONS

There are two primary indications for use of chloramphenicol. Note that this is in the context of what is presently available in the field of antimicrobial agents:

1. Typhoid fever.
2. Some infections caused by the so-called paratyphoid bacilli, that is, bacteria of the genus *salmonella* other than *Salmonella typhi*, the cause of typhoid fever.

The nontyphoidal salmonellosis should be treated with chloramphenicol in all patients when there is:

- (a) Bloodstream invasion.
- (b) Spread of infections outside the gastrointestinal tract, for example, to involve the joints or the bones.
- (c) Severe, protracted, actual dysentery.

In addition, all clinical forms of *salmonella* infection, regardless of severity, are indication for treatment with chloramphenicol in particularly vulnerable persons.

Senator NELSON. On the previous page, part c., severe protracted actual dysentery refers to that dysentery caused by *salmonella*; is that correct?

Dr. HOEPRICH. That is correct; yes. However, it must be understood that true dysentery of this severity is quite unusual as a consequence of *salmonella* infection. Gastroenteritis with nausea, vomiting, diarrhea, is the commonest clinical form of salmonellosis. This is best

treated symptomatically, without any antibacterial agent, specifically, without chloramphenicol.

Senator NELSON. Thank you.

Dr. HOEPRICH. On the other hand, all clinical forms of salmonella infection, regardless of severity, are indication for treatment with chloramphenicol in particularly vulnerable persons. These include:

- (a) The very young.
- (b) The aged.
- (c) Those with serious, underlying diseases that in some way compromise body defenses—neoplastic diseases, metabolic diseases, collagenvascular diseases. There are other examples in this particular category.

Mr. GORDON. Dr. Hoeprich, when you say there are two primary indications, does this mean when chloramphenicol is the drug of first choice?

Dr. HOEPRICH. Chloramphenicol is the drug of choice; yes.

Mr. GORDON. Does that mean first choice, when you say drug of choice?

Dr. HOEPRICH. Yes.

Mr. GORDON. It would be the drug of first choice for salmonella?

Dr. HOEPRICH. In treating the infections, typhoid fever, and those nontyphoidal salmonella infections previously described.

Mr. GORDON. I see. Typhoid fever is a type of salmonella infection?

Dr. HOEPRICH. Yes. It is caused by salmonella typhi.

Mr. GORDON. I see.

Dr. HOEPRICH. Now, there are secondary indications for use of chloramphenicol and these take the form of unusual circumstances:

1. Hypersensitivity that is so severe as to preclude use of another, otherwise preferable agent. For example, the agent of first choice for the treatment of Q fever is tetracycline; if use of tetracycline has provoked a life-threatening hypersensitivity reaction in the patient, chloramphenicol should be substituted. Hypersensitivity to tetracycline is quite unusual, but does occur.

2. Infection caused by a micro-organism proved to be resistant to the action of other antimicrobial agents but susceptible to chloramphenicol. Gram negative enteric bacilli with such characteristics are sometimes cause for infection in humans.

3. Augmented toxic hazards that mitigate against use of other, ordinarily preferable, antimicrobial agents. For example, severe infection in the newly delivered mother may be caused by bacteria that are susceptible to tetracycline. However, tetracycline is peculiarly liable to cause acute liver injury of lethal proportions in such circumstances. Chloramphenicol does not bear this risk and could be used, but only if the micro-organisms involved are not susceptible to other antimicrobics.

Mr. GORDON. In these two primary indications for chloramphenicol, would you be able to give an estimate, just off the top of your head, a rough estimate, as to the number of cases in the United States, say last year, of this type of infection?

Dr. HOEPRICH. Well, of typhoid fever, there is an epidemic surveillance of this sort of thing in this country, so there are accurate figures. My guess is it is a few hundred cases, 200 or 300, perhaps,

in the course of a year. Of the nontyphoidal salmonella infections, there are considerably greater numbers and I suspect that these will be increasing in number as years go on and our society prefers more and more to eat food that is prepackaged, that has been handled and prepared by somebody else. So, I have a more difficult time arriving at some figure for nontyphoidal salmonellosis. These do occur in epidemic proportions. For example, we had in the Salt Lake City area in 1963-64 an epidemic which resulted in the clinical occurrence of at least 1,000 cases.

Mr. GORDON. How many cases?

Dr. HOEPRICH. At least 1,000, which were of such severity that a physician was consulted. Now, if you add to this the number of infections that were of lesser severity, you probably would have to multiply by a figure of around 10.

All I am saying is that the nontyphoidal salmonellosis are much more common, much more frequent in occurrence and it is hard to arrive at an annual figure since there are, too, epidemic situations. By and large they are much less severe infections.

Mr. GORDON. Do they occur frequently?

Dr. HOEPRICH. They are occurring, I think, with more frequency—at least we notice them more now than we did in times past.

Senator NELSON. For my information, I notice in the primary indications you do not include the rickettsial infections.

Dr. HOEPRICH. No, I do not, Senator Nelson. As we see them in this country, and this is the basis on which I excluded them, the agent of choice is one of the tetracycline group of drugs. The occurrence of gastro-intestinal side effects of such severity that one cannot give tetracycline to a patient who has a rickettsial infection does occur. But in our society, in this country, it is very simple. You then put a needle in the vein and run in the drug and you handle it in that fashion.

Now, if you are treating a rickettsial infection in Southeast Asia and you cannot conveniently or practically administer tetracycline by injection, and you have the choice of no therapy, which is the result if you give it by mouth and the patient vomits the material back up, or going to chloramphenicol. But that is not our situation here. I think the context is very important.

CONTRAINDICATIONS

Infections caused by micro-organisms that are not susceptible to chloramphenicol should never be treated with this agent. These include:

1. All parasitic infections—multicellular, for example, worms, and unicellular, for example, malaria.
2. All mycotic infections, for example, histoplasmosis.
3. Some bacterial infections, for example, those caused by *Pseudomonas* species. My point is that there are some bacteria that are always resistant to chloramphenicol and these should never be occasion for use of this drug.
4. All viral infections, for example, influenza, the common cold.

Infections caused by micro-organisms that are susceptible to chloramphenicol but are equally, or more, susceptible to other agents, should

never be treated with chloramphenicol. Excepting only the situations noted under indications, above, this interdiction includes all infections caused by bacteria, rickettsia, bedsonia, and mycoplasma.

Undefined illnesses that might be infectious in cause should never be treated with chloramphenicol.

Similarly, chloramphenicol should never be used as a prophylactic agent.

Senator NELSON. Is it commonly used as a prophylactic agent?

Dr. HOEPRICH. I do not think it is. Again, this is a function of time. There was a period in the history of the development of antimicrobial therapy when this drug was used. At least as I observe it, as other agents have become available, and as the toxic hazards of chloramphenicol have been recognized, this kind of usage is quite uncommon.

Senator NELSON. In the study that Dr. Best compiled, of the 408 aplastic anemia cases submitted, 5.5 percent were ones in which the drug had been given for prophylaxis. Now, that was from 1953 to 1964. Has that statistic changed since then?

Dr. HOEPRICH. Well, I think so. There was, for example, a period of time when urologists would use this drug as prophylaxis against infection complicating prostatic surgery. I think that this use has largely disappeared. I may be mistaken about this. I see just a limited segment of practice, and use may vary from area to area, I am sure.

SIDE EFFECTS

In order of increasing seriousness, there are four major side effects to administration of chloramphenicol. These are: (1) ecologic disruptions; (2) irritative phenomena; (3) direct toxicity; and (4) hypersensitivity. All except hypersensitivity are dose related—the higher the dose and the longer the period of administration, the more likely become the adverse reactions (1), (2), and (3). Withdrawal of chloramphenicol, quite reasonably, is the first step toward reversing such adverse effects. On the other hand, hypersensitivity reactions are not clearly dose related and do not predictably abate on withdrawal of the drug.

