cells 5,100, and platelets 134,000. No more transfusions had been given. There was no renal disease, but liver function was impaired. The BSP (bromsulphalein) was 35% and the prothrombin time remained elevated 2 to 5 seconds over the control, despite parenteral vitamin K therapy. Other medicaments during the period included procaine penicillin, tetracycline, and propantheline bromide. His blood was essentially normal when he was transferred one month later to a psychiatric institution for custodial care.

Case 4.—A 48-year-old mildly diabetic Negro male was admitted for therapy of aseptic necrosis of the right femoral head resulting from a traumatic posterior dislocation 20 years before. He had cirrhosis of the liver (BSP 33%). Following an arthrodesis, he developed wound abscesses and chronic osteomyelitis. He was treated with procaine penicillin, streptomycin, and novobiocin with only temporary benefit. Chloramphenicol was given, 2 gm. (29mg/kg.) daily in 3 courses for 36, 69 and 7 days. Ten days later he was placed on 3 gm. (44 mg/kg.) daily for a total of 76 more days. At the end of this last period he complained of blurred vision, and the hematocrit reading was found to be 16.5 vol.%. No reticulocytes were found in the peripheral blood. White blood cell count was 7,800 and platelets 192,000. The bone marrow was cellular, but there was a decrease in red cell precursors, and the primitive rubriblasts contained vacuoles. The drug therapy was stopped and he was given 300 ml. of packed red cells. The reticulocyte count reached a peak of 8.7% 9 days after the drug was stopped. The hematocrit gradually returned to 40 four weeks later. The patient's visual disturbance disappeared. He had received iproniazid for 6 months prior to the episode of marrow depression but no other drugs for 5 months. Six weeks later he was again given 2 gm. of chloramphenicol daily for 18 days, and his hematocrit reading fell from 42 to 32 vol.%. However, during this period he had further surgery and a depressant effect of this trauma on erythropoiesis must be considered.

Case 5.—A 24-year-old paraplegic Negro male was admitted by transfer from another hospital 2 months after an auto accident in which he had suffered a fracture-dislocation of his neck. During the next 8 months he received 3 courses of chloramphenicol orally for a troublesome bladder infection. Two grams (39/kg.) were given daily for 72 days; 2 gm. daily for 16 days; and 4 gm. (77 mg/kg.) daily for 10 days. He also received sulfasoxazole and tetracycline for the same purpose. Other drugs included meprobamate, zoxazolamine, diphenylhydantoin, phenobarbital, nitrofurantoin, and tripelennamine for varying periods of time. Ten months after admission, 2 gm. of chloramphenicol were administered intramuscularly daily. After 21 days the dose was increased to 4 gm. daily orally and this was continued for an additional 19 days. At the end of this period the hematocrit reading was 21 vol.%, reticulocytes were 0.0% and the platelet count was 18,000. The white blood cells appeared normal on a peripheral smear, although the laboratory reported a count of 4,150. The bone marrow aspirate was cellular, but there were very few red blood cell precursors, and the primitive rubriblasts contained vacuoles. Megakaryocytes appeared adequate despite the thrombopenia. He was given 1,500 ml. of whole blood, and chloramphenicol therapy was stopped. Five days later reticulosytes were 0.1%, but 11 days after administration of the last chloramphenicol they had risen to 0.5%, and to 1.3% after 7 more days. The urinary tract infection was controlled with streptomycin, sulfasoxazole, and later vancomycin and tetracycline. Nitrofurantoin and methenamine mandelate (Mandelamine) were also given. Fourteen months after the acute episode of marrow suppression, chloramphenicol was again administered in several 6–10 day courses of 2 gm. daily. For this period very little laboratory data are available. However, during the last such course, the hematocrit reading fell from 35.5 to 27 vol.%, then spontaneously rose to 41.5 two months after the last dose of the drug. Despite the frequent urinary tract infections, his blood-urea-nitrogen level remained normal. Liver function as measured by the BSP, prothrombin time, and serum albumin and globulin was also normal.

