Herbert L. Ley Jr. M.D.
Commissioner of Food and Drugs
Department of Health,Education and Welfare
Washington,D. C. 20204

Dear Dr. Ley:

In my opinion Mysteclin F. Capsules 250 mg. has been my antibiotic of choice for years. The drug effectively controls the infection as well as monialia overgrowth.

I prefer the drug in female and elderly patient - the Diarrhea is an increasing problem. Mysteclin F, the combination Tetracyline Fungizone,should be a doctors choice.

The unavailability of this drug would create an unnecessary inconvenient restriction on any prescribing freedom to the detriment of my patients.

Very truly yours,

M.D.

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Department of Health,Education and Welfare
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Herbert L. Ley Jr. M.D.
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Department of Health,Education and Welfare
Wash'ngton,D. C. 20204

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[signature] M.D.

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Department of Health,Education and Welfare
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[signature] M.D.

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Department of Health, Education and Welfare
Washington, D. C. 20204

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Very truly yours,

M.D.

STATE OF ILLINOIS
DEPARTMENT OF MENTAL HEALTH
HAROLD M. VISOTSKY, M.D., Director

CHICAGO STATE HOSPITAL
6500 Irving Park Road, Chicago, Illinois 60634
Hyman C. Pomp, Ph.D., Superintendent

January 16,1969

Herbert L. Ley Jr. M.D.
Commissioner of Food and Drugs
Department of Health,Education and Welfare
Washington,D. C. 20204

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Very truly yours,

John Gelles M.D.

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Commissioner of Food and Drugs
Department of Health,Education and Welfare
Washington,D. C. 20204

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Very truly yours,

J. Blaylock M.D.

HARRISON L. ROGERS, JR., M. D.
SUITE 700 STRICKLER BUILDING
1293 PEACHTREE ST., N. E.
ATLANTA, GEORGIA 30309

January 16, 1969

Dr. Herbert A. Ley Jr.
Commissioner of Food and Drugs
Department of Health, Education and Welfare
Washington, D. C. 20204

Dear Dr. Ley:

I have read the recent articles on Mysteclin F, and would like to be on record as having said that according to my judgement the use of Mysteclin F to prevent intestinal candidia while treating the individual's problem requiring Tetracycline has been very beneficial.

Over the past eight years I have prescribed it for my patients who I feel would have not done so well had not Mysteclin F been available.

Mysteclin F has had a definite and useful place among the antibiotics in my practice. The absence of such a combination would create an unnecessary and inconvenient restriction on my prescribing procedure in the treatment of my patients.

Sincerely yours,

Harrison L. Rogers Jr. M.D.

HLR:aw

CS 3146

EDMUND G. LAWLER
ADMINISTRATOR

RICHARD B. OGILVIE
PRESIDENT
BOARD OF COMMISSIONERS

SEAL OF COOK COUNTY ILLINOIS

EUGENE J. CHESROW, M. D.
MEDICAL SUPERINTENDENT

KENNETH E. WILSON
CHAIRMAN
OAK FOREST COMMITTEE

WA TERFALL 8-4200 687 - 2300

OAK FOREST HOSPITAL
OAK FOREST, ILLINOIS 60452

January 17, 1969

Herbert L. Ley Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education and Welfare
Washington, D.C. 20204

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Louis M. Tennenbaum M.D.

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WA YERFALL 8-4200 687 - 2360

OAK FOREST HOSPITAL
OAK FOREST, ILLINOIS 60452

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M.D.

WA TERFALL 8-4200 687 - 2360

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OAK FOREST, ILLINOIS 60452

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M.D.

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Vere Leas M.D.

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BOARD OF COMMISSIONERS

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Very truly yours,

E. Kaiser M.D.

CRIST G. STROVILAS, M. D.
814 NORTH 4th STREET
TORONTO, OHIO 43964
TELEPHONE 537-2321

January 20, 1969

Herbert L. Ley M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington D. C. 20201

Dear Dr. Ley:

Mysteclin-F has had a difinite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections (women with a history of candiasis, elderly patients debilitated patients, diabetics, patients on corticosteroids, etc.)

Yours truly,

C. G. Strovilas, M. D.

AUGUSTUS L. BAKER, Jr., M.D., F.A.C.S.
HENRY C. BANKS, M.D., F.A.C.S.
HORMOZ H. MINOUI, M.D.
414 W. BLACKWELL ST.
DOVER, NEW JERSEY 07801
TELEPHONE 366-0333

January 21, 1969

Herbert L. Lay, Jr., M.D.
Commissioner of Food & Drug
Department of Health, Education & Welfare
Washington, D.C. 20204

Dear sir:

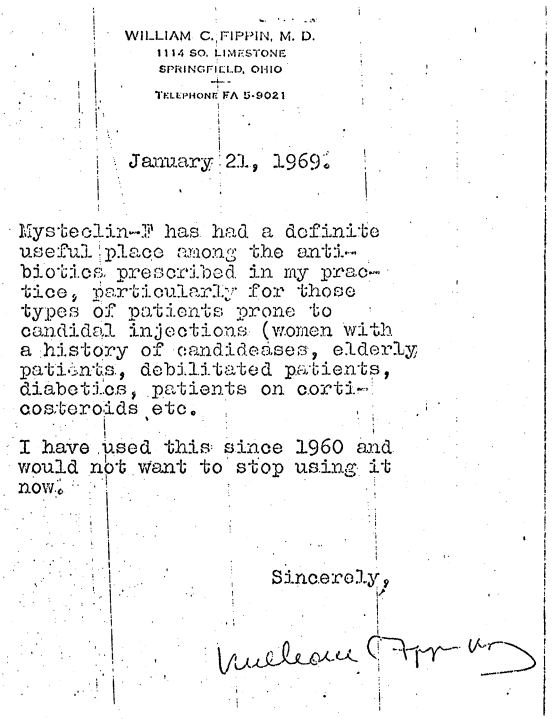
Mr. David Kuehne, Jr., the Squibb detail man in my area has indicated to me that the FDA is expecting to withdraw Mysteclin F from the market and has wanted to get my impression of this situation. I have been using Mysteclin F ever since it appeared in 1960 and my clinical impression is that this is definitely superior to antibiotics that do not have the antimonilial drug amphotercin B. During this period of time I have always used Mysterclin F in preference to any other tetracycline drug and for this reason.

I feel therefore that if the RDA were to withdraw this drug I would leave a difinite blank in the armormentarium particularly in treating women, elderly patients in general or patients who are taking other drugs paricularly in the treatment of diabetes, or corticosteroids.

Very truly yours,

Augustus L. Baker, Jr., M.D.

ALB/jb



WILLIAM C. FIPPIN, M. D.
1114 SO. LIMESTONE
SPRINGFIELD, OHIO
TELEPHONE FA 5-9021

January 21, 1969.

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal injections (women with a history of candideases, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc.

I have used this since 1960 and would not want to stop using it now.

Sincerely,

William C. Fippin

ROBERT H. WHITE, M. D.
1004 DYER STREET
MALVERN, ARKANSAS 72104

TELEPHONE ED 2-3481

January 21, 1969

Dr. Herbert L. Ley, M.D.
Commissioner of Food & Drugs
Dept of Health Education & Welfare
Washington, D.C. 20204

Dear Dr. Ley:

The NAS/NRC panel's report on Mysteclin-F indicates that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. However, my informed medical judgment as supported by widespread medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy. The combination contained in Mysteclin-F in my experience is convenient, useful, effective, and of definite value in the care of my patients.

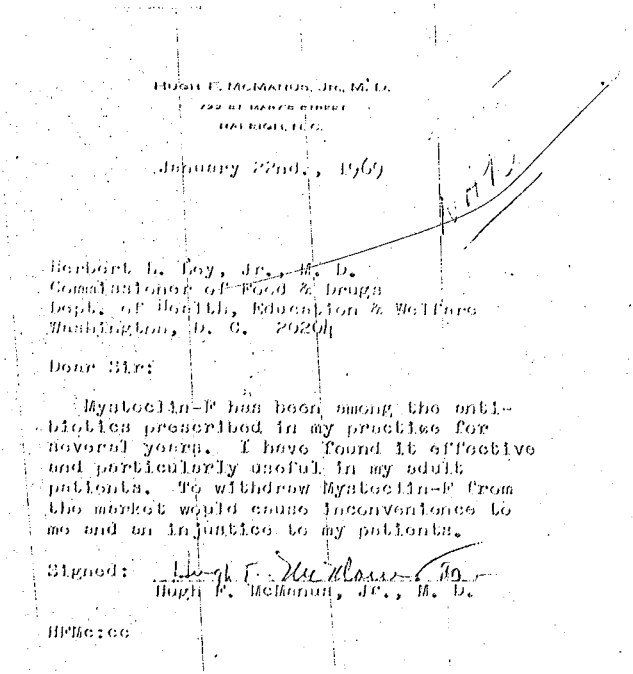
I have been using Mysteclin-F since it was introduced in 1960.

Sincerely,

Robert H. White, M.D.

Robert H. White, M.D.

RHW/jww



HUGH F. McMANUS, JR., M. D.
[illegible] ST. MARY'S STREET
RALEIGH, N. C.

January 22nd., 1969

Herbert L. Foy, Jr., M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C. 20204

Dear Sir:

Mystoclin-F has been among the antibiotics prescribed in my practice for several years. I have found it effective and particularly useful in my adult patients. To withdraw Mystoclin-F from the market would cause inconvenience to me and an injustice to my patients.

Signed: Hugh F. McManus, Jr., M. D.
Hugh F. McManus, Jr., M. D.

HFMc:cc

Jan. 23, 1969

Dear Sir:

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, especially for those types of patients prone to candidal infections.

The FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing habits.

Sincerely,

Vitoldas Gruzdys, M.D.

Jan. 23,1969

Dear Doctor:

My informed medical judgement as supported by widespread medical opinion is that spread of intestinal candida to cause canddiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy. The combination contained in Mysteclin-F in my experience is useful, effective, and convenient.

Sincerely,

A. Miliauskas, M.D.

January 24, 1969.

Dear Dr. Ley:

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections (women with a history of candidiases, elderly patients, debilitated patients, diabetics, patients on corticosteroids.)

The combination contained in Mysteclin-F in my experience is convenient, useful, effective and of definite value in the care of my patients.

I have used Mysteclin-F for several years and feel the FDA order to withdraw Mysteclin-F from availability for prescription use would created and unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

Sincerely,

Edward E. Smith, M.D.

344 West Berry St.
Fort Wayne, Ind. 46802

WALTER E. GOOZH, M. D.
MYRON L. LENKIN, M. D.
INTERNAL MEDICINE
2309 SHOREFIELD ROAD
WHEATON, MARYLAND 20902
TELEPHONE 933-5050

24 January 1969

Mr. Herbert L. Ley Jr.
Comm. Food & Drugs Dept.
Health, Education & Welfare
Washington, D. C. 20204

Dear Sir:

It was suggested to me by the Squibb Detail Man that I send you my opinion concerning the government's action on combination drugs Mysteclin F and Panalba. I am sure he would be surprised to know that my reaction is "Good for you."

In my private practice I have never seen any significant therapeutic results from the use of those combination drugs greater than that from Tetracycline alone nor have I seen any evidence of decrease in Monilial complications.

I personally feel that if the drug companies would stop putting out immense quantities of combination drugs and "minor variations in chemical structures" we would all be far better off.

Very truly yours,

WEG:JG

WALTER E. GOOZH, M.D.

TELEPHONE 285-9644

PETER J. IANNUZZI, M. D.
JOHN A. R. MARINO, M. D.
445 PORTAGE ROAD
NIAGARA FALLS, NEW YORK

January 24, 1969

Herbert L. Ley, Jr., M.D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C. 20204

Dear Dr. Ley,

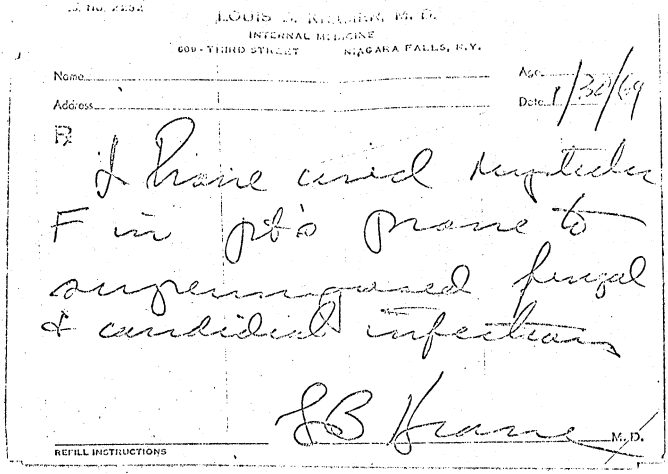
I have just received information regarding an FDA order to withdraw Mysteclin-F from the available market.