1. Ecologic disruption is consequent to the selective elimination or suppression of those micro-organisms normally resident on and in persons that are susceptible to the antimicrobial action of chloramphenicol. Elements of this resident microbiota that are resistant to chloramphenicol are freed of competition and can attain to abnormally high population densities. Also, micro-organisms resistant to chloramphenicol may be acquired from the environment external to the person—drawn in, as it were, by the shelter of chloramphenicol suppression of microbial competition. Termed superinfections when the overgrowing or invading micro-organisms cause disease, this side effect is not unique to chloramphenicol but is, to a greater or lesser extent, a liability of any antimicrobial used in therapy.

2. Irritation is most common in the gastro-intestinal tract, taking the form of nausea, vomiting, diarrhea that is often associated with a brassy, unpleasant taste in the mouth. There may be irritation in the crotch region.

3. Direct toxicity varies with age. In the adult, anemia is the most common manifestation. Prolonged, high dosage use of chloramphenicol can halt maturation of red blood cells in the bone marrow; anemia results. Rarely, there may be inflammation of the optic nerve, causing blurring of vision or perverted sensation—of a tingling, crawling feeling—in the skin.

Premature and newborn infants are especially vulnerable to direct toxicity because the capacity to eliminate chloramphenicol in the urine, and to inactivate this antibiotic by chemical change in the liver, is not fully developed until the human is more than a month old.

4. Hypersensitivity to chloramphenicol is quite uncommon. Skin rashes, fever, inflammation of the tongue are annoying when they occur but are not life-threatening.

Pancytopenia, a marked reduction in the numbers of all of the formed elements of the blood—the red and white blood cells, blood platelets—results when hypersensitivity to chloramphenicol brings about failure of production of these elements in the bone marrow. When such failure is complete, termed aplasia of the marrow, death is usually the outcome. Reactions of this severity are rare occurrences. Precise determination of incidence is not possible since:

- (a) The size of the population at risk is not known.
- (b) All cases of drug-associated marrow aplasia are not reported.
- (c) The incidence of bone-marrow failure without exposure to any cause is not known.¹

As a footnote to this statement (c), I put in the reference to the report from the California report which has been cited previously, wherein a figure is given of one in 524,600 persons not exposed to chloramphenicol will develop fatal aplastic anemia, fatal bone-marrow aplasia. In the portion of the report which I had access to, I did not find any basis for this particular calculation and this is why I say I have no feeling for how reliable it is or how it was arrived at. It is one of the few figures that are put down on paper, however, as the natural, normal incidence, if you will, of bone-marrow aplasia.

There is a certain risk, apparently, in just being alive to having bone marrow fail, and that is the problem of (c); I do not know what that risk is.

However, several estimates of the risk of induction of pancytopenia from use of chloramphenicol have been made, and these are tabulated. I must apologize here, Senator Nelson. The first reference is in error, so I discovered after the copies of this statement were made.

The first figure should actually be one in 80,000 and the reference is the *Scottish Medical Journal*, volume 7, page 96, 1962, and the reference as given, the first one, one in 800,000, that is incorrect and should not be in the table.

The second one is one in 10,000 to one in 100,000, which appeared in the *British Medical Bulletin* in 1960. The third one, one in 156,000 to one in 227,000, reference as given, and finally, the reference in the California State report.

¹ According to the report to the California State Assembly and senate, made by the California Medical Association and State department of public health, dated Jan. 1, 1967, one in 524,600 persons in California, not exposed to chloramphenicol, will develop fatal aplastic anemia.

(The table referred to follows:)

<i>Source</i>	<i>Incidence</i>
Am. J. Med. 19:274, 1955.....	1 in 800,000
Brit. Med. Bull. 16:67, 1960.....	1 in 10,000 to 100,000
Clin. Proc. Children's Hosp. Wash. D.C. 17: 171, 1961.....	1 in 156,000 to 227,000
Report to California State Assembly and Senate, California Medical Assoc. and the State Dept. of Pub. Health, 1 Jan., 1967.....	1 in 24,200 to 40,500

Dr. HOEPRICH. I would like to say with reference to this last estimate, one in 24,200 to one in 40,500, that the variation here was correlated with the assumed dose of chloramphenicol given to the patient. I think in the circumstance of bone-marrow aplasia where, so far as we understand it at present, hypersensitivity is the important mechanism, that the dose given to a particular individual probably is not the essential and entirely the critical factor. I would prefer, myself, in calculating this incidence, to regard any exposure to chloramphenicol as being significant; if this is done, then the incidence in the California report becomes one in 73,333 exposures to the drug, an incidence more nearly in keeping with other estimates.

You may or may not agree that this is a justified interpretation, but it is mine.

Mr. GORDON. Doctor, what is the importance of blood levels in treatment and in the production of side effects?

Dr. HOEPRICH. In treatment, I would say the importance of blood levels lies in the need to get enough antimicrobial to the site of infection to inhibit the growth of bacteria.

Ideally, we would like to measure, then, the concentration of the drug where the infection is. But suppose the infection is in the covering membranes of the brain, in a meningitis. It is very difficult to get a piece of this to make analysis for the content of the drug. Therefore, we do the next best thing, we get at the thing which we can get at, namely, the blood, and by correlating clinical experience and the susceptibility of micro-organisms to a particular antimicrobial, which can be determined very accurately in the test tube, we can arrive at some estimation of how much a person has to have aboard in his blood for there to be enough in the site of infection, where we cannot measure the drug, to bring about cure of an infection.

Mr. GORDON. Has it ever been determined how high a blood level you would need?

Dr. HOEPRICH. In a particular infection?

Mr. GORDON. Yes.

Dr. HOEPRICH. If you are treating, as an example, an infection caused by a pneumococcus—pneumococci are exquisitely susceptible to chloramphenicol, as well as to other agents. You would not need very much. I would say something like one or two micrograms per milliliter of blood.

On the other hand, if your problem was an infection caused by *Klebsiella*, a gram negative bacillus which is notably resistant to antimicrobial agents, you might well have to have 15, 20, 30 micrograms per milliliter of blood, and again if your infection is in an enclosed space, where we know penetration may be problem, or where there may be pus formation, or the infection may be walled off by an actual mechanical membranous structure that is not very well supplied with

blood vessels, then we would have to insist that there be more in the blood to soak into the site of infection.

Mr. GORDON. How about the relationship between aplastic anemia and blood levels?

Dr. HOEPRICH. I do not know that that has been demonstrated. In terms of a direct toxic effect, suppression of maturation, particularly of red cells in the bone marrow, this is definitely correlated with the quantity of chloramphenicol present in the individual. With bone marrow aplasia which is generally regarded as a form of hypersensitivity, I do not think the blood level is critical. A little bit has been enough to trigger bone marrow aplasia.

Mr. GORDON. But, the higher the blood levels, the greater chance you have of halting the maturation of the cell?

Dr. HOEPRICH. Yes. With the direct toxic effects, there is no question that the more you have the more successful you are going to be in blocking maturation, or injuring the retina, the optic nerve, or any of the direct, irritative effects of nausea, vomiting, diarrhea.

Rather than total failure of bone-marrow function, there may be selective depression yielding, by itself, anemia, or deficiency of white blood cells, or marked lack of blood platelets. Reactions of this kind are also not dependent on the dose of chloramphenicol but do occur most often in persons who have taken the drug on more than one occasion. There is some indication that complete aplasia will not result if chloramphenicol is discontinued as soon as adverse effect on the bone marrow is detected; for example, increase in serum iron concentration, fall in the number of white blood cells in the circulating blood. I mention these things because people do feel that there is a correlation here, that if you stop the drug, then nothing further ill will happen in terms of bone marrow aplasia. You have to add to that, of course, that you do not know that an aplasia would have resulted had you kept on with the drug. So, it is one of those situations in which the physician's judgment plays a very major part.