Case 6.—A 38-year-old chronic alcoholic Negro female was admitted because of abdominal pain, nausea, and vomiting. She had tuberculosis, and had had a thoracoplasty in 1950. She had received no chemotherapy for 5 months, and there was no evidence for activity of the tuberculosis at this time. Chloramphenicol was given prophylactically for presumtive pancreatitis, 3 gm. (90 mg/kg.) daily

for 5 days intramuscularly and then 2 gm. (60 mg/kg.) daily for 6 more days. The hematocrit reading had been 36 vol.% shortly after admission but was found to be 14.5 vol.% after the course of chloramphenicol. The platelet count was 22,000. Reticulocytes were not determined then, but 6 days later they were 0.8%. Bone marrow aspiration was cellular, but there was almost complete lack of red blood cell elements. The number of megakaryocytes was reduced. Granulocytes appeared normal in the peripheral blood smear and in the bone marrow. Primitive rubriblasts contained numerous vacuoles. She was given 600 ml. of sedimented red blood cells and 500 ml. of whole blood. Nine days after the chloramphenicol was discontinued, reticulocytes were 4.1%. Three weeks after cessation of therapy, the marrow contained adequate red cell precursors but maturation was atypical. Two weeks later it was frankly megaloblastic. After 6 days of treatment with approximately 1.25 mg. of folic acid daily (¼ of a 5 mg. tablet), the number of reticulocytes had risen from 0.6% to 6.6%. The hematocrit reading rose from 30 to 39 vol.% in 3 weeks. Later, a Schilling test was normal.

Case 7.—A 17-year-old Negro female with presumptive sickle cell anemia (complete genetic data are not available), was treated with chloramphenicol for osteomyelitis of the proximal tibia, receiving 1.5 gm. (29 mg/kg.) daily intramuscularly for one day, 2 gm. (38 mg/kg.) daily orally for one day and 3 gm. (58 mg/kg.) daily orally for 17 days. At the end of this time, the hematocrit reading had dropped from 31 to 16.5 vol.% and reticulocytes from 3.8% to 0.5%. The bone marrow aspirate contained decreased numbers of erythroid cells and a few of the primitive rubriblasts contained vacuoles (Fig. 1*b*). Recovery from the aplastic crisis was prompt after cessation of chloramphenicol therapy. Whereas aplastic crises unrelated to this drug are seen in patients with sickle cell anemia, both the time relationship and the presence of abnormal primitive red blood cells strongly suggest that the drug was responsible.

Case 8.—A 3-year-old, 42 lb. (19.1 kg.) Negro female was admitted because of a fever of unknown origin. Eight days later she was given chloramphenicol, 0.8 gm. (42 mg/kg.) daily for 2 days, followed by 2 gm. (105 mg/kg.) daily for 13 days because of an initial but later untenable diagnosis of typhoid fever. The hematocrit reading fell from 32 to 25 vol.%. Five days after the drug was stopped, the reticulocytes were 0.0%. On the next day, the marrow contained increased erythroid activity and there were no vacuoles in the rubriblasts. Nineteen days after therapy was stopped, the hematocrit value had spontaneously risen to 36 vol.% and reticulocytes were 2.2%. Other than a few days of tetracycline soon after admission, she received no other drugs.

Case 9.—A 50-year-old Negro female was found to have apathetic thyrotoxicosis and was treated with methimazole. She also received 2 gm. (43 mg/kg.) daily of chloramphenicol for 11 days. The hematocrit reading fell from 34 to 27 vol.% during this therapy and the reticulocyte count from 4.8% to 1.0%. White cells and platelets were normal. The marrow aspirate contained some reduction in red cell precursors and the rubriblasts were vacuolated (Fig. 1*c*). Methimazole therapy was not discontinued. Four days after the last chloramphenicol, the marrow was slightly more cellular and there were more erythroid elements. No vacuoles were seen. The reticulocyte count had risen to 3.2%. Seven days later the hematocrit value had returned to the prechloramphenicol level of 34 vol.%.