Because of the unusual number of patients with diabetes, debilitated patients and elderly women with a history of candidiasis, I have found Mysteclin-F a very efficacious antibiotic in the suppression of monilial overgrowth. I am sure that you can appreciate that the prevention of this organism is important; especially in view of many recent reports in medical literature regarding it as a cause of increased mortality and morbidity.

I still believe in the old adage, "an ounce of prevention is worth a pound of cure." I strongly feel that the removal of this drug from the available market would be a definite inconvenience and detriment to the practice of medicine, especially as pertaining to the above mentioned patients.

Yours very truly,

John A.R. Marino, M.D.



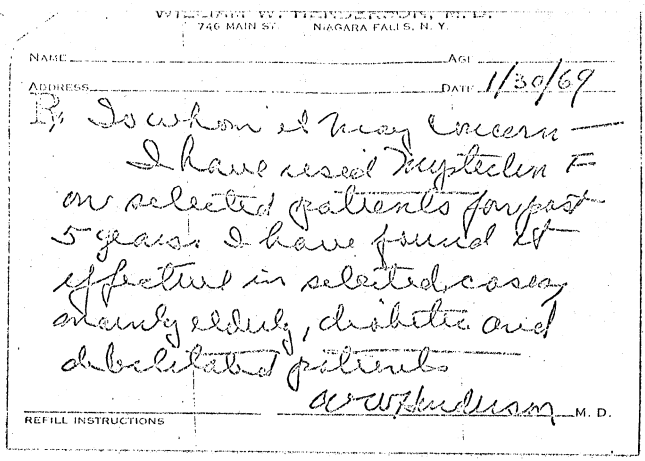
LOUIS A. KELLER, M. D.
INTERNAL MEDICINE
609 - THIRD STREET NIAGARA FALLS, N.Y.

Name
Address
Age
Date 1/30/69

℞ I have used Mycteclin F in pt's prone to superimposed fungal & candidial infections

S B Kramer M.D.

REFILL INSTRUCTIONS



WILLIAM W. THOMPSON, M.D.
746 MAIN ST. NIAGARA FALLS, N. Y.

NAME
ADDRESS
AGE
DATE 1/30/69

℞ To whom it may concern —
I have used Mycteclin F on selected patients for past 5 years & have found it effective in selected cases, mainly elderly, diabetic and debilitated patients

W W Thompson M. D.

REFILL INSTRUCTIONS

SD372

SQUIBB Representative's Correspondence

(Use separate letter for each subject)

To [illegible] Herbert L. Ley, Jr. M.D. Date

From Commissioner of Food & Drugs Written From

Subject: Dept. of Health, Education & Welfare
Washington, D.C. 20204

Mysteclin-F has been found to be useful and most beneficial in conditions where it is indicated. I consider it to have been especially valuable in several instances.

Wm [illegible]
1-22-69

EDWIN B. ABRAMSON, M. D.
1001 W. ROCKLAND STREET
PHILADELPHIA, PA. 19141

January 26, 1969

Herbert L. Ley, Jr., M.D.
Commissioner of Food & Drugs
Department of Health, Education & Welfare
Washington, D.C. 20204

Dear Dr. Ley:

The NAS/NRC panel's report on Mysteclin-F indicates that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished.

However, my informed medical judgment as supported by widespread medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy. The combination contained in Mysteclin-F in my experience is convenient, useful, effective and of definite value in the care of my patients.

Sincerely,

Edwin B. Abramson, M.D.

EBA/pmf

1-27-69

Dear Dr. Ley:

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections (women with a history of candidiases, elderly patients, debilitated patients, diabetics, patients on corticosteroids

The combination contained in Mysteclin-F in my experience is convenient, useful, effective and of definite value in the care of my patients.

I have used Mysteclin-F for several years and feel the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

Sincerely,

5110 N. Clinton
Ft. Wayne, Ind. 46805

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001
TELEPHONE (616) 345-8571

J. C. GAUNTLETT
Vice President
and Director

January 28, 1969

Dear Doctor:

Because of misleading and possibly misunderstood statements which have appeared in the lay press, we would like to take this opportunity to clarify our position and to assure you that Panalba remains available.

In the Federal Register of December 24, 1968, the Food and Drug Administration published a notice about Panalba and certain other combination antibiotics. The question is whether certain combinations of drugs should be allowed to remain on the market.

Approximately 40% of the drugs prescribed today are combinations of one form or another. In principle, if the physician's right to prescribe is denied for one category of useful drugs, it is conceivable this same right may be denied for others. We believe the decision as to whether these drugs are used should rest in the hands of the practicing physician.

In accordance with the Federal Register, all interested persons who may be adversely affected by removal of these drugs from the market are invited to comment. Correspondence should be directed to Dr. Paul Bryan, Special Assistant for Drug Ffficacy Study Implementation, Bureau of Medicine, Food and Drug Administration, 200 C Street S.W., Washington, D.C., 20204. If you elect to write to Dr. Paul Bryan we, too, would appreciate a copy of your correspondence.

Sincerely,

J. C. Gauntlett

JJS

C. H. Whiting, Sr., M.D.
238 Main Street
Oneida, N.Y. 13421
PN 3-2233

January 31, 1969

Dr. Herbert L Ley Jr .

I have used MYSTECLIN F for 9 years. I have found this product to be useful antibiotic, particularly for those types of patients prone to candidal infections.

A withdrawal of MYSTECLIN F from my prescription use would unnecessary restrict my prescribing freedom and be to the detriment of my patients.

Dr. C.H. Whiting Sr M.D.

CLYDE T. THOMPSON, M.D.
330 PARK STREET
MIAMI SPRINGS, FLORIDA
TELEPHONE TU 9-1024

January 31, 1969

TO WHOM IT MAY CONCERN

Dear Sirs:

The FDA order to withdraw Mysteclin-F from ayailability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

Respectfully yours,

C. T. Thompson, M. D.

CTT:kw

Maine Medical Association
P. O. BOX 250
BRUNSWICK, MAINE 04011
TELEPHONE 725-6414

Executive Director
DANIEL F. HANLEY, M.D.

Secretary-Treasurer
ESTHER M. KENNAN

February 3, 1969

Dear Doctor:

You may be aware of the FDA order to withdraw Mysteclin-F from the market due to the NAS/NRC panel's report on Mysteclin-F, indicating that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished.

IF you believe Mysteclin-F has had a definite useful place among the antibiotics prescribed in your practice, particularly for those types of patients prone to candidal infections (women with a history of candidiasis, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc); It definitely has

IF your medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy; yes

IF you feel that the combination contained in Mysteclin-F in your experience is convenient, useful, effective and of definite value in the care of your patients; It is

IF you feel the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on your prescribing freedom to the detriment of your patients - It would.

Please forward your opinion to:

James Patterson MD
1 Boy Road South Portland Me.
04106

Herbert L. Ley, Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education
and Welfare
Washington, D.C. 20204

Maine Medical Association
P. O. BOX 250
BRUNSWICK, MAINE 04011
TELEPHONE 725-6414

Executive Director
DANIEL P. HANLEY, M.D.

Secretary-Treasurer
ESTHER M. KENNARD

February 3, 1969

Dear Doctor:

You may be aware of the FDA order to withdraw Mysteclin-F from the market due to the NAS/NRC panel's report on Mysteclin-F, indicating that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished.

I believe Mysteclin-F has had a definite useful place among the antibiotics prescribed in your practice, particularly for those types of patients prone to candidal infections (women with a history of candidiasis, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc); I do

Your medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy; I do

You feel that the combination contained in Mysteclin-F in your experience is convenient, useful, effective and of definite value in the care of your patients; I do

You feel the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on your prescribing freedom to the detriment of your patients. I do

Please forward your opinion to:

Herbert E. Ley, Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education
and Welfare
Washington, D.C. 20204

Frederick C Dennison MD
Thomaston Maine 04861

Maine Medical Association
P. O. BOX 250
BRUNSWICK, MAINE 04011
TELEPHONE 725-6414

Executive Director
DANIEL F. HANLEY, M.D.

Secretary-Treasurer
ESTHER M. KENNARD

February 3, 1969

Dear Doctor:

You may be aware of the FDA order to withdraw Mysteclin-F from the market due to the NAS/NRC panel's report on Mysteclin-F, indicating that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished.

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IF your medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy;

IF you feel that the combination contained in Mysteclin-F in your experience is convenient, useful, effective and of definite value in the care of your patients;

IF you feel the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on your prescribing freedom to the detriment of your patients -

Please forward your opinion to:

Herbert L. Ley, Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education and Welfare
Washington, D.C. 20204

In my experience I find that Mysteclin F is very effective in Trench mouth. It does a very good job where the plain Tetracyclines fail. I would hate to see it removed from the market. Of course I don't use it for all infections, only the ones I feel it is indicated in. [illegible]

81-280 O-69-pt. 12——17

Maine Medical Association
P. O. BOX 250
BRUNSWICK, MAINE 04011
TELEPHONE 725-6414

Executive Director
DANIEL F. HANLEY, M.D.

Secretary-Treasurer
ESTHER M. KENNARD

February 3, 1969

Dear Doctor:

You may be aware of the FDA order to withdraw Mysteclin-F from the market due to the NAS/NRC panel's report on Mysteclin-F, indicating that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished.

IF you believe Mysteclin-F has had a definite useful place among the antibiotics prescribed in your practice, particularly for those types of patients prone to candidal infections (women with a history of candidiasis, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc);

IF your medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy;

IF you feel that the combination contained in Mysteclin-F in your experience is convenient, useful, effective and of definite value in the care of your patients;

IF you feel the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on your prescribing freedom to the detriment of your patients -

Please forward your opinion to:

Herbert L. Ley, Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education
and Welfare
Washington, D.C. 20204

no choice on this form for those supporting the FDA order — since this may tend to result in a biased impression (because most would simply [illegible])

[illegible] Maine, June 15-17, 1969 [illegible]

Office Phone: 838-2241
Residence Phone: 838-3550

JACK A. DAWSON, M. D.
DOCTOR'S BUILDING
NORTH WILKESBORO, N. C.

February 3, 1969

Deer Doctor Ley:

Mysteclin-F has been used extensively in my practice and on a comparative basis to the plain antibiotics has never caused a monilial overgrowth or stomatitis. I am not convinced by academic studies, but rather clinical results and therefore am of the opinion that there is absolutely no justification to remove Mysteclin-F from the market.

I have been using Mysteclin-F since 1962 and hope to continue.

Sincerely,

Jack A. Dawson, M. D.

Squibb Representative's Correspondence
(Use separate letter for each subject)

To.....

Date..Feb. 2nd.....

From.....Joe Kiker.....

Written From.....

Subject: Kysteclin-F Letter to FDA

Dear Doctor Dawson:

Hope the enclosed letter is satisfactory for your signature.

Sincerely,

Joe

Joe

E. ALLAN TOTTY, M. D.
2144 BURDETT AVENUE
TROY, N. Y. 12180

TELEPHONE: ASHLEY 2-5812

3 February 1969

Herbert L. Ley, Jr., M.D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D.C. 20204

Dear Dr. Ley:

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections.

I have been using Mysteclin-F for (5) years and the FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedon to the detriment of my patients.

Very truly yours,

E. Allan Totty M.D.

EAT:bcc

February 3, 1969

Howard J. Kerr, M. D.
3084 Henry St.
Muskegon, Michigan 49442

Herbert L. Ley, Jr. M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C. 20204

Dear Dr. Ley:

Mysteclin-F has an important place in my medical practice.

Having made Mysteclin-F my broad spectrum antibiotic of choice, especially in my patients prone to candidal infections, for the past seven years, it is my opinion that Mysteclin-F is a very useful and safe antibiotic.

The FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

Respectfully submitted,

Howard J. Kerr M.D.

Howard J. Kerr, M. D.

njk:pap

WILLIAM S. DOWNEY, JR., M. D.
337 UNION STREET
NEW BEDFORD, MASS. 02740
TEL. (617) 992-1442

February 5, 1969

Dr. Paul Bryan
Special Assistant for Drug Efficacy Study Implementation
Bureau of Medicine
Food & Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Dear Dr. Bryan:

I am responding to a letter from J.C. Gauntlett of the Upjohn Company to write to you about the misleading statements that have been in the newspapers about Panalba and Mysteclin. I had several patients who called me and questioned why I had used Panalba and Mysteclin on previous occassions and what kind of a doctor would use a medicine that was ineffective or no good. Without having all the material available to me that you have available to you, it still does not seem to be the most effective way for all concerned to have a statement in the newspapers suggesting that a preparation which is commercially available is ineffective when in truth, there is some effectiveness.

I am not and never have been a big user of Panalba and Mysteclin, but there are times when I find them effective. Panalba is effective for me in cases of croup and we have many cases of croup in our area. I use Mysteclin F when I have a newborn child who could use a broad spectrum preparation and I don't want to run the risk of developing thrush.