IMPACT OF ADVERTISING ON USE

This is most difficult to judge. Perhaps some indication could be gleaned from comparing dollar volume of sales of chloramphenicol with advertising outlay for identical periods of time. Such data are not readily available.

However, advertisements for chloramphenicol, as they appear in medical journals, quite clearly suggest wider use than the limited indications previously described in this statement. Always this is done with written, covering insertions such as, " * * * may be indicated * * *," " * * * in certain severe infections * * *," along with reference, in recent advertisements, to a, " * * * warning box." In the latter, the hazard of aplastic anemia is fairly and adequately described.

The device of display—an instrument, a patient, a physician—is freely used in this effort at subtle, implied, indirect recommendation to prescribe chloramphenicol. For example, the display of a bronchoscope in an ad for chloramphenicol vaguely, indirectly, subliminally suggests that in serious, occult bronchopulmonary disease—it must be serious, why else the instrument; it must be occult, why else

the difficult procedure of bronchoscopy—chloramphenicol is a useful agent.

Positive statement of the limited indications for use of chloramphenicol would be far preferable.

Senator NELSON. Are there certain bronchial conditions in which chloramphenicol is indicated?

Dr. HOEPRICH. One can conceive that there might be. For example, infections caused by the gram negative bacilli such as the *Salmonellae* sometimes involve the tracheobronchial tract and, indeed, I have seen what one would have to call pneumonia caused by *Salmonella typhi* murium, one of this kind of micro-organisms; this was an indication for use of chloramphenicol. The circumstances that I referred to, Q fever, occurring in a patient who had a severe, life-threatening hypersensitivity reaction to tetracycline, this would be another instance; Q fever is present as a pneumonia when it occurs in humans. So these situations can occur. I do not think they are utterly impossible, but they are uncommon, I am sure.

OTHER ASPECTS

Chloramphenicol is a remarkably effective antimicrobial agent. Indeed, chloramphenicol would be a nearly ideal antimicrobial were it not for the adverse reaction of bone marrow aplasia. Although quite infrequently in occurrence, fully developed aplasia is usually lethal. Because, at present, there is no way to predict who will have this kind of adverse reaction, and because there are now available many alternative antimicrobics, the use of chloramphenicol should be severely restricted to the few indications previously described.

In those few situations when chloramphenicol must be used, its use must be circumscribed in these ways:

1. The blood must be monitored every 48 hours by measurement of the volume of packed red cells, number of white blood cells, along with differentiation of the kinds of white blood cells and examination for adequacy in numbers of blood platelets. I might add, here, that it is not generally available, but some would regard measurement of the iron concentration in the blood serum as a much superior monitoring device to any of the ones I have indicated. This is technically a difficult procedure and is certainly not generally available.

Treatment must be stopped when any of these measurements falls below the accepted, minimal values.

Senator NELSON. Do you consider when chloramphenicol is administered to any patient that blood studies must always be made or sometimes be made?

Dr. HOEPRICH. I think they must always be made.

2. Dosage with chloramphenicol must—

- (a) Never be excessive, that is, 15 to 80 milligrams per kilogram body weight per day in the adult; no more than 25 milligrams per kilogram body weight per day by injection in the premature or newborn infant; no more than 50 milligrams per kilogram body weight per day by injection in infants over 1 month in age.

- (b) Never be unduly prolonged.

3. Repeated use in the same person must be avoided.

Senator NELSON. Today you heard Dr. Weston's testimony suggesting that some limitation, by legislation or otherwise, be imposed upon the use of this drug. We had similar testimony Tuesday from Dr. Lepper, and both Dr. Dameshek and Dr. Best, I believe, thought some kind of a limitation ought to be imposed. Do you agree or disagree with that?

Dr. HOEPRICH. I think something should be done. The question is whether it should be at the level of limitation by direct decree of use of the drug itself. I am not sure that this ought to be the only mechanism. I know the suggestion has been made that its use be limited to hospitalized patients. I think this might be an undue restriction in that people with severe salmonellosis are not always treated in hospitals. I, myself, think they should be. That does not mean that this always happens. So that I am concerned about that.

I would wonder if it would not be possible to approach the matter, at the same time, from the other end. As is obvious in my statement, I really think that this indirect suggestion for prescription in the advertisements is a point of attack that might be very useful.

Senator NELSON. What is that?

Dr. HOEPRICH. Well, this business of displaying a bronchoscope and saying it may be useful in bronchopulmonary infections. Indeed, it may be useful, but the approach should not be that it may be useful. Rather, say it is useful in salmonellosis, typhoid fever. In other words, I think a positive statement of indications and the complete prohibition of quasi, occasional, possible, indirect suggestions, would be of great impact in terms of misuse of the drug.

Senator NELSON. That would mean, I assume, that somebody with the authority, FDA, for example, would have to say with regard to drugs that create serious problems, "This is precisely the kind of advertising that you are allowed."

Dr. HOEPRICH. Yes. I am encouraged in this thought because of the abolition of the man in the white coat on television with reference to aspirin ads, for example. I am encouraged to think this kind of approach can be used. That the display business can be taken out of ads. It has been in some circumstances.

Senator NELSON. Tuesday the three doctors who testified made what they considered to be a guess, that only 10 percent of the patients who received chloramphenicol should, in their judgment, have received it. Today, it was Dr. Weston's judgment that 1 percent or less of all the patients that received it should have received it. Do you have any estimate of your own?

Dr. HOEPRICH. Yes. I would occupy a middle ground. I would say probably around 5 percent of those who received it should receive it.

Mr. GORDON. Let us come back to the advertising problem for a moment. Even if the written advertising was controlled to some extent, and I think the FDA does have jurisdiction over that, court cases have certainly shown that the detail man, the salesman who visits a doctor, through his blandishments, I was going to say, through his promotional activities, vigorous promotional activities, seems to water down or to cancel out the written warnings, and I understand that the FDA does not have any control over that type of promotional activity. Do you have any ideas along this line?

Dr. HOEPRICH. Oh, I am sure that this can happen. I have to add, immediately, that I have never seen it happen. I suppose that does not mean anything, for any detail man whom I have talked with who represents Parke, Davis would know better than to tell me that chloramphenicol does not have anything to do with bone-marrow aplasia. I just find it difficult to evaluate that statement. It may be true, and if it is true, I cannot conceive of any mechanism for getting at it. You really cannot eavesdrop on a conversation between two people in a room. That is what it amounts to.

Mr. GORDON. But something should be done about it, if possible?

Dr. HOEPRICH. Yes, I think so; and the sales of this drug certainly far exceed the indications for its use. You can say that about a lot of other agents but the fact is we are talking about this drug.

Senator NELSON. Thank you very much, Doctor. Your testimony has been very useful, very constructive. We appreciate your taking time from your busy schedule to come here and testify. Thank you.

(Whereupon, at 12:40 p.m., the hearing was adjourned, subject to the call of the Chair.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, FEBRUARY 27, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. We will open the hearing of the Monopoly Subcommittee of the Small Business Committee.

On the 6th and 8th of February five distinguished medical experts testified on the widespread and indiscriminate usage of chloramphenicol for the treatment of cases for which it specifically was not indicated. The result has been numerous cases of unnecessary illness, permanent injury, or death. The tragedy is that these were cases which would have recovered without any drug at all or cases in which another drug was available and indicated as the drug of choice.

The most shocking aspect of the whole matter is that the drug is much more frequently prescribed for cases where it specifically should not be used than where it should, thus exposing tens of thousands of patients to wholly unnecessary lethal risks.

The best estimate appears to be that from 3½ to 4 million people per year are given this drug. The estimate of the medical experts is that 90 percent of the people for whom it is prescribed should not receive it at all because it simply is not indicated for their case—and one witness put the figure at 99 percent.