Case 10.—A 25-year-old Negro male was admitted following a 2-week debilitating illness due to typhoid fever. The bone marrow was cellular; granulocytes were increased but red cell precursors were normal. The patient was treated with 3 gm. (44 mg/kg.) of chloramphenicol daily for 3 days followed by 4 gm. (60 mg/kg.) daily for 10 days, and then 2 gm. (29 mg/kg.) daily for two days. On the day following reduction in dosage from 4 to 2 gm. daily, the reticulocytes were 0.1% and the bone marrow contained reduced numbers of erythroid cells. The rubriblasts contained vacuoles. Three days after cessation of therapy, the reticulocytes were 0.2%. The next day they were 1.0%, and 6 days after administration of chloramphenicol was stopped they were 5.2%. The hematocrit

reading, low on admission, rose to 32 vol.%, first with transfusion and then as the patient's typhoid improved. It fell again to 27 vol.% as marrow suppression intervened. Twenty-three days after chloramphenicol therapy was stopped, it had spontaneously climbed to 41 vol.%. He received no other drugs. There was no evidence for functional impairment of kidneys but his BSP was 14%.

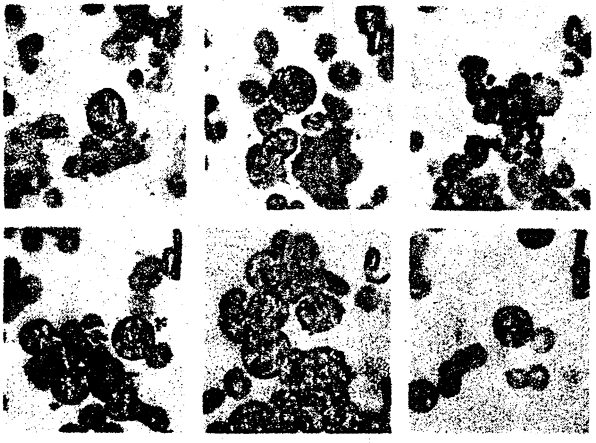

Fig. 2.—Serial marrow studies in chloramphenicol toxicity —*Case 11* severe liver cirrhosis: *a*, prior to therapy; *b*, day after cessation of therapy; *c*, 6 days after last dose of drug. *Case 12* severe liver cirrhosis: *d*, before chloramphenicol; *e*, after 9 days of therapy; *f*, 4 days after last administration of chloramphenicol.

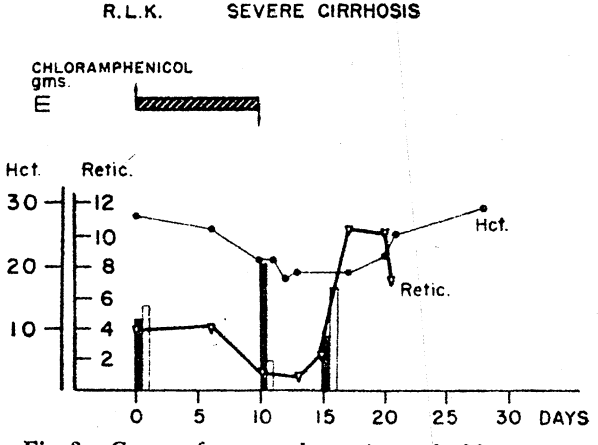

Fig. 3.—Course of marrow depression with chloramphenicol and recovery in 35-year-old Negress with severe alcoholic cirrhosis (Case 11).

Case 11.—A 35-year-old chronic alcoholic Negro female (R.L.K.) was admitted with severe decompensated cirrhosis. She had ascites and a mental picture resembling "pre-coma." Five days after admission she was given chloramphenicol 2 gm. (44 mg/kg.) daily by mouth. Photomicrographs of the serial bone marrow aspirates are shown in figures 2*a-c*. She received no other medicaments during this period. Her course is depicted in Figure 3. There was no evidence for depression of white blood cells or platelets. When her previous record was reviewed, it was found that 3 years previously she had received 1.5 gm. (33 mg/kg.) of chloramphenicol daily for 6 days and the hematocrit reading had dropped from 38 to 30 vol.%. Again, 2 years later, she was admitted with severe cirrhosis and was given 2 gm. chloramphenicol daily for 17 days. The number of reticulocytes dropped from 3.4 to 0.1% three days prior to the cessation of therapy because of diarrhea. They were 5.2% 18 days after the last dose of the drug. The fall in hematocrit value from 33 to 25 vol.% with a need for blood transfusion was unmistakably associated with chloramphenicol, although it was not so recognized at the time. No change in white blood cell count was noted. Platelet counts and bone marrow studies were not done.