As a result of the public statements on these two preparations, when I write for them I run the risk of someone picking this up and recognizing the names and saying, "Isn't that the drug that the Federal Government has withdrawn?" I would like to add my name to the list of those who are protesting.

Sincerely,

William S. Downey, Jr. M.D.

WSD/ja

M-10

2/5/69

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections (women with a history of candidiasis, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc.)

The NAS/NRC panel's report on Mysteclin-F indicates that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. However, my informed medical judgment as supported by widespread medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy. The combination contained in Mysteclin-F in my experience is convenient, useful, effective, and of definite value in the care of my patients.

(Number of years physician has used Mysteclin-F since 1960.) — 9 years —

The FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

P.S. - I agree completely with the above statement. Many times I have been impressed by the effectiveness of this medication. Tetracycline alone has high incidence of bowel and [illegible] problems. 144 [illegible]

[illegible signature] [illegible]

Anchorage Medical & Surgical Clinic
718 K STREET
ANCHORAGE, ALASKA 99501
TELEPHONE 272-2571

February 7, 1969

Herbert L. Ley, Jr., M.D.
Commissioner of Food and Drugs
Department of Health, Education and Welfare
Washington, D. C.
20204

Dear Dr. Ley:

Tetracycline and its associated "broad spectrum antibiotics" are life-saving drugs. There is no question but what they permit an over-growth of Monilial-like organisms at times.

I have reason to believe that Mysteclin-F and similar combinations with Fungisone or Nystatin exert a favorable influence toward suppressing over-growth of "candida".

I am not aware of any harm due to Fungisone or Nystatin used in the doeses prescribed with the "broad spectrum antibiotics".

I believe, like thousands of other doctors, that we should be allowed to continue the use of the combinations until it is proven that they are harmful or useless.

Sincerely yours,

Howard G. Romig, M.D.

HGR/gw
Encl. Guidelines which Physicians
May Want to Include in Letter
to FDA,

GUIDELINES WHICH PHYSICIANS MAY WANT TO INCLUDE IN LETTER TO THE FDA

Mysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections (women with a history of candidiasis, elderly patients, debilitated patients, diabetics, patients on corticosteroids, etc.)

The NAS/NRC panel's report on Mysteclin-F indicates that they are not aware of evidence of proved efficacy in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. However, my informed medical judgment as supported by widespread medical opinion is that spread of intestinal candida to cause candidiasis is a risk which in the indicated conditions should be considered in using antibiotic therapy. The combination contained in Mysteclin-F in my experience is convenient, useful, effective, and of definite value in the care of my patients.

(Number of years physician has used Mysteclin-F since 1960.)

The FDA order to withdraw Mysteclin-F from availability for prescription use would create an unnecessary and inconvenient restriction on my prescribing freedom to the detriment of my patients.

FEB 24 1969

[illegible] Jerry Smith, M. D.
193 Colony Way
Louisville, Kentucky 40207

Dear Dr. Smith:

Commissioner Ley has asked me to reply to your letter of February 10, 1969 concerning the drug Mysteclin F.

I am enclosing a discussion of the position of the Food and Drug Administration with respect to certain combination antibiotic drugs.

Thank you for taking the time to write.

Sincerely yours,

Paul A. [illegible], M. D.
Special Assistant
Task Force for Drug Efficacy
Study Implementation

Enclosure
CL-10: Mr. [illegible]
MD-8
MD-14
MD-16

[illegible] ss 2/20/69
MD-8

Discussion of the Food and Drug Administration's Position with Respect to Certain Combinations of Antibiotic Drugs

Under the Federal Food, Drug, and Cosmetic Act enacted in 1938, safety was the sole consideration for obtaining approval to market a new drug. The Drug Amendments of 1962 extended the requirements to include substantial evidence of effectiveness.

The Amendments also prescribed the criteria to be used in determining that a drug is effective. As defined therein, "the term 'substantial evidence' means 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 labeling or proposed labeling thereof."

These Amendments also conferred upon the Food and Drug Administration the responsibility to review the decisions made on the many hundreds of new drugs introduced to the market from 1938 to 1962, which had previously been approved only on the basis of evidence of safety, and to determine whether there is substantial evidence of effectiveness for each purpose for which they are labeled. It was also deemed necessary to re-examine all antibiotic drug products cleared for marketing between 1938 and 1962 and to apply to them the same criteria for substantial evidence of effectiveness.

The Food and Drug Administration did not have sufficient medical manpower to carry out the efficacy review by itself. The Agency needed the help of the broader scientific community and a means of bringing to this assignment the nation's best scientific and medical knowledge. The Food and Drug Administration sought out the assistance of the National Academy of Sciences-National Research Council in order to carry out the efficacy study.

In conducting these reviews the Academy had access to all information with respect to these drugs which the drug sponsors submitted in an effort to establish the effectiveness of their drugs; in addition to the submitted material, the Academy was privileged to use all the information concerning the product under review that appears in the scientific literature.

It is important to note that the Federal Register announcement, published December 24, 1968, on the combination drugs, which has been referred to in the public press, was directed only to the fixed combinations of the specific antibiotics mentioned.

Ideally, antibiotic therapy should be initiated only after laboratory testing to determine the susceptibility to various antibiotics of the organism causing infection. However, in practice, antibiotic therapy is often initiated on the basis of the clinical experience of the physician who prescribes an antibiotic which he thinks is appropriate. The supposed medical rationale for the use of combination antibiotics is that (1) they are better than one of the components alone by having an additive or synergistic effect; (2) they have a wider spectrum; or (3) they protect against overgrowth of organisms which are not susceptible to one or the other antibiotic.

One disadvantage of a fixed combination is that it limits the flexibility of the physician in prescribing different amounts of the individual components. If he were giving the antibiotics separately to a patient the physician would have the option of prescribing them in different ratios, according to the needs of the patient. Another major medical disadvantage of the combinations is increased possibility of adverse reactions without increased efficacy. Thus, to justify marketing of a combination antibiotic, it should have advantages that outweigh any increased risks.

The Food and Drug Administration has concurred in the evaluation of the following combination antibiotic drugs by the Academy and concluded that there is lack of substantial evidence that these fixed combinations are effective for the conditions for which they are labeled or that each active ingredient contributes to the claimed effect on the basis of the following medical findings:

1. Mysteclin F (tetracycline and amphotericin B). There is a lack of available scientific evidence that this product will prevent disease due to monilial organisms as claimed in the labeling for the drug. It is possible, in our judgment, to prescribe antifungal drugs (the amphotericin B component) when clinically indicated, rather than to use them indiscriminatively as "prophylaxis" against a clinical entity seen uncommonly during therapy with tetracycline and other antibiotics.

2. Albamycin G. U. (novobiocin calcium and sulfamethizole). The limitation of the combination are the limitations of the individual components. Novobiocin is limited by (1) its narrow antibacterial spectrum, (2) the rapid emergence of resistant strains, and (3) the great frequency with which adverse reactions occur. The novobiocin component has only modest efficacy in the treatment of urinary tract infections. Further, evaluation of the available evidence has led to the conclusion that therapeutic results occur, if at all, from the activity of one of the individual components and not by reason of their combination.

3. Albamycin-T (novobiocin sodium and tetracycline hydrochloride). It has not been shown that microorganisms are more susceptible to the combination than to either antibiotic singly. The comments in paragraph 2 regarding novobiocin also apply to this combination preparation.

4. Panalba products (tetracycline phosphate complex and novobiocin). This combination has not been shown to be more effective than when one of its components is used alone for the therapy of susceptible organisms. The preceeding comments regarding novobiocin also apply to this fixed combination preparation.

These combination antibiotic drugs are still on the market. The distributors have been given the opportunity to provide evidence that the drugs are effective for the purposes for which they are intended. If adequate data are not forthcoming, the distributors of the drugs will be given an opportunity for a hearing. If a hearing is held and decided in favor of the Government, the final order may be appealed to the courts. Withdrawal of the drugs from the market would not preclude clinical investigation of them through the investigational new drug procedures. Based upon a demonstration of effectiveness by adequate and well-controlled studies a drug may be returned to the market.

March 3, 1969

Dear Sir:
The message below signifies that I wrote a letter to your office in support of Mysteclin-F. I never wrote such a letter. If I had communicated with your office, it would be to support your action against such combined antibiotic drugs as Mysteclin-F.
Sincerely,
William V. Lyden, M.D.
2166 Hayes St.
San Francisco, Calif.
94117

R. Squibb & Sons, Inc.

Welch Road
Alto, California 94304
327-9340

March 25, 1969

W. Lyden, M. D.
2166 Hayes Street
San Francisco, Calif.

Dear Doctor Lyden:

We appreciate your consideration and support in taking the time to write the Commissioner of the Food and Drug Administration regarding a recent report on Mysteclin-F by the NAS-NRC.

Your faith in the product and assistance in helping to maintain the availability of Mysteclin-F is very much appreciated.

Very truly yours,

W. E. MULLALLY, Manager
San Francisco Region

WEM/sjs

MD-1

ROBERT D. GILLETTE, M.D.
816 WILLIAMS STREET
P.O. BOX 127
HURON, OHIO 44839

Telephone 433-2481

April 1, 1969

Food And Drug Administration
Washington, D.C.

Gentlemen:

A recent news report indicates that you have been receiving a lot of mail about your plan to remove a number of antibiotic combination products from the market. Since most of the mail reportedly has been opposed to the FDA decision, I feel obliged to write and take the opposite side.

In my opinion your judgement that these products should not be on the market is correct. Removing them from the market will do the American consumer no harm.

I have some misgivings about the wisdom of the government taking this much power, however. I think the government is right in this particular instance, but have no faith that it always will be in similiar circumstances.

Sincerely,

Robert D. Gillette, M.D.

RDG:dp

REPUBLIC 7-1541

R. L. E. A. RAILWAY LABOR EXECUTIVES' ASSOCIATION

RAILWAY LABOR BUILDING, 400 1st STREET, N. W., WASHINGTON, D. C. 20001

April 3, 1969

The Honorable Robert Finch
Secretary
Department of Health, Education
and Welfare
330 Independence Avenue, S.W.
Washington, D.C. 20201

My dear Mr. Secretary:

We noted with great interest the action taken by the Food and Drug Administration to remove a considerable number of "fixed-combination" drugs from the market.

Expert testimony before congressional committees and studies by the National Academy of Science have laid a solid foundation for this action by revealing that the "fixed-combinations" were merely high-priced trade-name concoctions of more simple, cheaper drugs that could be prescribed for a fraction of the combination's price.

Moreover, Dr. Herbert Ley, Jr., the Food and Drug Commissioner points out that to use a drug with two or more active ingredients when the patient can be cured with one "is irrational therapy." This also expresses his concern about giving a patient an unneeded drug and exposing him to additional possible side reactions.

Thus the drug companies stand accused of combining drugs for the sake of enlarging already substantial profits and doing this without regard for unnecessarily exposing the patient to possible harm from drug reaction.

We are aware that those who profit from these drugs are asking physicians to protest the Food and Drug Administration action to men in high government councils. Our reaction to this is that at no time should protests take the place of objective scientific evidence.

If the companies involved are able to produce solid evidence that the drugs are effective, let them do so within the 30-day period provided by the Food and Drug commissioner. He, incidentally, found it "curious" that in the six and one-half years in which they have had the opportunity to do this, the companies produced no shred of scientific evidence acceptable to the National Academy of Science panels.

15030

We fully support the actions of the Food and Drug Administration as being clearly in the public interest and urge you to back them up wholeheartedly.

We hope this action will reduce the high and burdensome cost of drugs for over 1 million active and retired railroad workers and their families.

Sincerely yours,

Executive Secretary

DAVID N. GREY, M.D.
JOHN P. BURNHAM, M.D.
HENRY L. STOUTZ, M.D.

UROLOGY

3003 LOMA VISTA ROAD, SUITE F
VENTURA, CALIFORNIA

April 4, 1969

Dr. Herbert L. Lay, Jr., Commissioner
Food and Drug Administration
Washington, D. C.

Dear Doctor Lay:

I have recently noted in the news that your organization has received quite a few letters protesting the "banning" of antibiotic combinations. I would like to indicate to you that I am definitely in favor of your actions and feel that such combinations offer no advantage over separate prescriptions, have some definite disadvantages, and that their main appeal is the saving of time involved in writing more than one prescription, which is certainly not an adequate reason.

Sincerely yours,

Henry L. Stoutz, M. D.

HLS:qb

D. J. ALLAN, M.D.
A. W. AXLEY, M.D.
J. R. BREWER, M.D.
J. E. ELLIOTT, M.D.

PHONE 265-7831 AREA CODE 406
301 FOURTH AVENUE
HAVRE, MONTANA 59501

J. O. ORLIE
BUSINESS MANAGER

G. G. KURTZ, M.D.
C. W. LAWSON, M.D.
D. S. MAC KENZIE, M.D.
J. H. O'LEARY, M.D.

April 4, 1969

Federal Drug Administration
Washington D.C.