According to the medical experts, chloramphenicol is a very useful and effective antibiotic but it is the drug of choice in a very limited number of cases where no other drug is effective and the disease is serious. Yet, the drug has been widely prescribed for minor conditions such as head colds, sore throat, acne, and other minor infections,

as well as serious conditions where other equally effective drugs were available.

The testimony before this committee and the accumulated evidence of the past few years raise important public policy questions:

Who is responsible for the widespread overprescribing of this drug?

What accounts for the dramatic communications gap between the medical specialists who for 15 years have known and written about this drug and those who have continued to prescribe it for cases where it should not be used?

What responsibility has the AMA assumed in notifying the medical profession about the proper use of this drug? And how effective have they been?

Has the FDA effectively warned the profession and controlled the advertising of this drug? If not—as seems to be the case—why not?

Is this not a dramatic example of the compelling effectiveness of advertising even on a sophisticated audience in its own area of expertise?

These, certainly, are questions which deserve careful attention and will get it from this committee.

Since the hearings, the subcommittee staff and I have received letters and calls describing tragic cases of serious illness and death resulting from the unnecessary use of chloramphenicol. These letters speak for themselves. They will be printed in the record. Ironically and sadly one of our telephone calls was from an employee in the Department of Health, Education, and Welfare who lost his son because he was given Chloromycetin for an infected toe.

I shall have printed in the record at the conclusion of my statement the letters and communications that the committee, subcommittee or I have received. We have as carefully as possible deleted the identification of any of the parties as well as the cities, unless they happen to be a particularly large city, simply because it is not the purpose of the committee to single out any particular case that comes to its attention since these only represent a small sampling of the total number of cases across the country.

These letters will be printed and included as part of the record.

(The letters referred to follow:)

COLORADO, February 20, 1968.

HON. GAYLORD NELSON,
U.S. Senator,
Washington, D.C.

DEAR SIR: In the February 16 issue of *Time* magazine, I learned of your chairmanship of the Senate Monopoly Subcommittee. With reference to the article regarding Chloromycetin, our family would like to state our interest in this antibiotic.

In June, 1966, our then 19-year-old daughter went to ——— Michigan, to work at a summer camp. She had just completed her sophomore year at Colorado State University. Upon arrival in ——— she had a sore throat and was referred

to a local ——— doctor. Upon examination, he gave (no prescription) her a number of pills or capsules (which we later learned were Chloromycetin).

To make a long story short, she continued on until Labor Day, 1966, when she returned home very ill. Within a week she was in the hospital and her condition was diagnosed as aplastic anemia caused by the taking of Chloromycetin. She spent 8½ weeks in the hospital during which time she received about 60-70 pints of blood by transfusion.

Since her discharge from the hospital in November, 1966, she has had to return to the hospital every four weeks to receive 4 pints of blood by transfusion at a cost of \$100. to \$200. a month—this in addition to the original transfusions.

She was able to return to college in January, 1967, and by going to summer school last summer, is now into her last few months of college.

We have a living example in our home of a physician's negligence in the use of a powerful drug. We do not know what the future holds for Lois as she is soon going to be ready to apply for teaching positions, and we do not know if she will be hired with an incurable affliction—or *how* she will be able to manage "blood bills" on a normal salary. If another family can be spared the heartache we have felt and the expenses we have been faced with, we feel we must speak up in attempting to have this drug controlled.

The history of ——— case may be checked at the University of Colorado Medical Center, Denver, Colorado.

Thank you for your courtesy in hearing us through to the end of this letter and we hope to learn of progress in the very near future in the control of the use of this potentially dangerous antibiotic.

Respectfully,

NAME WITHHELD.

COUNSELLORS AT LAW,
Philadelphia, Pa., February 19, 1968.

Re ——— of the Estate of ———, deceased, Civil Action No. ———, Our File: ———.

Senator GAYLORD NELSON,
Chairman, Senate Small Business, Monopolies Subcommittee,
Washington, D.C.

DEAR SENATOR: Our office represents ——— who died on June 25, 1967 at the young age of 25 as a result of two prescriptions for chloromycetin. I enclose herewith a certificate of death from the Commonwealth of Pennsylvania as proof of ——— demise and cause of death.

I have read with great interest the latest newspaper commentary regarding the investigation of your committee into the infamous history of the drug chloromycetin. As a consumer I wish to add my thanks for your courageous stand against the giants of the drug industry and wish you all the success in the future.

The main purpose in writing, Senator, is to inquire if any records of testimony by officers or executives of Parke Davis are available to the public in limited cases such as the one which confronts our office.

We would readily make available any and all information that we have compiled in pursuing the claim ———. Thanking you in advance for your cooperation, I remain

Very truly yours,

NAME WITHHELD.

12603

Date No.

This is to certify that this is a true copy of the record which is on file in the Pennsylvania Department of Health, in accordance with Act 63, P. L. 304, approved by the General Assembly, June 29, 1953.

(Fee for this certificate, \$1.00)

C. L. Wilbar, Jr.
C. L. Wilbar, Jr., M.D.
Secretary of Health
Harrisburg, Pennsylvania

12603

COMMONWEALTH OF PENNSYLVANIA
DEPARTMENT OF HEALTH
VITAL STATISTICS
CERTIFICATE OF DEATH

1. DEATH OCCURRED IN: a. County b. City or borough
PHILADELPHIA

2. OCCASION'S MAILING ADDRESS: a. Street address, R. D., or care number b. Post Office, zone, and state

3. VETERAN: Yes ☐ No ☐

4. NAME OF DECEASED: a. (First) b. (Middle) c. (Last)
G. L. S. Wilbar, Jr.

5. DATE OF DEATH: (Month) (Day) (Year)
6/25/67

6. WHERE DID DECEASED ACTUALLY LIVE: a. State b. County
PENNA. PHILADELPHIA

7. SEX: a. Male b. Female
MALE

8. RACE: a. White b. Negro c. Other
WHITE

9. MARRIED: ☐ NEVER MARRIED ☐ WIDOWED ☐ DIVORCED ☐

10. DATE OF BIRTH: (Month) (Day) (Year)
NOV 23, 1941

11. USUAL OCCUPATION (even if retired):
ENGINEER

12. SOCIAL SECURITY NO.:
2-20-72-7871

13. DATE OF PLACE (State or foreign country):
PA

14. CITIZEN OF WHAT COUNTRY:
U.S.A.

15. FULL NAME OF DECEASED: G. L. S. Wilbar, Jr.

16. FATHER'S NAME: G. L. S. Wilbar, Sr.

17. MOTHER'S NAME: M. L. Wilbar

18. MEDICAL CERTIFICATE (Items 19 through 23 must be completed by physician only)

19. CAUSE OF DEATH: Enter only one cause per line for (a), (b) & (c).

20. PART I. Death was caused by: IMMEDIATE CAUSE (a) b. c.
Bacterial septicemia
Pneumonia
Chronic heart disease

21. CONDITIONS, if any, which gave rise to above cause (a) stating the underlying cause last. DUE TO (a) b. c.
Due to (a) b. c.

22. PART II. OTHER SIGNIFICANT CONDITIONS: contributing to death but not related to the immediate cause given in Part I (a) b. c.

23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.

BROOKLYN, N.Y., February 19, 1968.

Dr. WILLIAM R. BEST,
University of Illinois,
Chicago, Ill.

DEAR DR. BEST: I am enclosing copies of correspondence re the drug Chloromycetin.

After I wrote to Senator Dirksen, I came upon the attached article in Time Magazine, February 16th issue.

How can you oppose the restriction of this drug when the evidence is such that it is not only administered in serious cases, but for minor colds, sore throat, etc. As you will note from the correspondence, my niece was the unfortunate statistical "1" out of 100,000. When it comes so close to home, even that "1" is too much.