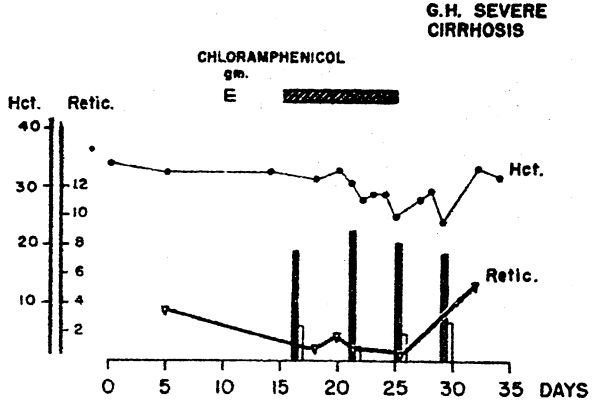

Fig. 4.—Course of marrow depression with chloramphenicol and recovery in 38-year-old Negro male with severe alcoholic cirrhosis (Case 12).

Case 12.—A 38-year-old Negro male was admitted with decompensated cirrhosis, ascites, and "pre-coma." He was given chloramphenicol succinate intramuscularly, 2 gm. (34 mg/kg.) daily for 10 days. His course is shown in Figure 4, and serial bone marrow aspirates are illustrated in figures 2*d-f*. He also received menadione, tetracycline, and methenamine mandelate during the period of study.

Case 13.—A 60-year-old Negro male was admitted because of generalized arteriosclerosis. He had moderate liver disease, with a BSP of 16%. He was given 2 gm. (34 mg/kg.) of chloramphenicol daily for 10 days. After 4 days, a tracer dose of Fe^{59} was given intravenously and 14 days later, only 54% had appeared in the red blood cells. Serial bone marrow aspirations were performed and at the end of chloramphenicol therapy, there was a reduction in red cell prescursors and the primitive rubriblasts contained vacuoles (Fig. 1*d*). Four days after therapy was stopped, there was slight erythroid hyperplasia and marrow morphology was normal. During therapy the hematocrit reading fell only 2 points but reticulocytes were 0.1% on the day chloramphenicol was stopped and rose to 2.4% five days later.

Case 14.—A 54-year-old Negro female was hospitalized for anemia and uremia due to chronic glomerulonephritis. She was given chloramphenicol 3 gm. (48 mg/kg.) daily for 28 days. Prior to therapy, the reticulocyte count was 3.6% and after 11 days of therapy it was 0.3%. There was no leukocyte depression and no clinical evidence of thrombocytopenia. Bone marrow aspirates prior to therapy showed moderate erythroid hyperplasia. None was obtained later. One day after chloramphenicol therapy was stopped, she died. No postmortem marrow specimens are available.

Case 15.—A 45-year-old Negro female was admitted with pulmonary tuberculosis. During her first 3 weeks in the hospital, she was treated with isoniazid, para-aminosalicylic acid, and prednisolone. The findings in a bone marrow aspirate were consistent with an acute and chronic infectious process. The hematocrit value remained at 25 vol.%. At the end of this period she was given a 2-week course of chloramphenicol 2 gm. (44 mg/kg.) daily because of a superimposed pneumonia. The hematocrit reading rose to 30, then fell to 28 vol.%. The day after this drug was discontinued reticulocytes, which had been about 1.0% on several occasions, dropped to 0.0%. Four days later they were but 0.1%. Six days after the last chloramphenicol administration they had risen to 1.2% and the bone marrow showed moderate erythropoietic activity. The next day reticulocytes were 4.0%. The hematocrit value had returned to pre-treatment levels by the 16th day. Isoniazid was not discontinued. No other drugs but procaine penicillin were given during the period of chloramphenicol therapy.