Dear Sirs:

I noticed with some consternation that you have received over 3,000 letters opposed to your recent decision about drug combinations, such as Pan Alba. I am writing this letter in order to be put on record that I am heartily in favor of your decision.

I have long felt, as have many of my colleagues, that the combinations are not useful and that the drugs in the combinations are not first or quite often not second choice drugs for the indications that are given by the detail men and the drug ads.

Sincerely,

John R. Brewer

John R. Brewer, M.D.
Pediatric and Adolescent Medicine

JRB/lw

UNIVERSITY OF KANSAS MEDICAL CENTER
RAINBOW BOULEVARD AT 39TH STREET
KANSAS CITY, KANSAS 66103 • AREA CODE 913 • ADams 6-5252

CLINICAL PHARMACOLOGY STUDY UNIT

April 10, 1969

Herbert C. Ley, M.D.
Commissioner
Food and Drug Administration
Washington, D. C. 20204

Dear Dr. Ley:

I have been reading, with increasing alarm, the numerous tirades and testimonials of practicing physicians concerning the attempt by the FDA to implement the NAS--NRC report on combination antibiotic products. I am also a practicing physician and treat patients on a daily basis as well as investigate the clinical effects and responses of drugs. To my knowledge, the increased effectiveness of two antibiotics of over only one, has been demonstrated that with organisms resistent to many antibiotics, the judicious administration of two or more carefully selected antibiotics can be life saving. However, this type of approach must be carefully tailored to the in vitro sensitivity studies for that particular organism and cannot be accomplished with the available multiple antibiotic preparations.

Please accept this letter as my vigorous support for your stand in this matter.

Sincerely yours,

Daniel L. Azarnoff

Daniel L. Azarnoff, M.D.
Professor of Medicine and
Pharmacology

DLA/bt

MEMORIAL CLINIC
P. O. BOX 1174
SENECA, SOUTH CAROLINA 29678

F. B. ADAMS, JR., M. D.
DON RICHARDSON, M. D.
E. L. RICE, M. D., F. A. C. S.

April 19, 1969

Paul A. Bryan, M.D.
Special Assistant for Drug Efficacy
Study Implementation
Bureau of Medicine
Dept. of Health, Education, and Welfare
Washington, D. C. 20204

Dear Dr. Bryan:

Thank you for your kind letter of April 17. My plea for combinations of medications was not in the antibiotic field but rather in the anti-hypertensive field.

I am in entire agreement with your publicly stated position about combining antibiotics.

Yours very truly,,

F. B. Adams, Jr., M.D.

FBAjr/mg

Responses to Federal Register Announcements (12/24/63) Concerning Certain Antibiotic Combination Drugs

Subsequent to the FEDERAL REGISTER announcements of December 24, 1963, we received approximately 3500 letters disagreeing with our position. To date we have had 10 responses favoring our conclusions. It is obvious that nearly all of the responses were prompted by efforts made by Squibb and Upjohn to barrage us with testimonials in support to their products. Upjohn issued a "Dear Doctor" letter to physicians encouraging their protest. Squibb made available to physicians a set of "Guidelines Which Physician May Want to Include in Letter to the FDA." These were a series of "form paragraphs." Numerous letters contained some of these form paragraphs, either paraphrased or verbatim. In some cases identical letters were received from several physicians in the same clinic or hospital. A number of such letters were received from the Oak Forest Hospital, Oak Forest, Illinois, which were identical to a number received from Chicago State Hospital, Chicago, Illinois. The Maine Medical Association apparently circularized to its membership a paraphrased list of the Squibb guidelines. There is evidence that a Squibb detail man actually prepared a letter for the physician's signature. In some cases the physician's letter was mailed to us in a Squibb envelope.

The content of the letters ranged all the way from thoughtful comments--to testimonials--to form statements--to condemnation of our position. No useful data could be obtained from this mass of correspondence. Several physicians, disturbed by the publicity occasioned by these protests, wrote recently to express support of our conclusions. One physician received a letter from Squibb thanking him for taking the time to write to the FDA in support of Mysteclin. He forwarded a copy of this to us with a note stating that he had not written such a letter, but that if he had written it would have been in support of our action.

Robert B. Hahn
April 29, 1969

Senator NELSON. Thank you very much for your valuable contributions.

We appreciate it.

We will adjourn to June 19 in the caucus room at 9 a.m.

(Whereupon, at 12 noon, the subcommittee was adjourned, to reconvene at 9 a.m., Thursday, June 19, 1969, in the caucus room.)

APPENDIXES

APPENDIX I

[From the AMA Archives of Internal Medicine, April 1957, pp. 536–538]

THE CLINICAL USE OF ANTIBIOTICS IN COMBINATION

At a recent informal meeting of a large group of internists who are leaders in the field of infectious diseases, held in connection with the Central Society for Clinical Research, unanimous concern over the increasing numbers of antibacterial agents packaged in combination for oral or intramuscular use was expressed.

The accompanying editorial was suggested at this meeting. While American physicians owe a great debt of gratitude to the drug houses of this country for the quality of their products, there can be no question that the trend toward promotion of combination preparations of this type is a dangerous one. The reasons for this are outlined in the following combined statement. It is recognized that physicians have the opportunity to use combinations of single antibiotics in any way they thing best, but availability of the scores of antibacterial products already put up in combinations decided upon by the manufacturer and not arranged for each individual patient will unquestionably lead to abuses if unchecked.

PAUL S. RHOADS, M.D.

The recent appearance on the market of preparations containing two antibiotics in the same capsule calls for an appraisel of the rationale of such therapy. Theoretical or practical reasons for administering more than one antibotic to a patient at one time are as follows:

1. A second antibiotic may delay the emergence of bacteria resistant to the first antibiotic.
2. Two antibiotics may be synergistic with one another.
3. In the initial emergency treatment of seriously ill patients where the establishment of an etiological diagnosis and appropriate antibiotic sensitivity tests may be delayed, two or more drugs may properly be used as "insurance."
4. Mixed infections caused by more than one micro-organism may be better treated by antibiotics found most effective against each one.
5. Reduction of dosage of each of two "additive" drugs may result in lowered incidence of toxic effects to each, as in the case of streptomycin-dihydrostreptomycin.

The emergence of streptomycin-resistant tubercle bacilli is delayed when aminosalicylic acid or isoniazid is given in conjunction with streptomycin. In the realm of nontuberculous bacterial infections the application of this principle is not so clear. Numerous clinical-epidemiological studies have shown that the introduction of a new antibiotic into a hospital or a community is frequently followed by an increase in staphylococci resistant to that antibiotic. An attempt to prevent the development of antibiotic-resistant staphylococci by employing a combination in the treatment of ordinary bacterial infections was carried out during the winter of 1955–1956, employing novobiocin and spiramycin. In this study the emergence of staphylococci resistant to both these anibiotics was somewhat delayed, but after a few months bacteria resistant to both of them were easily found. In any event, the strain must be originally sensitive to the individual antibiotics if the combination is to delay or depress the development of resistance to any of them when they are used together.

THE CASE FOR AND AGAINST SYNERGISM

Penicillin and streptomycin have a synergistic effect against enterococcus and probably against penicillin-sensitive viridans Streptococcus as well, Also, laboratory evidence of synergism of various combinations of drugs against individual strains of several microbial species has been published, but much remains to be done before these studies can be applied at the clinical level. Furthermore, different combinations would seem to be synergistic against different species or even against different strains within the same species.

There is some clinical evidence that tetracycline derivatives or tetracycline in combination of with streptomycin result in a lower relapse rate in the treatment of brucellosis than occurs with either drug alone. If the treatment period with a tetracycline is greatly prolonged, however, a similar low relapse rate will be achieved.

THE "INSURANCE" PRINCIPLE

In the treatment of serious staphylococcal and other infections the life of a patient may be jeopardized by withholding treatment until a satisfactory etiological diagnosis can be obtained or until antibiotic sensitivity tests are completed. In such situations the employment of more than one antibiotic is frequently justified, but these should be used in full doses.

DIMINISHED TOXIC EFFECTS

When equal amounts of streptomycin and dihydrostreptomycin are administered, an additive therapeutic effect is obtained. The toxic effect of streptomycin is chiefly upon the vestibular portion of the eighth cranial nerve, whereas dihydrostreptomycin affects the auditory portion. When a 50–50 combination is used, diminished toxicity results without loss to therapeutic efficacy.

The question may be asked: "Why not use combinations since they do no harm?" Possible harmful effects are five in number. First, the use of fixed combinations of antibiotics tends to encourage inadequate therapy. Though suboptimal doses of each of two antibiotics may occasionally provide a synergistic action against certain strains of bacteria, it certainly cannot be assumed that more can ordinarily be accomplished by suboptimal than by optimal amounts of therapy. Nor is there any evidence that the spectrum of activity will be broadened beyond that provided by the type and amount of individual antibiotics actually administered. Hypersensitivity and toxicity may be expected to increase when two drugs are used instead of one; furthermore, when a physician encounters a toxic effect, such as a rash, he will not know which of the drugs was responsible. A third harmful effect is the probable development of bacteria resistant to either or both of the drugs used in the combination. And the fourth, a direct corollary of the second, is the accumulation of antibiotic-resistant microbes within hospitals or other semiclosed communities. The fifth is that if this trend is not checked now, the practicing physician will soon be confronted with such a bewildering array of antibotic combinations supported by multicolored promotional material piling up daily upon his desk that rational chemotherapy will give way to chaos.

The indications for the use of combined antibiotics all apply to clinical situations which at the present time demand selection of specific doses for individual cases. The one exception is the streptomycin-dihydrostreptomycin combination. There are no data or experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless adequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.

HARRY F. DOWLING, M.D.
MAXWELL FINLAND, M.D.
MORTON HAMBURGER, M.D.
ERNEST JAWETZ, M.D.
VERNON KNIGHT, M.D.
MARK H. LEPPER, M.D.
GORDON MEIKLEJOHN, M.D.
LOWELL A. RANTZ, M.D.
PAUL S. RHOADS, M.D.

University of Cincinnati College of Medicine, Department of Internal Medicine, Cincinnati General Hospital, Cincinnati 29 (Dr. Hamburger).

APPENDIX II

[From the Wall Street Journal, May 6, 1969]

FDA CRACKDOWN—GOVERNMENT, INDUSTRY CLASH OVER BID TO CURB COMBINATIONS OF DRUGS—AGENCY CALLS FOR WITHDRAWAL OF 100 ANTIBIOTIC PRODUCTS; MAKERS DEFEND EFFICACY—LONG TERM EFFECT ON PROFITS

(By Jonathan Spivak, staff reporter of the Wall Street Journal)

WASHINGTON.—A new struggle, with high economic and political stakes, is looming between the nation's drug manufacturers and Uncle Sam.

The focal point this time is the medical merits of combination drugs—widely used prescription products that contain two or more active ingredients.

Government and academic experts increasingly contend that many of these mixtures unnecessarily expose patients to several drugs at once, permit physicians to avoid careful diagnosis and prevent tailoring of prescriptions to the patient's particular needs.

Drug company executives challenge these assertions and point to the long and extensive popularity of combinations among physicians and patients. They insist the products offer effectiveness, economy and convenience.

The Food and Drug Administration is bringing the conflict to a head by ruling that almost 100 antibiotic combinations are ineffective and proposing to remove them from the market. Democratic Sen. Gaylord Nelson of Wisconsin, who has been holding months of hearings hostile to the drug industry, is seizing on the FDA's action in an effort to embarrass the drug makers further; his small business subcommittee will air criticisms of the antibiotic combinations in a new set of hearings starting today.

SETTING PRECEDENTS

The action against antibiotics could set precedents for FDA policy toward many other kinds of drug mixtures, including pain-killers, cough and cold preparations, compounds used against high blood pressure, and arthritis and ulcer remedies. Some of these combinations may come under attack on grounds of ineffectiveness.

"I don't think the pattern will evolve as a general anticombination bias of this agency," says FDA Commissioner Herbert Ley Jr. "But I think where these combinations are irrational and illogical there will be a confrontation."

It's likely that the FDA will prevail in forcing the most questionable products off the market. But other long-established remedies may escape unscathed. And industry-Government compromises may be reached for others, permitting continued marketing with restrictions on claims for their effectiveness.

The Government's objective is to enhance the quality of health care received by the American public. But industry spokesmen argue that in the end its action could tend to curb drug-company profits and development of new products. Certainly the stakes for the industry are large. Dr. Ley estimates that retail sales of the antibiotic mixtures alone total $200 million or more a year. Combinations comprise about 40% of all drugs on the market.

SUBCOMMITTEE'S PLANS

In the short run, the attack on the combinations may simply tarnish further the image of the pharmaceutical industry. Sen. Nelson, a persistent and powerful critic of the industry, has invited academic medical men and FDA regulators to air their objections to the antibiotic mixtures; the manufacturers may not get an equal chance to defend their products. The subcommittee hopes to show that the drug companies frequently foist costly and valueless products on the public by needlessly combining already available drugs. Physicians are then persuaded to prescribe them through high-pressure promotion, the critics will charge.