I am shocked, that as a respected member of the medical profession, you feel that "infringing on a doctor's prerogative to administer whatever drug he sees fit" supersedes safeguarding that "1" out of 100,000.

I am naturally upset and bitter about your stand on the unlimited dispensing of this lethal drug, and am, therefore, writing to ask you to please help someone else avoid the horrible tragedy of losing a young child because of lack of information, disregard of warnings on labels and indiscriminate prescribing.

It seems so ridiculous to have to plead with a doctor to help save lives.

Very truly yours,

NAME WITHHELD.

ATTORNEY AT LAW,
New Mexico, February 16, 1968.

HON. GAYLORD NELSON,
Senate Office Building, Washington, D.C.

DEAR SIR: Publicity on your excellent work in exposing the laxity of the drug industry in protecting the public from the latent dangers of antibiotics have filtered even out into my corner of New Mexico.

You have conducted hearings within the past two weeks in which Chloromycetin a Parke Davis product was the focal point. I would appreciate very much your assistance in helping me obtain copies of the testimony before your committee concerning Chloromycetin. I am representing a rancher's family whose 16 year old daughter was prescribed a strong dosage for tonsillitis and then a refill after she had apparently recovered. The child died an excruciatingly painful death from aplastic anemia which developed as a result of her susceptibility to the drug.

My investigation in the matter has left me with the opinion that there must be many such cases which have never been accurately diagnosed. My concern, however, is for my client and in order to have optimum understanding of this problem I would like to have a record of your recent investigation and will appreciate your office's help in obtaining it. Needless to say I shall pay the customary charges for such publication as it come from the Superintendent of Documents.

Yours very truly,

NAME WITHHELD.

OREGON, February 16, 1968.

HON. GAYLORD NELSON,
Senate Office Building, Washington, D.C.

DEAR SENATOR NELSON: I have read with interest in the Drew Pearson column and Time Magazine of your efforts to control the drug chloromycetin. I want to personally thank you and encourage you in your efforts.

The reports indicate that only a few hundred people have died as a result of this drug. Something is wrong with the reporting. I lost a little boy at the age of seven, sixteen years ago, because a doctor gave him chloromycetin for a mild cold. There was no warning to the doctor and I could not blame him because he had accepted some of the information in the Parke Davis advertising which was, to say the least, misleading. At the same time my son was in the hospital dying, three more children died in that same hospital within a two-month period. I have personally known several adults who, as a result of chloromycetin given by doctors for colds, influenza and the like, developed aplastic anemia and died.

I didn't sue Parke Davis because no amount of money would have repaid me for the loss of my son. However, I think I made a mistake, and if all of us who have been affected by this drug would have sued Parke Davis and pursued the matter further, perhaps it would have been corrected by this time.

I encourage you to continue your efforts and investigate the use and controls of this drug. I am fully aware that in some instances it can be life-saving, but its indiscriminate and wide use for minor ills has resulted in the loss of the lives of many people.

Every few years some congressman complain about the loose way in which Parke Davis is handling the drug and a few newspaper articles appear. The death rate goes down, and soon afterwards the whole thing starts over again and the death rate increases.

Again let me congratulate you on your efforts to correct the misuse of this drug. I hope you will be successful in bringing it under control.

Sincerely,

NAME WITHHELD.

PENNSYLVANIA, February 16, 1968.

Senator GAYLORD NELSON,
Washington, D.C.

DEAR SENATOR NELSON: I have just read in the Time magazine of February 16, 1968, the article on the hearings before the Senate Monopoly Subcommittee, of which you are the chairman, about the drug Chloromycetin.

I had an adverse reaction from the patent drug Chloromycetin.

June 1965 I had four abscessed teeth. I was running a temperature of 101°-104°. I went to a local physician, was given a prescription for Chloromycetin 250 mg. of 4 hrs. On June 14, 1965, I had all of my lower teeth extracted by Dr. _____

I was taken from Dr. _____ office to Binghamton, N.Y. and was admitted to their I.C.U. I was under the care of Drs. _____. Lab work, sternal punctures was done, white count was 600 diagnosis, complete blood dyscrasia caused by the drug Chloromycetin.

I received 42 transfusions—whole blood, packed cells, extra refined plasma with extra platelets.

I have been ill since June 1965 and continue under the physician's care. I reported this adverse reaction to the drug Chloromycetin to Dr. James L. Goddard, Comm. of N.F.D.A. They sent an investigator from their regional office, _____, Pa., to my home.

I gave Mr. Chine (investigator) my statement, also signed depositions for him to have access to all of my hospital records, name and addresses of the attending physicians. Mr. Chin told me that he would send the report of his findings to the N.F.D.A., Washington, D.C., that I would hear from them. I never heard from them. After six months, I wrote to the N.F.D.A. I received a reply from Laurence H. Stern, also two pamphlets about Chloromycetin.

I hope that this letter is not ignored by you. Suggestions—(1) Physicians should warn patients of adverse reaction from this drug; (2) Druggist should be compelled to put the name of the drug on the label when prescriptions are filled, also to give patient the leaflet issued by Parke-Davis Drug Co. with each prescription for Chloromycetin; (3) News media to be used to bring to the attention of the public the adverse reaction of this drug.

Respectfully,

NAME WITHHELD.

NEW YORK, N.Y., February 10, 1968.

SEN. GAYLORD NELSON,
Chairman, Senate Subcommittee on Drugs,
Washington, D.C.

DEAR SENATOR NELSON: I am vitally interested in the current investigation carried on by the Senate Subcommittee on Drugs with particular reference to the drug Chloromycetin manufactured solely by Parke, Davis and Company.

As Chairman of this Committee, you may be interested in some of the background leading to the death of my sister, _____, at age 44 years. Marion took the drug, chloromycetin, in connection with a minor ailment while in Europe (Spain) during a vacation in October, 1966. I enclose copies of correspondence from my file on the matter.

Your investigation indicates grave concern that doctors are not aware of the possible consequences after a drug such as chloromycetin is administered to a patient. This too, has been the concern of _____'s family. The sole purpose of our contact with Parke Davis after her death was to attempt to prevent the same tragedy to another family. We are advised by those physicians attending my sister before her death, that aplastic anemia which ultimately caused her death was most probably brought on by the drug chloromycetin.

Can you imagine our frustration as we read the Parke Davis pronouncement Anacin could have been the cause of death? Then, the frustration compounded by the last paragraph of their correspondence of September 19, 1967 stating positively that physicians are universally aware of the possible fatal results of the drug chloromycetin; finally, that Parke Davis would not contact the doctor in Spain about the administration of the drug for fear he would think them critical of him.

Needless to say, we are *not* convinced doctors are universally aware of the potential fatal effects of chloromycetin. Furthermore, my sister was able to pur-

chase a second dose of 12 capsules while in Spain without further written prescription. This surely indicates either a lack of knowledge regarding the drug, or a complete lack of professional responsibility concerning it.

Senator Nelson, if my sister's death could save the life of another, our loss would be easier borne. We would like to make any further information we have regarding this case available to you if it would help your investigation. In the meantime, we wish the work of your Committee every success and hope this case may assist you in someway as you investigate the failure of drug companies to adequately warn the medical profession here and overseas, of dangerous drugs.

Sincerely yours,

NAME WITHHELD.

TEXAS, February 13, 1968.

HON. GAYLORD NELSON,
Democrat of Wisconsin,
Washington, D.C.

DEAR SIR: I have just read an article by Drew Pearson in the Wall Street Journal on the subject of the danger of the drug Chloromycetin, and of your interest in protecting people from the drug.

I am sorry to say that I too am a victim of the drug, in the fact that my husband was given sixty (60) capsules of Chloromycetin in Sept. for a kidney infection, (which later was diagnosed as hepatitis) and is in a most critical condition, which has been diagnosed as "thrombocytopenia purpura" caused by the bone marrow's being destroyed from taking the drug.