RESULTS

The clinical features of these patients are summarized in the table. There were 8 females and 7 males, ranging in age from 3 to 68 years. All were Negro, reflecting the preponderant patient population of the hospital. Results of hemoglobin electrophoresis were available in 13. Of these, 10 had normal hemoglobin; one had sickle cell trait; one had hemoglobin C trait; and one had sickle cell anemia.

CLINICAL AND LABORATORY FEATURES OF 15 PATIENTS WITH CHLORAMPHENICOL BONE MARROW TOXICITY

	Age, years	Sex	Prev. chloro.	Dose			Days, duration	Depression of				Marrow vac.	Liver disease	Renal disease	Other drugs
				Gm./D.	Route	Mg./kg./D.		RBC	Reticulocyte percent	WBC.	Pits.				
Case No.:															
1	64	M	0	2	P.O.	28	24	+	0.4	0	+	+	+	±	None within 2 weeks of marrow disorder.
2	50	F	—	2	P.O.	42	27	+	0	0	0	+	0	0	None.
3	55	M	0	2	P.O.	37	22	+	0	+	—	+	+	0	Penicillin, tetracycline, propantheline bromide.
4	48	M	+	3	P.O.	44	71	+	0	0	0	+	+	0	Iproniazid.
5	24	M	+	4	P.O.	77	40	+	0	0	+	+	0	+	Diphenyihydantoin, meprobamate, zoxazolamine, nitrofurantoin, tripelennamine.
6	38	F	0	3	I.M.	90	5	+	—	0	+	+	+	0	None.
				2	P.O.	60	6 (11)								
7	17	F	0	3	P.O.	58	19	+	0.5	0	0	+	0	0	None.
8	3	F	0	2	P.O.	105	15	+	0	0	0	0	0	0	None.
9	50	F	0	2	P.O.	43	11	+	1.0	0	0	+	+	0	Methimazole—not discontinued.
10	25	M	0	3	P.O.	44	3	+	.1	0	0	+	+	0	None.
				4	P.O.	60	10 (15)								
				2	P.O.	29	2								
11	35	F	+	2	P.O.	44	10	+	.8	0	0	+	+	0	None.
12	38	M	0	2	P.O.	34	10	+	.3	0	0	+	+	0	Menadione, tetracycline, methenamine mandelate.
13	68	M	0	2	P.O.	34	10	+	.1	0	0	+	+	0	None.
14	43	F	0	3	I.M.	48	28	+	.3	—	—	—	0	+	None.
15	45	F	0	2	P.O.	44	14	+	0	0	0	—	+	±	Isoniazid—not discontinued, para-aminosalicylic acid prednisolone.

+=present, P.O.=per os. 0=absent. I.M.=intramuscular. —=not observed.

All patients had evidence for depression of erythropoiesis coincident with chloramphenicol therapy, in which depression was not judged to be the result of their underlying disease. In one patient (Case 6) a rapidly developing anemia (hematocrit reading 14.5 vol. %) heralded marrow depression. In all patients the reticulocyte counts during toxicity were low, usually below 0.5%. In all 12 available bone marrow aspirations obtained within 48 hours of the last dose of chloramphenicol, there was striking vacuolization of primitive rubriblasts (Fig. 1). Marrows obtained 4 days or longer after cessation of drug therapy did not show these changes. In one instance, vacuolization was observed as early as 6 days after the institution of chloramphenicol therapy. Four days later, another bone marrow smear from this patient showed progression of these changes. No similar abnormalities were observed in control studies of the marrow done after three or more weeks of chloramphenicol therapy in 2 patients who did not develop anemia. Serial marrow observations that were made in 2 patients are illustrated in Figure 2. The course of the erythropoietic depression in these 2 individuals is shown in Figures 3 and 4.

Thrombocytopenia was seen in 4 and leukopenia in one of the patients of this series. Reversal of marrow hypoplasia followed withdrawal of chloramphenicol in the 14 patients who survived more than a few days after the drug was stopped. The rapid marrow recovery which followed cessation of chloramphenicol treatment was usually accompanied by evidence for marrow hyperplasia, such as reticulocytosis and sometimes thrombocytosis and leukocytosis. One patient (Case 1) died of other causes before recovery was complete and another (Case 14) died of unrelated medical causes the day after chloramphenicol was discontinued.