Particular attention will probably focus on the Upjohn Co.'s widely promoted Panalba, a mixture of the antibiotics novobiocin and tetracycline. Panalba is one of the compounds the FDA wants to remove from the market. The company has adamantly resisted, urging physicians to write the agency in protest.

Many infectious-disease experts argue that Panalba and other antibiotic combinations are useless and potentially dangerous. They claim the mixtures need-

lessly expose patients to highly toxic drugs and encourage physicians to avoid the laboratory diagnosis necessary to pick the proper drug for the most successful treatment. These experts maintain that whenever two or more antibiotics are needed to overcome an infection, good medical practice demands carefully adjusting the dosages of each ingredient to the individual patient's requirements; fixed combinations do not permit such flexibility, although proponents claim the proportions are calculated property for most patients. Furthermore, the critics say, indiscriminate use of antibiotic combinations results in the emergence of dangerous bacterial strains that are resistant to all drugs.

"The only defense I can see for a combination is that the physician says, 'I don't know, I'm guessing.' Would you want to be treated that way?" demands Dr. Robert Wise of Jefferson Medical College in Philadelphia.

ANOTHER CRITIC

There is "very little rationale that we can see in these antibiotic combinations," says Dr. Calvin M. Kunin, of the University of Virginia, who is scheduled to testify at the Senate hearings. Dr. Kunin headed a group of advisers from the National Academy of Sciences who urged the FDA to remove the drugs from the market because of lack of efficacy.

The drug companies will defend the combinations as vigorously as they can. "Clinical reports show that our combination of tetracycline and novobiocin has retained its clinical efficacy after 11 years," insists R. T. Parfet Jr., Upjohn president.

Combinations of all kinds have important advantages, industry medical men say. Among their claims: The mixtures may be more effective than single drugs, attacking a wider variety of infections treating several medical problems simultaneously such as depression and anxiety or incorporating different attacks on a single ailment. Combinations can be safer minimizing the amount of a toxic ingredient by including other less harmful agents. They can offer added convenience by reducing the number of pills to be taken and easing the risk of medication mistakes by patients particularly the aged. Finally the products can save the public money by curtailing the need for extra prescriptions.

Drug industry men also contend the antibiotic combinations may be a practical necessity for many small-town doctors, who don't have sophisticated laboratory facilities and must treat many patients without careful diagnosis. "When a busy physician doesn't have time to see what bacteria is causing infection, it probably makes good sense to give as wide a spectrum antibiotic as you can," insists a spokesman for the Pharmaceutical Manufacturers Association. The motive behind most mixtures, of course, is to combine antibiotics that are effective against a variety of bacteria.

But if the Nelson hearings follow their past pattern, the companies will have little chance to present their rebuttal. The committee is interested in spotlighting the industry's mistakes, not in giving it a platform for self-defense, spokesmen for drug manufacturers assert.

In any case, the drug firms may be somewhat vulnerable on the issue of the antibiotic combinations. Privately, some of their own experts express doubts about the value of many mixtures. With the development of highly effective new drugs, such as the synthetic penicillins, and with the growth of knowledge about bacterial infections, the touch-all-bases theory behind some of the combinations has become harder to defend. Medical men outside the industry almost university condemn them; these critics claim that although there may have been some medical justification for these products years ago, profit-making has now become the prime purpose in selling them.

The companies will counterattack, however, by demanding Administrative hearings and a chance to argue their case before the FDA. That could temporarily stay most agency orders to withdraw their products from the market. The first confrontation will probably come this year over Upjohn's Panalba. E. R. Squibb & Sons, the Lederle Laboratories division of American Cyanamid Co., Chas. Pfizer & Co. and other companies may join the fray later.

But the FDA has the authority to take immediate action, particularly if it finds hazards exist. Thus, one type of antbiotic mixture—combinations of penicillin and streptomycin—may be barred from sale without the formality of a hearing. The reason: Streptomycin's known risk of causing deafness by damaging the auditory nerve. Though the penicillin and streptomycin combinations are small-volume items. they are sold by many companies, including Squibb, Upjohn, Pfizer and Eli Lilly & Co.

The most important issue affecting other combinations will be the FDA's interpretation of effectiveness. The agency insists that in order to remain on the market the combinations must be proven more effective than the individual ingredients. "This obviously means that each active ingredient be effective and make a contribution to the product's therapeutic effect," says Dr. B. Harvey Minchew, acting director of the FDA's Bureau of Medicine.

The companies will argue this standard exceeds the language of the law. As long as a combination is useful at all, they maintain, it should be legally authorized for sale; physicians can then make a choice based on their scientific knowledge and professional judgment. Both sides expect the antibotic battle to be protracted. "It could drag on for years in the courts," worries one FDA man.

Most of the drug mixtures were first marketed many years ago when the FDA required proof only of drug safety; very few passed carefully controlled clinical trials of efficacy. Although practicing physicians now rely on many of them, the FDA must decide which are worthwhile and which are not. Delicate considerations enter in: Should the agency apply exacting modern-day standards of medical effectiveness or can it rely on the informed opinion of experts and the medical profession's acceptance?

Dr. Ley's decisions will be watched not only by industry but by pro-consumer forces, particularly Democratic Rep. L. H. Fountain of North Carolina. Mr. Fountain heads a House investigating committee that is deeply dissatisfied with some of the FDA's recent regulatory decisions. The Congressman contends the FDA has been dilatory and uncertain on protecting the public, and he will probably goad the agency if he detects what he considers reference to the economic concerns of the companies.

Along with the possibility of abandoning some popular produts, the pharmaceutical companies face the burden of expensive and extensive testing to prove the efficacy of other combinations. One firm estimates that it may cost $250,000, require as many as 300 volunteer patients and consume over a year to test just one combination. The trials are difficult because the efficacy of the mixture must be compared with that of each active ingredient. Some experts insist the task is almost impossible. "This is the kind of research that it's hard to get talented people to do," says Dr. Louis Lasagna, a Johns Hopkins Hospital drug-testing expert.

APPENDIX III

[From McCall's Magazine, March 1969]

Who needs a cold?

Colds are difficult to avoid—but Neo-Synephrine Nasal Spray can make them less inconvenient by helping to restore free breathing in seconds—an advantage over slower-acting medicine taken by mouth. Swollen nasal passages shrink on contact with Neo-Synephrine, permitting drainage and easing that stopped-up feeling. By promoting adequate drainage during a cold, Neo-Synephrine helps prevent lingering sinus congestion after the cold.

Ask your druggist for Neo-Synephrine Nasal Spray or Nose Drops. He will recommend the proper strength Neo-Synephrine for adults, children, or infants.

Neo-Synephrine® Hydrochloride

(11980)

APPENDIX IV

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., May 26, 1969.

Hon. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: This will acknowledge your letter of May 14, extending an invitation to the Pharmaceutical Manufacturers Association to appear before your Subcommittee to discuss certain drug efficacy studies on fixed combination drugs, conducted by the National Academy of Sciences-National Research Council. Since your letter arrived on the day I was leaving the city to attend the PMA's Annual Meeting, this is the first opportunity I have had to reply.

Inasmuch as you have already conducted two days of public hearings and have other witnesses scheduled to appear on the subject of antibiotic combinations, it would be impossible for our Association or individual companies, whose products are involved, to appear *first*, as your letter suggests. In any event, we do not desire to appear for the reasons stated below.

According to recent testimony before the House Subcommittee on Intergovernmental Relations, various panels of the National Academy of Sciences-National Research Council have, since 1967, submitted to the FDA 2824 reports covering approximately 3700 drug formulations manufactured by 237 different companies. The NAS-NRC itself, has estimated that its review to date has required at least 10,000 therapeutic judgments.

I wish to note that not one of these NAS-NRC reports, until such time as notice of it is published in the Federal Register, has been made available to the PMA or to the manufacturer of the drug under study. Further, according to the testimony before the House Subcommittee, only 182 of the 2824 reports have been the subject of a Federal Register notice to date. Whether these published notices encompass all or some, a majority or minority, of the fixed drug combinations which were under review, we have no way of knowing.

For the purposes of this reply, it is immaterial whether the studies you propose to discuss before your Subcommittee include all "fixed combinations" or only those of "fixed antibiotic combinations." Neither the PMA nor individual companies has seen nor had an opportunity to study the reports of the NAS-NRC on "fixed combinations" or on "fixed antibiotic combinations." We are as a consequence, in no position to discuss them.

But whether the PMA had or had not made a study of these reports, we would still decline your invitations on the ground that the issues raised by the NAS-NRC panel studies involve medical and scientific matters to be decided under established laws and regulations.

It is our considered opinion that the safety and efficacy questions which have been raised with respect to combinations, should be decided in the medical and scientific forum, which functions within the FDA and the Department of HEW. This decision making should embody a judicious evaluation of all of the evidence and should be as free as possible of public and political non-scientific pressures, of disputations of scientific facts by non-medical individuals, or of the written or oral statements by non-professionals.

We feel strongly that the status of "fixed combination drugs" or any other category of drug products should be decided through the procedures now prescribed by the Federal law and implementing regulations. The administrative and legal remedies which the law and regulations authorize should be permitted to follow their course without prejudging of the issue in a Committee hearing or in the press.

Sincerely yours,

C. JOSEPH STETLER.

APPENDIX V

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
1155 15TH STREET, NW.,
Washington, D.C., February 28, 1969.

Hon. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: Testimony presented to the Senate Subcommittee on Monopoly on December 18, 1968, by Dr. Paul Lowinger, Associate Professor of Psychiatry, School of Medicine, Wayne State University, has created the erroneous impression that various pharmaceutical companies have failed to comply with Federal drug laws and regulations. We believe that Dr. Lowinger did not intend to create this impression and that the Record of the Subcommittee's proceedings should be clarified.

In his testimony, Dr. Lowinger stated that during the period 1954–1966 inclusive, he had made 27 new drug study reports for 19 drug companies. Of these, he contended only 10 reports were subsequently submitted by the companies to the Federal Food and Drug Administration. Implicit in these statements is the charge that the alleged failure of the drug companies to submit the other reports to the FDA was in violation of Federal drug law and regulations.

In response to an inquiry in this matter, we have heard from 9 of our member companies, concerning 15 of the reports. Seven companies have stressed the important fact that the present reporting regulations concerning investigational drugs first went into effect in May, 1963. Prior to that date, there was no requirement that manufacturers keep the FDA informed of the progress of investigations of new drugs in humans during investigational new drug trials. Toxicity data developed from such investigations was to be submitted to the FDA only when new drug applications on such drugs were filed.

Three companies dispute Dr. Lowinger's allegation that he ever sent them such reports. In fact, two categorically state that they have no record that Dr. Lowinger did any work for them on their products he listed.

In the interest of clarifying the Record of the Subcommittee's hearings on the drug industry, I would, therefore, respectfully ask that you include this letter in the hearing record, immediately following Dr. Lowinger's testimony.

Sincerely yours,

C. JOSEPH STETLER.

CC: Members of the Subcommittee on Monopoly, Senate Select Committee on Small Business.

APPENDIX VI

[From the New England Journal of Medicine, May 22, 1969, vol. 280, No. 21, pp. 1149–1154]

SPECIAL ARTICLE—FIXED COMBINATIONS OF ANTIMICROBIAL AGENTS*

National Academy of Sciences—National Research Council, Division of Medical Sciences Drug Efficacy Study

Abstract.—A review of the claims put forward for the use of penicillin-sulfonamides, penicillin-streptomycin and certain other fixed combinations of antimicrobial agents has convinced five panels organized under the auspices of the National Academy of Sciences—National Research Council that such combinations are "ineffective as fixed dose combinations." Although the individual active ingredients may be useful in specific entities, no greater effectiveness can be expected for the combination than for any one ingredient. Use of a proper dose of one ingredient may require excessive or inadequate doses of the other.

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*This report was prepared by Anti-infective Panels II and IV of the Drug Efficacy Study, Division of Medical Sciences, NAS–NRC; the chairmen of these panels are Dr. Calvin M. Kunin and Dr. William L. Hewitt. Subsequently, the report was circulated to Anti-infective Panels (I, III and V) and was approved by the respective chairmen: Dr. Heinz Eichenwald, Dr. William M. M. Kirby and Dr. William B. Tucker. In its present form, therefore, the report has approval of all Anti-infective Panels of the Drug Efficacy Study. Members of Panel II are Drs. William McCabe, John Nelson, Edward L. Quinn, Jay P. Stanford and Ian MacLean Smith. Members of Panel IV are Drs. M. Glenn Koenig, Floyd W. Denny, Sidney M. Finegold, Donald B. Louria and Arthur C. White.

Address reprint requests to the Drug Efficacy Study, Drug Research Board, National Academy of Sciences—National Research Council, 201 Constitution Ave., N.W., Washington, D.C. 20418.