I called the Doctor attending my husband, who had said that a medication had destroyed the bone marrow and asked him "what drug had destroyed the bone marrow, that I didn't want any given to me." He said "we think Chloromycetin did it. It is a good drug used for some things, but in some people it destroys the bone marrow the same way it has done in your husband." He did not say may have done but has done.

He has been in hospital since the 11th of November, living on blood transfusions. Some days as many as 4 pints of blood a day. I have no hopes of him ever getting well, but we have to keep giving him blood. One just can't say "let him die, its just one more death caused from taking Chloromycetin."

I called the Doctor that gave him the drug and told him what the Doctors in Houston had told me. He said "we are well aware of the fact that it causes bone marrow depression. I had a patient to die from the same thing your husband has." I asked him if it were a child that I had heard of an 8 year old girl dying here from taking the drug and he said "no it was a young adult lady." And then he gave it to my husband!

I have heard of others dying from the drug, but the one the Doctor told me died I would take as a fact, not hear say. If you could see my husband, he is bleeding under the skin so he is spots all over his body and black & blue since he has no blood platelets to make blood coagulate. Of course he bleeds inside too, you would understand my concern about the drug and do all you could to keep others from dying or going through what we have been. My husband is 59 which in these days isn't old. So I think the drug is killing him.

I wrote Parke-Davis & Company, and Doctor Goddard in Washington the same thing I have written you. These are copies of the letters they wrote me. You can see that others will continue to die from Chloromycetin from what they wrote me.

_____ has 45,000 people here, so for two to die from one Doctor giving it is two too many. There are 50 or so Doctors here so no one knows how many others have died from the drug.

Can you advise me what procedures we should take to help right a wrong and be sure that others don't die or suffer the way we have suffered?

Thank you for any consideration you may give me.

Yours Truly,

NAME WITHHELD.

NEW JERSEY, February 12, 1968.

HON. GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

SIR: I am writing to urge you to take the necessary steps to control chloromycetin because as Dr. Dameshek has said, according to the enclosed clipping, it is being used without the proper precautions.

I have enclosed a picture of our small son, ———. We lost him five years ago at age six because our Doctor, one of the finest in ———, prescribed chloromycetin every time he had a cold and never over a three year period took a blood test.

I won't go into detail about the last terrible six months of our child's life but if you have the power to save one child the suffering that he endured, and parents the terrible loss that we have had, you should move swiftly to do so.

We place our faith in Doctors and when they prescribe medicine for our loved ones we take their advice. If some Doctors will not heed the warning about the dangers involved with a drug, it would be far better to remove it from the market. I was told (too late) that this had been done with chloromycetin for a few years because of its danger but was made available again. With that knowledge, a very fine Doctor prescribed it and made no effort to follow up on the results.

Since this is a subject I feel so strongly about, I will be waiting to see what your committee can do to see that things like this do not continue to occur.

I feel that this is not as uncommon as you may think since the hematologist that was called in to diagnose asked immediately if my child had been given any antibiotics. We also sent a case history to Johns Hopkins in Baltimore and received a call to bring him down and they would do what they could—on the day that he died.

Sincerely yours,

NAME WITHHELD.

WISCONSIN, February 12, 1968.

HON. GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

MY DEAR SENATOR NELSON: Earlier today, we heard a news broadcast in which you were quoted citing the potential danger of a drug called Chloromycetin. Both my wife and I were shocked beyond words.

Allow me to explain. Several weeks ago, our youngest daughter (age 10 years) was confined to the hospital with a suspected virus attack. It appeared to become localized in the upper right abdomen. After numerous tests, the doctor prescribed the use of Chloromycetin. Instead of improving, she became much worse—becoming very weak and pale. On two occasions, she fainted—something that never occurred before. After several days of this, we transferred her to a more specialized hospital ———. She underwent countless tests there without the doctors arriving at a diagnosis. After eight days, we brought her home.

What worries us is the fact she never completely recovered after being administered this drug. As I write this now, she is home in bed—having suffered another weak, fainting spell this morning.

We need your help. Specifically, please verify the symptoms your committee attributed as serious side effects. In addition, please advise if there is a known remedy to counteract the side effects.

Very truly yours,

NAME WITHHELD.

BROOKLYN, N.Y., February 8, 1968.

HON. EVERETT DIRKSEN,
Senate Office Building,
Washington, D.C.

DEAR SIR: Although I am not a member of your immediate constituency in Illinois, I feel you are a concerned and learned representative of the greater constituency, the citizens of the United States. I, therefore, again seek your help.

I must bring this to someone's attention. This, to me, is unbelievable complacency and neglect on the part of either the F.D.A., the A.M.A., the doctors, drug manufacturers or who knows.

This past Christmas, our ten-year-old niece died from aplastic anemia (a blood disease related to leukemia). Her six-month-old long-illness was definitely attributed to the administering by a physician of chloromycetin for a previous cold or flu. After going through the months of suffering with these parents, I could hardly believe my eyes when reading this small article attached, tucked away in the back pages of the Daily News (N.Y.)—especially the sentence stating that

the Senate committee investigating this *might* impose restrictions on the prescription of it.

After seeing the horrible results of the administration of this drug, this should be screamed from the housetops to every doctor and parent in the land. How can a condition of this sort exist? Are we not protected from these lethal drugs by our supposedly thorough F.D.A.? Are not doctors definitely warned about the possible death-dealing effects of this drug?

After witnessing this terrible tragedy happen to a laughing, healthy youngster because she was given a supposed cure for a cold bug, which in turn caused her death, I cannot remain silent. Her parents have been urged to see the doctor, etc. This will not bring the child back. But definite action in preventing recurrences of this to other children (or adults) is, without a doubt, mandatory.

Without your knowledge of our seemingly ponderous government machinery, what can be done?

I am sending copies of this letter and article to the several parties noted below, with the hope that public exposure of this situation might generate positive action and perhaps some poor, unsuspecting patient will be given a more concrete safeguard than the chance reading of an article "tucked away on the back page of a newspaper."

Thank you.

Sincerely,

NAME WITHHELD.

WISCONSIN, February 8, 1968.

Hon. Senator GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: May I commend you on your interest in and work on the use of the drug chloromycetin (chloramphenicol).

As a father, who lost a lovely seven year old daughter in a dreadful death due to a doctor's repeated prescription of chloromycetin for trivial infections without observing the precautions spelled out by Parke, Davis & Co., I do appreciate your concern.

A matter which still troubles as greatly is that this doctor who was aware of the precautions advised me after Ann's death that he wouldn't adopt them in the future because the "odds" were such that he wouldn't see another case in his lifetime.

As you point out it is inconscionable that physicians in some foreign lands don't know of these dangers. How much worse to know and ignore them!

Again, I hope your efforts are successful in correcting a terrible situation.

Sincerely,

NAME WITHHELD.

ATTORNEY AT LAW,
Washington, February 8, 1968.

Hon. GAYLORD NELSON,
U.S. Senate, Senate Office Building,
Washington, D.C.

DEAR SENATOR NELSON: I read with great interest reference to your subcommittee on drugs in Drew Pearson's article of February 6, 1968. I represent the parents of a deceased three year old child whose action for the loss of the child is pending in the Superior Court of the State of Washington in and for the county of Adams, at ———, Washington. The child, ———, repeatedly received prescriptions from a doctor for Chloromycetin in treatment of upper respiratory infections. On two occasions the prescriptions were refilled by the local druggist without so much as a telephone call to the doctor—at least according to the doctor. Even after ——— showed petechiae and widespread, strange ecchymotic areas on her body, her doctor continued to prescribe Chloromycetin. He made no blood test to determine whether she was sustaining any diminishment in any of the components of the blood.

——— died a painful death in June, 1966. The hematologist who tried to save her gave the opinion that her aplastic anemia from which she died was induced by the use of Chloromycetin.