Ten of the patients had mild to severe preexisting liver disease. Three of the four patients selected for serial marrow aspiration had severe alcoholic cirrhosis with hepatomegaly. Although it is known that chloramphenicol is detoxified by conjugation with glucuronic acid in the liver,[5] and that patients with seriously damaged livers may achieve quite high serum levels of free chloramphenicol when treated with 2 gm. a day,[6] we could come to no conclusions regarding the role of these factors in this group of patients.

Four patients in this group had received previous chloramphenicol therapy. Ten received the drug for longer than 2 weeks. In one patient, marrow depression became evident after 71 days of treatment and in another after 40 days. In 8 the drug was given for 2 to 4 weeks. In 5 patients chloramphenicol was administered for less than 2 weeks. Two adult patients received 4 gm. daily (60–77 mg/kg. per day) and four more were given 3 gm. daily (44–90 mg/kg. per day) for a part of the course of therapy which preceded the development of toxicity. The one child in this series received a rather high dose of 2 gm. daily (105 mg/kg. per day). Although 8 patients received no more than 2 gm. daily, every patient in this entire series either received more than 40 mg/kg. per day, or had liver disease.

COMMENT

From the above data, it appears that suppression of erythropoiesis is the most frequent toxic effect of chloramphenicol on the bone marrow. In this series measurable depression of thrombopoiesis and leukopoiesis coincident with treatment with this antibiotic was less common. The frequency with which depression of red cell production by chloramphenicol has been found when sought [2, 3, 3a] strongly suggests that some degree of marrow depression is a common consequence of treatment with this drug. Since the red cell life span is 120 days and the average course of chloramphenicol therapy is 5 to 10 days, brief mild erythropoietic depression easily may be overlooked. In this study the reticulocyte count was found to be the most readily available tool for measuring the effect of chloramphenicol on erythropoiesis. In 12 of the 15 patients that form the substance of this report, the reticulocyte count during drug toxicity was 0.5% or lower. In 2 others, the values represented a significant fall from previous levels. In the remaining case, reticulocyte counts were not done at the height of toxicity.

The bone marrow morphologic changes of chloramphenicol toxicity including reduction in red cell precursors with vacuolization of primitive rubriblasts have been reported by others.[3, 3a, 7] It is likely that vacuolization is a nonspecific change which may result from other causes as well. When these changes are found in a patient who is taking chloramphenicol, until proved otherwise they are indicative of marrow depression by this drug.

The present studies suggest the following modus operandi for chloramphenicol therapy: (1) for trivial infections avoid the use of the drug altogether; the risk of chloramphenicol treatment may be greater than that of the disease itself; (2) obtain serial reticulocyte counts on all patients receiving chloramphenicol; and (3) if the reticulocyte counte drops abruptly or falls below 0.5%, obtain a bone marrow aspirate for study. Stop therapy with the drug if vacuoles are seen in the primitive rubriblasts or if there is a marked reduction in the erythropoietic activity of the marrow. Although in this series leukopenia and thrombopenia were always accompanied by erythropoietic abnormalities, the possibility of selective depression of these elements can not yet be completely discarded.

At the present time lack of knowledge regarding the mechanism of toxicity makes it difficult to predict which patients will develop irreversible marrow depression as a result of chloramphenicol treatment. On the one hand, the morphologic changes in the marrow and their frequency along with evidence of dose-dependency in some patients suggests a direct chemical effect.[1, 3a] On the other hand reports of bone marrow hypoplasia after token doses of chloramphenicol are compatible with a hypersensitivity phenomenon.[8] Both direct toxic poisons and hypersensitivity reactions[9] may cause vacuolization of cells. The fact that in vitro studies done outside the humoral environment within the host have failed to demonstrate metabolic abnormalities induced by therapeutic levels of the drug[10, 11] is consistent with but does not prove a hypersensitivity mechanism for toxicity. The sensitivity of erythropoiesis to chloramphenicol noted in this study may be a result of the more ready diffusion of free chloramphenicol into red cell precursors than into the other cells of the marrow.[12] Despite common belief, the toxicity is probably not related to the nitrobenzene ring of chloramphenicol, since an analogue without this structure proved to be considerably more toxic.[13]