It is the judgment of the panels that the use of these fixed combinations should be discontinued and that the physician should use the individual components according to his best clinical judgment.

The Drug Amendments of 1962 to the Federal Food, Drug and Cosmetic Act of 1938 fix requirements for the effectiveness as well as the safety of drugs. As an aid to the Food and Drug Administration (FDA) in this formidable task of evaluation, the National Academy of Sciences—National Research Council (NAS–NRC) undertook the Drug Efficacy Study in 1966 under contract (FDA 66–197 [Neg.]) with the FDA. Essentially, the NAS–NRC agreed to review the claims for effectiveness of drugs approved between 1938 and 1962 and to rank each claim for each drug for its degree of effectiveness. Reports embodying the recommendations of the Study have recently been submitted to the FDA.

The Study was conducted by a group of 30 panels, each consisting of a chairman and five additional members. Policy guidance was provided by a Policy Advisory Committee consisting of 22 members. Four of the 30 panels (anti-infective panels I–IV) were concerned primarily with the use of anti-microbial agents for indications other than tuberculosis. Two of these four panels (anti-infective panels II and IV), under the chairmanship of Dr. William L. Hewitt and Dr. Calvin M. Kunin, respectively, had cognizance of fixed combinations of penicillin and sulfonamides and of penicillin and streptomycin as well as of a series of single drugs. The principles stated herein have specific regard to fixed combinations of penicillin and sulfonamides and of penicillin and streptomycin; however, they are judged equally applicable to such other fixed combinations as tetracycline and amphotericin B and tetracycline and novobiocin. Special considerations set forth for each of these fixed combinations, together with the general statement of principle, support the unanimous agreement of the five panels that all these combinations are *ineffective as fixed combinations.* This judgment implies that, although the individual active ingredients may be useful in specific entities, efficacy is no greater for the combination than for any one ingredient, and that the disadvantages of the fixed combinations far outweigh any small advantages such combinations may seem to have.

The first section of this report is in the form of a "white paper" on penicillin and sulfonamides. This section is concerned with overall problems relating to combinations of drugs. The second section, concerned with penicillin and streptomycin, treats each of the claims as they are set forth in the respective package inserts. The reports of the Study panels on penicillin and sulfonamides and on penicillin and streptomycin are incorporated in a form that has been edited to meet the requirement for brevity and clarity of presentation. The general format of these reports is common to all reports of the Drug Efficacy Study. Although the reports differ greatly in style, they demonstrate that the reasoning supporting the final judgments of the panels is based on fundamental principles of antimicrobial practice as applied to the treatment of specific disease.

PENICILLIN-SULFONAMIDE COMBINATIONS FOR USE BY THE ORAL ROUTE

Various combinations incorporating some form of penicillin and some form of sulfonamide (or sulfonamides) have been developed by several pharmaceutical manufacturers for use by the oral route. It seems reasonable to consider the effectiveness of these combinations in a single review, since the indications suggested in the package inserts for their use are indentical or very similar.

Treatment of mixed bacterial infections

One of the most common indications cited for the use of oral sulfonamide-penicillin combinations is in mixed bacterial infections. Bronchiectasis, peritonitis, urinary-tract infections and chronic otitis media are the most common entities that can be caused by simultaneous infection with more than one kind of bacterium. Because many different species of bacteria are associated with these infections, and because patterns of antimicrobial sensitivity are highly variable, it is very doubtful whether oral penicillin-sulfonamide mixtures would ever be the drugs of choice in such cases. (1)

Weinstein (2) has shown that, under some circumstances, a "broad-spectrum" effect is produced when sulfonamide-penicillin mixtures are given. He points out, however, that the degree of antibacterial activity is generally unpredictable

NOTE.—Numbered references at end of article, pp. 5264–5266.

and that antimicrobial effectiveness is often decreased by this type of therapy. Thus, the use of penicillin-sulfonamide combinations is not recommended in the treatment of "mixed" bacterial infections. (3)

Enhancement of antibacterial activity

Another reason commonly given for the use of drug combinations is that some types of infections are more effectively treated by two or more drugs given in concert. Tuberculosis, subacute bacterial endocarditis due to Group D streptococci, and probably some strains of *Streptococcus viridans* are cited as examples of such infections. Some data have also suggested treatment of some forms of brucellosis and some infections due to *Proteus mirabilis* by combinations of drugs. Combinations of penicillin and sulfonamide, however, are not the agents of choice in any of these infections.

Careful laboratory studies have demonstrated that the use of the combination of penicillin and a sulfonamide can have three possible effects: enhancement of antibacterial activity beyond the additive effects of the two drugs (synergism); activity equal to the additive effect of the two drugs (addition); or activity less than the sum of the separate activities (antagonism). (4) It is not generally possible to predict which of these effects will be encountered in a given case. Fixed sulfonamide-penicillin combinations should not be used, since the antagonistic effect is an ever present possibilty.

Treatment of infections before etiology is known or in case it is impossible to determne etiology

At times it is necessary to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such cases; however, in all cases the drugs used should be given at least initially by the parenteral route. This requirement in itself would preclude the use of oral sulfonamide-penicillin mixtures. Furthermore, the use of other drug mixtures has been shown to be much more effective than the sulfonamide-penicillin combinations. (1)

Many of the same factors affect the use of sulfonamide-penicillin combinations in cases in which it is difficult or impossible to determine the etiology of an infection. A possible exception is the use of penicillin-sulfonamide combinations in the treatment of acute otitis media. Group A streptococci, pneumococci and *Haemophilus influenzae* are the common bacterial causes of acute otitis media. It should be noted, however, that *H. influenzae* very rarely causes otitis media after the age of three or four years, and multiple antibacterial agents are thus not indicated for the treatment of this entity in older children or adults. Because *H. influenzae*, Group A streptococci and penumococci cause otitis media during the first few years of life, it has been common practice to use sulfonamide-penicillin combinations in this early age group. Data to support this regimen are minimal, and, indeed a recent in vitro study indicates that sulfonamides in the commonly used triple formulation inhibited only 20 percent of typable and 40 percent of the nontypable strains of *H. influenzae* at concentrations within the usual therapeutic range. (5) The results of treatment of otitis media with penicillin alone appear to be about as good as those with penicillin in combination with the sulfonamides. (6) It should also be noted that other drugs, such as the tetracyclines and ampicillin, have been shown to be effective against *H. influenzae* when given alone.

Exposure of patients to multiple drugs

The sulfonamides and penicillin are potentially dangerous drugs. (1) Reactions are common, and the reactions can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient, and the combination is to be avoided for this reason. Another troublesome aspect of this problem is that it is difficult to detect the drug causing an untoward reaction when multiple drugs are used.

Use of fixed drug mixtures

The question of the control of drug dosage should always be considered when fixed drug combinations are used. In this situation, the physician never finds it possible to increase or lower the dose of one component of the mixture without at the same time affecting the dose of the other. In such circumstances the tendency is either to raise the dose of one drug to a desired level, and thus inadvertently to give an overdose of the other, or to lower the dose of one

component to a desired level, and consequently to give an insufficient dose of the other. This subject is well treated by Weinstein (1):

The most important problem in the field of combined chemotherapy is the use of "fixed-dose" mixtures. On the basis of the presently available knowledge, it appears patently clear that these mixtures have no place in the treatment of infection. The attitude that physicians should adopt toward such preparations has been outlined in an editorial by Finland (1957), written as a joint expression of the views of investigators and teachers in the field of infectious diseases, as follows (7):

> Considerable caution is warranted in accepting the trend to fixed antibiotic combinations as inevitable or in lending support to a trend that may not be desirable. We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot cosider to be as good as, or no better than, those previously shown to be good, even if they are legally certified. It is particularly incumbent on us to be very circumspect about the use of drugs of any sort in fixed combinations that do not offer the physician discretion as to the choice of components, or of the ratios in which they are used. The presence in any combination of a new or unproved component, or of a substance that may be inferior to others that might well be used instead, should make us even more cautious. They should be recommended and adopted, if at all, only after adequate, carefully controlled, and critically evaluated study shows them definitely to be useful and superior.

Encouragement of the use of such "fixed-dose" antibiotic mixtures and the manner in which they are being exploited represent a major backward step in the management of infections.

Recommendations

In the foregoing discussion, the anti-infective panels of the Drug Efficacy Study state that the contraindications for the use of any sulfonamide-penicillin combination by the oral route far outweigh any indications for such use. Citations from the more recent literature in support of this view are amply supplemented by editorial comment from the early 1950's. (8, 9) On these bases, it is strongly urged that use of these fixed combinations no longer be recommended.

PENICILLIN-STREPTOMYCIN COMBINATION FOR PARENTERAL USE

The reports prepared for the Drug Efficacy Study by the anti-infective panels offer a convenient format for discussion of the penicillin-streptomycin combination for parenteral use. This report format, appropriately edited for economy of presentation, is as follows (each claim cited as an indication in the package insert for this combination is reviewed):

Indications

A. *Bacterial Endocarditis in Patients with:*

1. Pencillin-susceptible streptococcal endocarditis (0.1 mcg/ml or 0.1 unit/ml or less).

a. *Evaluation:* Ineffective as a fixed dose combination.

b. *Comment:* Treatment of this specific form of bacterial endocarditis with injections of a fixed combination providing a maxium of 2.0g of streptomycin and at least 2.4 million units of penicillin per day would probably be effective, but only one of the 17 preparations submitted will provide ths dosage. In most instances, this form of endocarditis can be treated with penicillin alone. If streptomycin were added, it could readily be given in a separate dosage form.

c. *Documentation:* References 10–17.

2. Endocarditis due to enterococci or other streptococci not sensitive to 0.1 mcg/ml or less.

a. *Evaluation:* Ineffective.

b. *Comment:* These more resistant types of bacterial endocarditis would not be optimally treated with any of these fixed combinations. There is so little procaine penicillin in the combinations that adequate dosage of penicillin would be accompanied by doses of streptomycin that would be seriously toxic.

c. *Documentation:* References 10–17.

B. *Lung Abscess*

1. *Evaluation:* Ineffective as a fixed dose combination.

2. *Comment:* A fixed dose combination of penicillin and streptomycin is not considered the regimen of choice. Most clinicians would rely primarily on large dose of penicillin G and on occasion would add another agent, depending on the flora found by culture.

3. *Documentation:* References 18–20.

C. *Aspiration Pneumonia*

1. *Evaluation:* Ineffective.

2. *Comment:* The term "aspiration pneumonia" is vague and will be considered here to represent the pulmonary inflammatory process that follows aspiration of acidic gastric contents incident to vomiting or the exclusion of aspiration of mixed bacterial flora of the oral cavity incident to alteration of consciousness from a variety of causes. This condition is primarily a chemical pneumonia and requires no antibiotic.

Small amounts of a single agent are sometimes used to prevent pneumococcal or streptococcal superinfection. If there is staphylococcal infection, better antimicrobials than these combinations are available. Aspiration of oral cavity microflora should be regarded as the initiating event for putrid (anaerobic) lung abscess (see indication B—lung abscess, supra).

3. *Documentation:* References 21–24.

D. *Mediastinitis*

1. *Evaluation:* Ineffective.

2. *Comment:* The invading organisms in mediastinitis are variable and have not been well defined. The microorganisms include both aerobic and anaerobic oral flora (*Streptococcus viridans*, anaerobic streptococci, Bacteroides species, fusiform bacilli, and Enterobacteriaceae). Although pencillin is effective against some of the potential pathogens and streptomycin against others, the amount of penicillin in these combinations is not sufficient for adequate therapy.

3. *Documentation:* References 25–27.

E. *Peritonitis*

1. *Evaluation:* Inffective as a fixed combination.

2. *Comment:* Many types of peritonitis exist, e.g., spontaneous coliform peritonitis in patients with hepatic cirrhosis, pneumococcal peritonitis, tuberculosis peritonitis, and peritonitis secondary to rupture of an abdominal viscus in hospitalized or non-hospitalized patients.

There is little question but that antibiotic therapy has improved the prognosis in peritonitis secondary to fecal spillage. This has been most apparent, however, with aqueous penicillin G or tetracycline. Penicillin and streptomycin have been used together in such infections, but it is difficult to asses whether effectiveness is due to the penicillin or to the streptomycin.

3. *Documentation:* References 28–34.

F. *Mixed Wound Infections and Abscesses*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* Antibiotic therapy in combination with proper local management has been effective in the treatment of mixed wound infections and abscesses. One would expect these fixed combinations of penicillin and streptomycin to be less effective than other agents in the treatment of postoperative wound infections, because the organisms most commonly encountered are often resistant to these drugs. Wounds following trauma are often contaminated with clostridia. These organisms are usually sufficiently non-susceptible to preclude their eradication with the recommended dosages of penicillin-streptomycin.

3. *Documentation:* Reference 35.

G. *Abdominal Surgery in a Contaminated Area*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* This combination of antimicrobials has not been shown to prevent postoperative infection.