The doctor's insurance company has taken the position that the rate of deaths from aplastic anemia is no greater now than it was before the advent of Chloro-

mycetin, They claim that Benzine and certain cancer medications are a more probable cause. I would like very much to obtain copies of any reports by your committee in order to be as well prepared as I can be in this forthcoming trial. I would greatly appreciate it if you would inform me as to how I might obtain reports from your committee which have to do with Chloromycetin.

Yours very truly,

NAME WITHHELD.

ATTORNEYS AT LAW,
February 7, 1968.

HON. GAYLORD NELSON,
U.S. Senator, *Chairman, Senate Small Business Committee's Monopoly Subcommittee, Senate Office Building, Washington, D.C.*

DEAR SENATOR NELSON: I noticed from an account in the newspaper that your Committee has held hearings on the side effects of the proprietary drug Chloromycetin.

At the present time we are interested in a man who was killed by the use of this drug when aplastic anemia developed after use of the drug.

I am writing to inquire if it would be possible to get a transcript of the testimony before your Committee as it may concern the harmful side effects of the drug Chloromycetin which is manufactured and marketed by Parke-Davis Company.

Yours very truly,

NAME WITHHELD.

ATTORNEYS AND COUNSELORS AT LAW,
New York, N.Y., February 7, 1968.

HON. GAYLORD NELSON,
U.S. Senator, *New Senate Office Building, Washington, D.C.*

HONORABLE SIR: I read a column written by Drew Pearson which appeared in the New York Post on February 6th, 1968 concerning your Hearings involving Parke, Davis & Co. who are the manufacturers of a drug called chloromycetin.

At present, we are suing this company on behalf of a client whose daughter died from aplastic anemia, after having taken chloromycetin for a minor throat infection.

We would greatly appreciate receiving from you a copy of the testimony given by Parke, Davis & Co. concerning chloromycetin. If there is any charge for this transcript, please advise us and we shall pay same.

Thanking you in advance for any and all courtesies extended herein.

Very truly yours,

NAME WITHHELD.

Iowa, February 7, 1968.

DEAR SENATOR NELSON: I read Drew Pearson's article on your rift with Parke, Davis on chloromycetin. This restores my faith in people such as you.

Our daughter passed away at Methodist Hospital in Rochester November 3, 1967, due to aplastic anemia, at the age of 15 years, 10 months.

We were fairly sure she had had chloromycetin—but it was not until we arrived home Nov. 3 when I asked our doctor—he told me she had 12 capsules in June and that that amount would not cause aplastic anemia and that he was going to continue to use it. My wife and I were in shock and I got to thinking about his statements. Three weeks later I turned my grievances over to the Iowa Medical Society and I have more grievances than just the drug. They are meeting this Sunday in Des Moines.

My daughter went to the Dr. with her mother in June for a throat infection and was given 18 capsules of chloromycetin—w/o a throat culture—she later was given dosages of 18 and 16 without any blood tests taken while on the drug—this adds up to 52 rather than the 12.

Her first symptoms were hemorrhages under the skin, and we were sent to ——— and then back home—back to Iowa City to ——— back home—in the local hospital 2 or 3 times and then back to Rochester where she lived for 2 weeks—so from Aug. 28 to Nov. 3 she failed rather fast.

My wife and I, like many other citizens, had never heard of chloromycetin—or its possible dangers.

We had so much faith in the F.D.A.—Drug Mfr. and Doctors—that we cannot yet comprehend this terrible thing. Dr. _____ hematologist _____ termed her death “a monumental disaster and a great tragedy.”

If Parke-Davis and the Doctors could realize how it takes lives needlessly, and ruins families, I cannot believe they would allow it to be used so freely.

This is a personal plea for more action to safeguard others.

Money could never replace my daughter—but a lawsuit either against the Doctor who administered the drug or Parke-Davis might impress upon them that the victims will not tolerate the present methods.

I would appreciate an answer from you at your convenience—do we have any chance in a lawsuit?

I telephoned your Administrative Assistant last night and he requested I write you this letter.

I wish to thank you in advance for any consideration you give us. The count is now 61 rather than 60 needless deaths.

Respectfully,

NAME WITHHELD.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., February 2, 1968.

_____, TEXAS.

DEAR NAME WITHHELD: This responds to your letter urging that the drug Chloromycetin be taken off the market because of the serious side effects it can have.

We can understand your personal concern and know you will be interested in details on the re-evaluation of this drug as long ago as 1952, when the harmful side effects became recognized as a serious problem, and again in 1961. We accumulated all available data on the drug and presented the facts to a special committee of outstanding medical experts appointed by the National Research Council. After careful deliberation, that committee concluded that Chloromycetin is a life-saving drug in certain illnesses where other safer drugs are not effective, and recommended that it be permitted to remain on the market for such purpose. They recommended that its labeling plainly warn physicians that the drug may cause serious blood disturbances and that it should not be used indiscriminately or for minor infections.

Sincerely yours,

JEANNE M. MANGELS,
Consumer Inquiries Staff, Office of Education and Information.

WISCONSIN, December 28, 1967.

DEAR SENATOR NELSON: I have been informed you are presently investigating, some drugs. I would like to know if one of them is Chloromycetin. I was prescribed this drug for a minor infection in 1965 and the result was my getting aplastic anemia. Which is the destruction or depression of the bone marrow. After many times in the hospital and much doctoring, I am hopeful of making a complete recovery. Due to my own experience, I am interested in the drug, Chloromycetin. Due to the serious complications this drug can cause, I would like to see it taken off the market, so what I have experienced wouldn't happen to anyone else.

I am enclosing a copy of an article in Good Housekeeping magazine November 1966 about Chloromycetin.

Yours truly,

NAME WITHHELD.

PARKE, DAVIS & Co.,
Detroit, Mich., December 28, 1967.

_____, TEXAS.

DEAR MRS. NAME WITHHELD: I have your letter of December 17 with respect to the illness and hospitalization of your husband and can appreciate your concern.

Unfortunately, there are probably no effective drugs which may not on occasion give rise to serious adverse reactions in some patients. This is a continuing

concern not only of manufacturers and physicians but of the public represented through the Federal Food and Drug Administration.

In the case of Chloromycetin, the matter of whether its marketing should be continued has been the subject of special reviews by Committees of the Division of Medical Sciences and of the National Research Council appointed at the request of the Food and Drug Administration. These Committees have decided that its benefits outweigh its possible risks and that its marketing should be continued.

You should know, perhaps, that bone marrow depression may occur without any known exposure and is also attributed to many agents other than Chloromycetin.

It is realized, of course, that this does not alleviate your personal situation or afford you any comfort. I do sincerely hope, however, that your husband experiences a recovery. In the meantime, perhaps you might be willing to let us know the name of your physician since we may wish to correspond with him.

Cordially yours,

JOSEPH F. SADUSK, Jr., M.D.

PARKE, DAVIS & Co.,
Detroit, Mich., September 19, 1967.

_____, NEW YORK.

DEAR MR. NAME WITHHELD: Please accept my apologies for not replying sooner to your letter of August 21.

Review of the material so kindly sent on to us at your request by Drs. _____ does not enable us to make a positive determination that Chloromycetin was necessarily the cause of the terminal illness of your sister.

In this connection, may I point out that there does not seem to be any clear agreement among the physicians involved of the nature of the illness for which it was prescribed, the dosage directions or the duration of treatment. The situation is further obscured by the fact that acetophenetidin, an ingredient of Anacin (which your sister also received), has also on occasion been associated with the development of blood dyscrasias.

As indicated in my first letter to you, physicians are universally aware of the possible association between Chloromycetin and the development of blood dyscrasias. Under the circumstances, I do not see how any approach by us to Dr. Diez could be helpful or considered by him in any light other than as being critical of him. There is, of course, no reason why you should not write him directly if you so choose.