This and other studies indicate that most patients developing chloramphenicol toxicity seem to pass through 2 phases of marrow depression, an initial reversible period of variable duration followed by an often serious period of damage which does not remit until the drug is stopped and may not remit, no matter what is done. Early in the reversible stage rapid recovery follows cessation of treatment. Later in the reversible stage, cessation of therapy is followed by a slower return of the marrow to normal. These same principles which apply to the erythropoietic system also apply to depession of thrombopoiesis and leukopoiesis by chloramphenicol. In a few patients, the reversible stage may be quite short. This may be because of prior therapy, high doses, or of hypersensitivity. One or all of these factors may be enhanced by high drug levels caused by high doses or abnormalities in drug metabolism as in liver disease. Our present state of knowledge does not permit more than a speculative explanation for the underlying mechanism for the toxic effects of chloramphenicol reported in this study.

SUMMARY AND CONCLUSIONS

Fifteen patients with bone marrow depression associated with chloramphenicol treatment are presented. Erythropoiesis was most often affected, followed in order by suppression of thrombopoiesis and leukopoiesis. Monitoring erythropoiesis by serial reticulocyte counts during chloramphenicol therapy has been found to be of value in detecting early evidence of drug toxicity.

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[From the Journal of the American Medical Association, Dec. 3, 1960, pp. 1853–1854]

CHLORAMPHENICOL—A NEW WARNING

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

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

It is becoming increasingly clear that chloramphenicol, an excellent broad-spectrum antibiotic, has antimetabolic effects as well—that is, it may injure the intrinsic "machinery" of certain rapidly proliferating cells, notably of the bone marrow. Thus, Rubin and associates, using radioactive techniques, demonstrated a depressant effect of chloramphenicol on erythropoiesis; this occurred in 5 of 15 subjects receiving ordinary doses and in all of 4 cases with cancer who were given unusually large doses of the drug.[1] In another study by Saidi and Wallerstein [2] 10 of 22 cases treated with chloramphenicol for various infections developed striking vacuolization of nucleated red cells in the bone marrow, associated with a maturation arrest phenomenon and marked reduction in blood reticulocytes. The possibility is present that these temporary changes could go on to complete or partially complete destruction of the bone marrow providing (a) that sufficient drug was used or (b) the patient became sensitized in some manner and was given a second course of drug therapy at another time. It is thus conceivable that both an immediate or direct effect as well as an indirect or hypersensitivity mechanism may be responsible for the marrow reactions seen.

Following the introduction of chloramphenicol in 1948 and the reports of the first cases of aplastic anemia between 1950 and 1952, many editorials and reports of special *ad hoc* meetings appeared. Evidently the medical profession was profoundly influenced; in any event, the sales of chloromycetin declined sharply, reaching their lowest level in 1954. This lull was short-lived. By 1958,

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[2] Saidi, P., and Wallerstein, R. O.: Effect of Chloramphenicol on Erythropoiesis. To Be Published.

there was a five-fold increase in the sales of the drug and by 1960, enough chloramphenicol was being distributed, and presumably used, in the United States to supply 3,732,416 persons with 10 Gm. courses of the drug! (These data were supplied through the kind cooperation of Dr. Harry Carnes, Parke Davis & Co., Detroit, Mich.)

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

Is it the physician, then, who is largely responsible? In a way he is, for without his prescription, the drug would not be administered. Certainly, if he regards chloramphenicol lightly, to be dispensed like aspirin, for every minor cold and respiratory infection, he is not without blame. But are there certain mitigating factors? Some say that a person ill is a person to be treated! The urge to make a person comfortable and to cure his illness as quickly as possible is an urge each of us has. It follows then that a good antibiotic of the broad spectrum variety and which can be readily administered is something to be used at every opportunity. This is part of the mores in this affluent society of ours. We have potent medicines; the patient is ill; we must treat! The days of simple herb medicines and of simple galenicals have long since passed. More often than not, the newer synthetics, most of them composed of molecules with benzene rings and nitrogen, NH, NH_2, or NO_2 groupings—are used, and all of them, it should be said, are potentially harmful.