3. *Documentation:* References 30, 36–40.

H. *Gonorrhea*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* The combinations offer no advantage over adequate dosage of penicillin alone. It is also noted that strains of *Neisseria gonorrheae* have been

isolated that are highly resistant to streptomycin. The recommended dosages of procaine penicillin are 2.4 million units for males and 4.8 million units for females. There is so little procaine penicillin in the combination that an adequate dosage of penicillin would be accompanied by seriously toxic doses of streptomycin.

3. *Documentation:* References 41–45.

I. *Urinary Tract Infections*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* These infections may be caused by a wide variety of bacteria, some of which may be sensitive to one or both of the ingredients of this mixture. Such sensitivity is highly unpredictable.

Infections with enterococci do occur; however, they are unusual and account for fewer than 5 percent of infections. When present, enterococci are frequently associated with resistant gram-negative bacilli which are better treated with agents other than penicillin and streptomycin. Enterococci are the major pathogens that are predictably more sensitive to the combination of penicillin and streptomycin than to either agent alone; however, in those rare cases in which they might be used, the two agents could readily be given in separate dosage forms.

3. *Documentation:* References 16. 47, 48.

J. *Middle Ear Infections and Mastoid Infections*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* Acute otitis media is most commonly due to pneumococci and streptococci (other than enterococci) and, in infants, to *Haemophilus influenzae.* Penicillin is optimal therapy for pneumococcal and streptococcal infections. Simultaneous administration of streptomycin is of no value. Enterococci are responsible for an exceedingly small proportion of streptococcal middle ear infections, and amounts of penicillin considerably greater than are available in these combinations would be needed for treatment of these entities. The relative effectiveness of procaine penicillin alone or in these combinations in treatment of *H. influenzae* ear infections has not been the subject of critical study, and tetracycline or ampicillin would constitute a better drug choice for treatment of such infections.

Chronic otitis media is usually due to staphylococci or gram-negative bacillary aerobes and anaerobes. These organisms are usually resistant to penicillin and streptomycin or, in the case of gram-negative bacilli, are likely to become so very early in the course of treatment.

3. *Documentation:* Reference 6.

K. *Bronchiectasis, Bronchitis, and Other Respiratory Infections*

1. *Evaluation:* Ineffective as a fixed combination.

2. *Comment:* It is misleading to imply that these antibiotic combinations would be preferable to the penicillin component alone if a specific clinical-microbiologic diagnosis were made. Group D streptococci are more susceptible to the combination but are virtually never implicated in respiratory tract infections. Chronic bronchitis is often associated with a mixed bacterial flora, but a penicillin-streptomycin combination is not the regimen of choice. *H. influenzae* is a very important pathogen in this condition and would be better treated with tetracycline or ampicillin.

3. *Documentation:* References 10, 16, 49, 50.

L. *Brain Abscess*

1. *Evaluation:* Ineffective.

2. *Comment:* The bacteriology of brain abscess is exceedingly diverse. Microorganisms commonly isolated include anaerobic cocci, gram-negative anaerobic bacilli, staphylococci, Actinomyces, Veillonella, Enterobacteriacae, and enterococci. Although penicillin is effective against some of the potential pathogens and streptomycin against others, only enterococci (group D streptococci) are more susceptible to the combination, and then only if the penicillin is used in very high doses and in the aqueous form. Large doses of penicillin are required to achieve adequate levels across the blood-brain barrier. The use of this fixed combination would be unwise.

3. *Documentation:* References 51, 52.

M. *Osteomyelitis*

1. *Evaluation:* Ineffective.
2. *Comment:* Primary non-tuberculous osteomyelitis is most commonly caused by staphylococci. Many of the strains are non-susceptible to penicillin G and streptomycin. If the infecting strain is susceptible to penicillin, adequate dosage of penicillin would be accompanied by doses of streptomycin that would be likely to be seriously toxic. In addition, the duration of treatment usually considered desirable poses a serious risk of streptomycin toxicity. Osteomyelitis following surgical procedures may be caused by gram-negative bacilli; however, such hospital-acquired infections are usually resistant to both agents.
3. *Documentation:* Reference 46.

N. *Secondary Infections in Patients Being Treated for Tuberculosis.*

1. *Evaluation:* Ineffective as a fixed combination.
2. *Comment:* Patients with tuberculosis may develop staphylococcal, pneumococcal, streptococcal, Klebsiella, or Hemophilus pneumonia. The promulgation of these fixed combinations to avoid such infections is undocumented, unnecessary, and unrealistic.
3. *Documentation:* None applicable.

O. *Other Infections in Which the Causative Agent Cannot be Identified without Operative Procedures*

1. *Evaluation:* Ineffective.
2. *Comment:* This claim is too broad to permit its proper evaluation.
3. *Documentation:* None applicable.

GENERAL COMMENT ON REVIEW OF INDICATIONS

These fixed combinations will rarely provide optimal therapy for the complex clinical problems that are encountered with these conditions. In each case, the characteristics of the invading organism and the results of in vitro bacterial sensitivity tests must be known. Many of these infections could be treated with penicillin alone, with penicillin and streptomycn in a different ratio or with other antimicrobial agents.

JUDGMENT OF ANTI-INFECTIVE PANELS II AND IV

Anti-infective panels II and IV wish to record their judgment that the availability of fixed combinations of streptomycin and penicillin has had the following results:

It has led to inappropriate use of these drugs for treatment of diseases in which the combination is no more effective than one of the components or in which the fixed combination is not the treatment of choice.

Patients have been exposed to the increased toxicity that is inherent in a combination without increasing the benefit.

Flexibility in dosage of the individual components of these combinations has been denied.

The marked changes that have occurred in the pattern of bacterial susceptibility in recent years and the development of new and better antimicrobial agents have been ignored.

The availability of penicillin and streptomycin individually for combined use at the discretion of the physician has also been ignored.

These considerations, and the limited indications for the use of these combinations, have rendered fixed dosage forms of penicillin and streptomycin obsolete. Accordingly, it is the judgment of the panels that these combinations no longer belong in the therapeutic armamentarium.

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[Editorial]

The Drug Efficacy Study

The April issue of the *Archives of Internal Medicine* contains a report of an 18-year-old girl with agranulocytosis caused by chronic ingestion of Pamolin,

an antidiarrhea mixture containing sulfaguanidine, the earliest of the nonabsorbable sulfonamides. (1) The mixture was prescribed by the patient's father, a physician. Some years earlier a lecturer, who had discussed the uses and abuses of antibiotics, was approached by a physician from the audience for advice about his four-year-old daughter; she had become totally deaf as a result of repeated administration of Combiotic, a combination of procaine penicillin and dihydrostreptomycin, by a pediatrician colleague for impetigo that kept recurring in spite of several courses of this agent.

These are not uncommon examples of serious untoward effects that are totally unnecessary and directly attributable to a component of a fixed drug combination that was not making any therapeutic contributions. They are all the more impressive for having involved the immediate families of physicians. The protection of the public, and also of practicing physicians against just such improper therapy, was one of the main reasons for the concerted but frustrated efforts over many years, by most of the leading clinical experts, teachers and research workers in the field of infectious diseases, to discourage manufacturers from marketing and physicians from prescribing antimicrobial agents in fixed combinations. Now the 1962 Kefauver-Harris New Drug Amendments to the Food Drug and Cosmetics Act of 1938 and the regulations promulgated by the Food and Drug Administration under authority of those laws are being invoked to achieve this purpose.

The Kefauver-Harris Amendments introduced new and in some respects radical concepts. Most important was the requirement that new drugs must be effective as well as safe before they can be marketed. The manufacturer is required to provide proof that the drug has all the effects that it is claimed to have in the "labeling" (which includes the "package insert" and all advertising material) for the purposes and under the conditions of use for which it is recommended. Safety—that is, freedom from serious toxic effects—may also be taken into account in the evaluation of efficacy in that a toxic drug may not be acceptable if safer and more effective drugs are available for the same indications. "Substantial evidence," consisting of adequate and well controlled investigations by qualified experts, must be presented in support of each claim before it is accepted. When drugs are marketed in fixed combinations, the law and regulations require that each active ingredient must be shown to have not only the effect claimed for it as a single drug, but must also contribute to the efficacy with respect to each separate claim made for the combination in the dosage ratio present in the combination.

Soon after Dr. James L. Goddard became commissioner of the Food and Drug Administration he decided that the provisions of the Kefauver-Harris Amendments relating to efficacy should apply to all drugs marketed under new-drug applications that had been "approved for safety" since the passage of the Food Drug and Cosmetics Act of 1938. (2) This required a review of all claims for an estimated 4000 drugs and about 7000 formulations, a task far beyond the capabilities of the FDA. To accomplish this Herculean task expeditiously, Goddard succeeded in enlisting the co-operation of the National Academy of Sciences-National Research Council Division of Medical Sciences, under its chairman Dr. R. Keith Cannan, and the Drug Research Board, under the chairmanship of Dr. William S. Middleton, to gather up and organize the experts and provide leadership and guidance for this task. Some 30 panels were eventually enrolled, each consisting of a chairman and five members, most of them recommended by the major national professional and biomedical societies. Some additional experts were consulted on an ad hoc basis when special advice and experience was needed.

The guidelines of the Drug Efficacy Study were set up with the help of a Policy Advisory Committee, after joint consultations with the FDA, representatives of industry and the chairmen of the panels. The staff work was done by Mr. Duke C. Trexler (who already had experience as executive secretary to the Commission on Drug Safety) and a group of physicians and staff members of the FDA specifically assigned to the Drug Efficacy Study to assist the panels and expedite their work. The entire task from inception to its expected completion next June, when all the last reports are submitted to the FDA, will have taken more than three years.

As anticipated, many new problems requiring decisions arose in the course of the review; these were considered by the panels with the help of the Policy Advisory Committee headed first by Dr. Middleton and later by Dr. Alfred Gil-

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NOTE.—Numbered references at end of article, p. 5269.

man. Each panel reviewed not only the various distinct chemical entities but also all formulations and dosage forms of all suppliers and all claims made for each of them. They used the data furnished by the manufacturers or suppliers, the findings reported in the literature, the original new drug application and their collective experience to determine whether the claims were supported by substantial evidence of efficacy and to place each into one of the categories provided in the guidelines.

The simplest categories and earliest decisions were for drugs and claims determined to be either "effective" or "ineffective," but between these black and white categories there were shades of gray termed "probably effective" or "possibly effective" depending on the amount and nature of the supporting data available. Still others, which might strictly speaking be effective, but which the panels considered undesirable or which they could not support for good clinical reasons were called "effective but . . ." —and the reasons for this classification were spelled out. For drugs in fixed combinations still another category was required when one component was effective with respect to a given claim, but the other or others either were not effective for that claim or added an unnecessary risk of toxicity; the term "ineffective as a fixed dose combination" was then applied.

Obviously, these determinations, though simple for a majority of useful agents and for most of the claims made for each of them, unveiled many defects in the current labeling. For some the panels suggested specific changes or even rewrote or prepared prototype "package inserts" to expedite the revisions that would eventually be required to make the claims acceptable. In others, suggestions were offered about the type of data still required to make the claims acceptable. The ultimate responsibility for acceptance or modification of the recommendations of the Drug Efficacy Study rests with the present commissioner of the FDA, Dr. Herbert L. Ley, Jr., to whom the last report was delivered on April 15. However, since the various panels and the Policy Advisory Committee already included a major segment of the expertise of the country, and since the FDA could hardly expect its own limited staff to add more than legal, regulatory and practical administrative features to expedite the problems of compliance, very few changes of substance are likely to be made by that agency.

The reports of the Drug Efficacy Study are sent to the interested manufacturers for their comments and objections before orders for compliance are officially promulgated. Manufacturers may ask for and usually would be granted additional time to provide or accumulate additional data. Hearings may be held to air objections, and although the manufacturer also has recourse to the courts for final adjudication if he considers the decisions improper, it should be possible to settle most of the details amicably without prolonged legal procedures. However, because of the tremendous financial stakes, there are certain to be some legal battles ahead. (3) If those who oppose the panels' conclusions can provide "substantial evidence" for their views with data acceptable to the FDA and expert advisers, some of the decisions can be altered.

Elsewhere in this issue appears one of the summary reports prepared by the chairmen of two of the five panels that dealt with anti-infective agents. The report, which was approved by the members of all five panels and the Policy Advisory Committee, concerns only two of the many types of combinations of anti-infective drugs, and its essence has been well publicized. The *Journal* prints the report in fuller detail, however, so that physicians may examine the reasons for the recommendations made, and may understand how the panels applied themselves to consider both general principles (as in the section of the report dealing with oral penicillinsulfonamide preparations) and specific therapeutic claims (section on combination of penicillin and streptomycin for parenteral use). Such examination and understanding of the panels' difficult task is crucial, for the decisions may have a tremendous impact on the practices of the drug industry and the medical profession.