Cordially yours,

JOSEPH F. SADUSK, Jr., M.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., July 10, 1967.

_____, NEW YORK.

DEAR NAME WITHHELD: This refers to the copy of your letter to the manufacturer of Chloromycetin which you sent to us, describing your sister's illness and death after use of the drug.

We can certainly understand your personal concern and believe you will be interested in details on the re-evaluation of this drug as long ago as 1952, when the possible side effects became recognized as a serious problem, and again in 1961. We accumulated all available data on the drug and presented the facts to a special committee of outstanding medical experts appointed by the National Research Council. After careful deliberation, that committee concluded that Chloromycetin is a life-saving drug in certain illnesses where other safer drugs are not effective, and recommended that it be permitted to remain on the market for such purpose. They recommended that its labeling plainly warn physicians that the drug may cause serious blood disturbances and that it should not be used indiscriminately or for minor infections.

We are enclosing a photocopy of the news release and copy of the committee recommendations that issued at that time.*

Sincerely yours,

EDNA M. LOVERING,
Consumer Inquiries Staff, Office of Education and Information.

*These copies are not enclosed, since I am sure all of this material is available to the committee.

NEW YORK, July 10, 1967.

JOSEPH F. SADUSK, Jr., M.D.,
Vice President, Medical Affairs,
Parke-Davis & Co., Detroit, Mich.

DEAR DR. SADUSK: Relative to our correspondence concerning the death of my sister, ———, I have recently learned the name of the doctor in Spain who examined and prescribed the drug Chloromycetin while she was in that country: Dr. ———, Seville, Spain.

I know this a very common name in Spain, but I understand from Marion's companion on the trip, ——— serves as the hotel physician and hopefully, may be contacted at the above address.

As previously stated, it is our sincere wish that everything possible may be done to prevent a similar tragedy. We hope Parke-Davis & Co. will be able to contact the doctor involved so that he may be completely aware of the potential consequences when administering the drug Chloromycetin. We are convinced Marion's illness did not warrant the use of this powerful antibiotic.

I will appreciate your continued advice as you proceed with inquiries concerning Marion's illness and death.

Very truly yours,

NAME WITHHELD.

PARKE, DAVIS & Co.,
Detroit, Mich., July 20, 1967.

———, NEW YORK.

DEAR NAME WITHHELD: This is just a short note to tell you that I have recently returned to the office after an extended trip to find your letter of June 30.

I have written to both Dr. ——— and Dr. ——— requesting the details of your sister's illness.

Cordially yours,

JOSEPH F. SADUSK, Jr., M.D.

NEW YORK, June 30, 1967.

JOSEPH F. SADUSK, Jr., M.D.,
Vice President, Medical Affairs,
Parke, Davis & Co.,
Detroit, Mich.

DEAR DR. SADUSK: Thank you for your prompt response to my letter of May 19, 1967 written shortly after the death of my sister, ———.

I very much appreciated your comments, and we are all particularly pleased that you will contact and discuss Marion's illness and death with the doctors who were directly involved with the case. As I stated before, the tragic consequence of taking the drug Chloromycetin appears to be the untimely death of a beloved daughter and sister. It is our sincere hope that a review and study of these circumstances may help, in some measure and in some way, to prevent a similar tragedy to another.

——— was ——— doctor in ———. During her illness she was referred to Dr. ——— who examined and did blood studies.

These men may be contacted as follows: ———, New York; ———, New York. Thank you again for your interest in Marion's case. We will be most happy to hear from you again after you have had the opportunity to discuss the matter with the doctors involved.

Very truly yours,

NAME WITHHELD.

PARKE, DAVIS & Co.,
Detroit, Mich., June 8, 1967.

SENECA FALLS, N.Y.

DEAR (name withheld): I am hastening to respond to your letter of May 19 which has just been received in an envelope postmarked June 1, from Seneca Falls. We at Park-Davis deeply sympathize with you in the loss of your beloved sister ——— and, needless to say, we should like to discuss the matter of your sister's illness with your physicians if you will send us their names and addresses.

The matter of the possible association of blood diseases with Chloromycetin treatment has been the subject of review by many authorities and, indeed, I believe the National Research Council of the National Academy of Science in

Washington, D.C., carefully reviewed the matter in late 1960 and early 1961. While it appears that Chloromycetin may be one of the causes of such blood disorders, it is likewise recognized that other drugs, as well as exposure to certain other toxic agents, may produce a similar effect. And, indeed, these disorders may occur without definable cause. Consequently, it is important to review each patient's record thoroughly in order to arrive at a decision. Even after a thorough review, it may not be possible to completely clarify the issue.

In your sister's case, it would be important to review the history from the standpoint of all the other drugs she may have received. For instance, aminopyrine and dipyrone are commonly prescribed in Europe for symptomatic relief of infection, and since these agents are known to have a deleterious effect upon the blood, they must be taken into consideration along with other agents.

I believe that physicians are universally well educated on the possibility of association of Chloromycetin with aplastic anemia so that this point generally is taken into consideration when Chloromycetin is prescribed. With every drug a physician prescribes he must balance off the benefit to be obtained against the risk involved since there is no drug which is free of the potential of toxic reaction.

The questions asked and suggestions made in the next to the last paragraph of your letter are all good, but would be difficult to implement since these points would have to be applied against practically all drugs. As you may know, there are a number of drugs regularly used by physicians which are considerably more toxic than Chloromycetin. Even the other antibiotics carry certain risks which under appropriate circumstances may lead a physician to decide to use Chloromycetin as a lesser risk.

I hope you will consider my reply responsive to your inquiry and, as I noted above, we should be most pleased to correspond with the physicians involved.

Cordially yours,

JOSEPH F. SADUSK, Jr., M.D.

NEW YORK, May 19, 1967.

PARKE DAVIS & Co.,
Detroit, Mich.

GENTLEMEN: My sister, ———, died May 3, 1967 after taking, by prescription, the antibiotic chloromycetin produced by Parke Davis and Company. Marion was 44 years old. To the best of my knowledge, after discussion with the attending doctors, the medication was responsible for the complete destruction of blood platelets at the beginning. General infection at the end because of the absence of white corpuscles in her blood was the immediate cause of her death.

A post-mortem has been authorized, the results of which are not completed.

——— took the antibiotic while on a trip to Europe. The prescription was filled in Spain, after a doctor's examination. She refilled the prescription once, twelve capsules. The total intake was 22 capsules. Two capsules were not taken.

The first administration of the drug occurred in October, 1966. The first indication of the nature of her illness was discovered state-side in February, 1967. We hope your interest in the case will prompt you to discuss the illness in detail with the doctors involved whose names I will gladly furnish on request.

I am sure you will understand that I have made attempts to become familiar with this drug since my sister's tragic illness and death. I understand that serious and fatal blood dyscrasias have been known to occur in the past. I understand that the serious consequences of the administration of the drug are published for the benefit of the medical profession. I understand precautions are urged stating blood studies are essential during treatment with the drug. Perhaps it is not practical to advise the patient in the same manner, but I assure you Marion would have weighed the advice carefully before accepting the treatment prescribed had she been given the opportunity to do so.

The illness for which chloromycetin was prescribed was not of a serious nature. Furthermore, the writing on the bottle containing the two remaining capsules is in Spanish, a language not understood by Marion.

We know that the drug is beneficial to countless more people than it is fatal to others. It is difficult to find comfort in this fact. ——— was a vital, well regarded, loved person who held a responsible, well paying job and supported her mother. I cannot be bitter or vindictive, because this fine woman has suffered a greater loss than I, and she is neither bitter or vindictive. I can, however, write to tell you of the tragic consequence of the drug taken by my sister. I can write to complain that her death seems needless to those left behind and that this drug, manufactured to cure, has taken a life.