The entire Drug Efficacy Study should greatly affect research workers and clinical investigators as they evaluate the efficacy and safety of new drugs. Its influence on patient care may be even greater. Many physicians obviously have found fixed drug combinations convenient and, on the basis of their own clinical impressions, believe them to be useful and effective. They may have felt encouraged in their faith by the facts that these drugs were available with the implied sanction of the FDA, and that they were marketed by some reputable firms. At the same time, however, those who used the fixed combinations either ignored or were unaware of repeated contrary admonitions of experts in the field. Now, in the best interests of their patients, physicians should be willing to re-examine the bases of their prescribing practices in the light of the sobering judgment submitted by the Drug Efficacy Study.

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APPENDIX VII

COLLEGE OF MEDICINE, DEPARTMENT OF MEDICINE,
UNIVERSITY OF ILLINOIS AT THE MEDICAL CENTER, CHICAGO,
Chicago, Illinois, June 17, 1969.

SENATOR GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: I am happy to respond to your request for a statement of my views on the uses of fixed combinations of antibiotics. I have been interested in this problem for some time through teaching, research, and the care of patients, and as a result of membership in the Revision Committee of the United States Pharmacopeia, the Council on Drugs of the American Medical Association, the Medical Advisory Board of the Food and Drug Administration and a number of ad hoc committees relating to the regulation of drugs. (A full curriculum vitae is attached.)

The reasons that can be brought forward for the use of fixed combinations of antibiotics and other drugs used in infections are:

1. Two or more anti-infective drugs may be effective against a larger number of infections than one alone,
2. One drug may delay the appearance of micro-organisms resistant to another drug in the combination,
3. Synergism may result, i.e., a better result than could be obtained with maximal doses of either antibiotic alone.

In addition, certain reasons may be given for the use of combinations of drugs in general:

4. Greater convenience to the patient, and
5. Greater convenience for the physician.

How do the combinations of antibiotics that are marketed today fulfill these criteria? Combinations of penicillin and streptomycin are recommended for fixed infections. If by this is meant peritonitis following a ruptured appendix, for instance, the dose of penicillin which would be effective should be from 16 to 25 times the quantity contained in a single dose. It would be impossible to give this intramuscularly, and, if it could be given, such a dose would contain 8 to 12 times the highest recommended dose of streptomycin and thus would be in the toxic range for that drug. If the combination is intended for use in mixed infections of the urinary tract, it is doubtful whether either antibiotic in the doses used would be effective against the great majority of bacteria which infect the urinary tract, and certainly several other antibiotics are much more effective than this combination. If it is intended to treat chronic bronchitis with this combination, there is no evidence that this combination is more effective than penicillin alone, nor is it anywhere nearly as effective as the tetracyclines.

The sulfa drugs have been combined with several antibiotics, especially the erythromycins, tetracyclines and penicillin. If it is intended that they be used in acute upper respiratory tract infections, there is no evidence that the sulfonamides add anything. All three antibiotics are so much more effective in pneumococcal infections than the sulfa drugs that if one of them fails to cure or improve a pneumococcal infection, the addition of sulfonamides will surely not be of any help. Penicillin and erythromycin are very effective in infections caused by the hemolytic streptococci (such as scarlet fever); sulfonamides only slightly effective if at all. Penicillin or one of its newer analogues, such as oxacillin, are effective against practically every staphylococcus. Erythromycin and the tetracyclines are effective against some; the sulfonamides have a very weak effect against a few staphylococci and no effect against many. Infections caused by mycoplasmas, microorganisms intermediate in some respects between viruses and bacteria, are not affected by the sulfa drugs but are rapid-

ly eradicated by the tetracyclines and probably also by the erythromycins. And this just about covers all of the acute upper respiratory infections that are amenable to any specific therapy; in none would a combination of two antibiotics, or antibiotics with sulfa drugs, be indicated.

The tetracyclines are marketed in combination with analgesics such as asprin and phenacetin. Here, the superfluous drugs are usually the antibiotics. The discomfort or pain that occurs in the common cold is usually relieved by drugs such as aspirin, but it has been shown that the antibiotics have no usefulness in the common cold. In the sinusitis that sometimes follows a common cold, antibiotics may occasionally be helpful (although other antibiotics are more likely to be effective than the tetracyclines), but the doses should be given at regular intervals and for a definite period of time until the infection is cleared and is not likely to recur, whereas the pain-relieving drugs should be given for the symptoms of pain, which sometimes would require doses at more frequent intervals than the antibiotics are given, and at other times no analgesics at all. Also, therapy is usually needed only for a day or two in contrast to the longer period of time required for the tetracyclines.

Possible synergistic effects cannot be used as a reason for giving any of the fixed combinations of antibiotics that are on the market. The cases where combinations of antibiotics can be given for a synergistic effect before sensitivity tests are done on the infecting microorganism, are limited to the use of penicillin and streptomycin in endocarditis, and even here it is wise to check the effect of the combination in the laboratory. The dose of the two antibiotics needed in the treatment of endocarditis would prevent the use of the fixed combinations of penicillin and streptomycin that are on the market. Sometimes, other antibiotics are given concomitantly in serious infections until sensitivity tests can be done, but never in the doses or combinations that are marketed.

The use of antibiotics concomitantly has also been shown to be effective in delaying the appearance of resistant bacteria in the treatment of tuberculosis, but the doses and routes of administration used prevent the use of fixed combinations. My colleagues and I showed that spiramycin given concomitantly with novobiocin would delay the appearance of resistant staphylococci, as compared with novobiocin given alone; but this delay was not very great, and other drugs are now available which are so much more effective that this study is of no practical value.

The only one of these fixed combinations that has any rationale is the combination of a tetracycline and nystatin. The latter has been shown to lower the number of candida in the intestinal tract of patients receiving tetracyclines, as compared with those receiving a tetracycline alone. Although it has not been proved that candida infections are less frequent following the use of these infections, it seems reasonable that this combination might be used in high-risk patients.

One might ask, even if a combination is effective only once in 10,000 times when the most active drug in the combination is not effective alone, why should the combination not be used. The answer is that the increased number of adverse reactions that occur as a result of using two or more drugs instead of one does not justify the possibility that in a very rare instance the combination may have an added advantage. In addition, as has been mentioned, the optimal doses and dosage-intervals for any two drugs are usually not the same.

Antagonism, the diminution of the effect of the one antibiotic when a second antibiotic is used concomitantly, although infrequent, is a real possibility when two antibiotics are used at the same time. Although some general rules have been devised for predicting whether synergism or antagonism will occur, there are enough exceptions to these rules to make it advisable in most cases to determine what a combination of two antibiotics will accomplish in the test tube before it is used clinically.

One frequently hears the statement that it is all very well for someone in an academic position to recommend the use of laboratory tests before therapeutic procedures, but that such procedures are not practical for the practicing physician. Yet, as one who was in the private practice of medicine for sixteen years and who has been in a full-time academic position for nineteen years, I am confident that the good physician in either locality approaches diagnosis and treatment in the same way. Neither in the academic community nor in the private

practice of medicine does the doctor need to depend alwas on laboratory diagnosis before starting treatment. A good example is pneumonia caused by the pneumococcus, the commonest type of pneumonia. The diagnosis can be made in a majority of cases by taking the patient's history and performing a physical examination, and the physician is justified in initiating therapy with penicillin without laboratory tests, whether the patient is at home, in a community hospital or in a university teaching hospital. On the other hand, if a patient has a severe, long-standing infection of the urinary tract, the doctor, whether in his office or in the university hospital, should be guided by sensitivity tests on the microorganisms cultured from the urine.

The problem is not one of the location of the doctor, but rather the difficulty in keeping up with the uses and contraindications of the newer drugs. This is made worse by the barrage of advertising from which the doctor cannot escape. As I have said elsewhere:

"We might compare the doctor's encounter with drugs to driving a car at night. It is not like driving on a dark road where his headlights will pick out the signs he is looking for. Instead, it resembles driving on a busy city street where the myriad lights of automobiles approaching, receding, and crossing are surrounded by other lights of red, yellow, and blue, steady, bright, or dim. Out of this bewildering array he tries to pick the signal lights of red, amber, and green as they wink on and off to tell him whether he may proceed with safety or whether he invites a disastrous crash if he does not stop. Part of the driver's skill comes in learning to ignore the irrelevant, just as the doctor must ignore nine-tenths of the printed material that comes to his eye. But even with the exercise of this skill, the driver's safety would not be assured unless the most glaring signs were removed and those that obstructed the signal lights were forbidden. This is also true of advertising." [1]

What should be done about the problem? I believe that we are well on the way toward better things. The provisions of the Drug Amendments Act of 1962 make it possible for the Food and Drug Administration to disallow claims for efficacy of most fixed combinations of antibiotics on the basis that the effectiveness of each ingredient has not been proved and because the adverse effects of the combination outweigh any possible benefits.

The same Act also allows the FDA to insist upon truth in the advertising of drugs to physicians. But the FDA cannot do the job alone. I believe that medical societies and editors of journals should (1) aid the FDA in devising regulations regarding advertising, (2) become familiar with the regulations as they are made, (3) interpret the regulations, (4) set their own standards even higher, and (5) screen advertisements in the journals they control. Just as important is the job of interpreting to the practicing physician what he should look for and what he can expect to derive from advertisements. Also we must find out how the doctor is using these advertisements and what information he is getting from them under the new system of regulation. The drug companies will study the ability of these advertisements to sell drugs, we may be sure. Who will study how they improve (or worsen) the practice of medicine? Here is a clear challenge to the medical profession.

In summary: I believe there is no valid theoretical or practical reason for the physician to use any of the fixed combinations of antibiotics with antibiotics, or antibiotics with other drugs that are now on the market, with the possible exception of the combination of a tetracycline and an antifungal agent, such as nystatin.

Second, it is necessary for the organized medical profession to help the Food and Drug Administration implement the law requiring proper advertising of drugs to physicians and to go even further than the FDA can, in improving the quality of these advertisements.

Yours sincerely,

HARRY F. DOWLING, M.D.

Enclosure.

[1] Dowling, H. F.: "How Do Practicing Physicians Use Drugs?" Journal of the American Medical Association, Vol. 185 (July 27, 1963), pp. 233–236).

CURRICULUM VITAE

(Harry F. Dowling, M.D.)

Birth Date: November 11, 1904.
Birthplace: Washington, D.C.
Education: 1927 A.B. (Magna cum laude) Franklin and Marshall College. 1931 M.D. (with distinction) George Washington University. 1953 Sc.D. Franklin and Marshall College.

MEDICAL POSITIONS

1931–32: Internship, Baltimore City Hospital.
1932–33: Assistant in Medicine, Johns Hopkins University.
1933–34: Fellow in Medicine, Harvard University.
1934–40: Clinical Instructor in Medicine, George Washington University.
1940–50: Clinical Professor of Medicine, George Washington University; Chief, Medical Division, Gallinger Municipal Hospital.
1950–51: Professor and Head, Department of Preventive Medicine, University of Illinois, Chicago.
1951: Professor and Head, Department of Medicine, University of Illinois, Chicago.
1966–67: Health Sciences Scholar, National Library of Medicine.

AFFILIATIONS

American Association for the History of Medicine.
American Board of Internal Medicine, Diplomate.
American College of Physicians, Fellow.
American Federation for Clinical Research.
American Medical Association.
American Society for Clinical Investigation.
Association of American Physicians.
Central Society for Clinical Research.
Chicago Medical Society.
Chicago Society of Internal Medicine.
Infectious Diseases Society of America, President 1965–66.
Alpha Omega Alpha (Honor Medical Fraternity).
Phi Beta Kappa.
Sigma Xi.

COMMITTEE MEMBERSHIPS

1952–59: Member, Subcommittee on Infectious Diseases, National Research Council.
1955: Member, National Citizens Committee on the Food and Drug Administration.
1955–57: Vice Chairman and Chairman, Section on Experimental Medicine and Therapeutics, American Medical Association.
1955–present: Associate Member, Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board.
1956–present: Member, U.S. Pharmacopeia Committee on Revision; Chairman, Panel on Antibiotics.
1957–59: Member, Board of Scientific Counselors of the National Institute of Allergy and Infectious Diseases.
1960–62: Member, House of Delegates, American Medical Association.
1960–63: Member, National Advisory Allergy and Infectious Diseases Council of the United States Public Health Service.
1960–66: Member, Council on Drugs, American Medical Association.
1961–65: Vice Chairman and Chairman, Council on Drugs, American Medical Association.
1965–present: Member, Medical Advisory Board, Food and Drug Administration.
1965–66: Vice-Chairman, Section on Internal Medicine, American Medical Association.

EDITORIAL BOARDS

1961–65: Annals of Internal Medicine.
1955–present: Chemotherapia.
1961–present: Clinical Pharmacology and Therapeutics.
1960–present: Disease-a-Month Series, Editor.
1957–present: GP (Journal of the Academy of General Practice).

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