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

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

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

WILLIAM DAMESHEK, M.D., *Boston, Mass.*

[From the Journal of the American Medical Association, June 28, 1952, p. 840]

BLOOD DYSCRASIA FOLLOWING THE USE OF CHLORAMPHENICOL

Chloramphenicol (chloromycetin®) has been accepted by the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies. Its antibiotic properties are well known, and when the council accepted this product there was much evidence to demonstrate its therapeutic value. At the same time there then was little reason to believe that serious or fatal side-reactions would be demonstrated. Nevertheless, following a study of the chemical structure of the drug, the Council issued a warning at the time of acceptance even though there was meager evidence to prove that such a warning was necessary. Thus, on page 116 of New and Nonofficial Remedies, 1951, there appears the following statement:

"Changes in the peripheral blood or the blood-forming organs have been reported only during the use of chloramphenicol. Mild hemolytic anemias, granulocytopenia (no cases of agranulocytosis so far) and an arrest the maturation of the formed elements in the marrow have been described."

Recently there have been additional reports of the effects of chloramphenicol on the blood and bone marrow. At least two types of reaction have been encountered. In one there is a transient depression of the formed elements of the blood, involving red cells, white cells, and platelets during therapy with the drug. This type of reaction has been very uncommon, and in the experience of one group well versed in the field of antibiotic therapy it has seemed to occur in patients who were receiving very large doses of the drug or in patients who had renal insufficiency. The blood of these patients returned to normal, or at least showed pretreatment values, as soon as therapy with the drug was stopped, and no permanent deleterious effect was observed.

A second and more serious type of reaction that has been encountered is production of a true aplastic anemia. In the experience of one group, this anemia has occured in patients who have previously received one or more courses of chloramphenicol without untoward effect. When the drug was subsequently administered, even in small doses, a severe blood abnormality has appeared. Even deaths have been reported. Whether chloramphenicol continues to remain as one of the more useful antibiotics or whether it will be relegated to a place where its use will be confined to the treatment of patients with typhoid or serious infections for which no other therapy is available, remains to be seen. Further observations are in order. In the meantime, physicians should be on the alert for reactions following therapy with this and any other antibiotic, or in fact any of the newer drugs.

New therapeutic agents, which are being introduced with ever increasing rapidity, are characterized not infrequently by their beneficial or life-saving qualities but also by their ability to cause injury or serious side-effects. A calculated risk is involved whenever one prescribes any medication. The physician is confronted constantly with the difficult task of determining whether the use of a given drug is likely to do more good for a particular patient than any possible harm. In spite of the bast amount of laboratory and clinical study that a new drug usually undergoes before it is placed on the market, subtle or insidious toxic effects. often of a serious nature, frequently are not recognized and brought to the attention of the medical profession in general until after the drug has been on the market for some time and has enjoyed widespread clinical use. A propensity to cause injury to the hematopoietic system is particularly likely not to be generally appreciated until a new drug has undergone extensive use for a considerable period of time. Physicians who observe hitherto unreported toxic effects or injuries attributable to a recently introduced therapeutic agent have the obligation or duty of bringing this information to the attention of the entire profession. If a physician does not have the time or inclination to prepare case reports of drug injuries for publication in a medical journal, he can perform a useful service by advising the office of the Council on Pharmacy and Chemistry of the pertinent facts in such instances. By this means the Council will be provided with necessary information that may serve as the basis for an early authoritative report or warning statement.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

May 7, 1968

Dear Doctor:

Serious and often fatal blood dyscrasias are known to occur following the administration of chloramphenicol. Prominent warning to this effect has been part of the approved labeling for this drug since 1952, and this information has been disseminated in the medical and lay press, including editorials in the Journal of the American Medical Association.

Because the amount of chloramphenicol distributed exceeds that to be expected if the drug were prescribed only for its valid indications, the Food and Drug Administration believes that chloramphenicol is often prescribed for conditions for which it is not indicated, including trivial conditions such as acne, the common cold, and simple infections. Fatal reactions have been associated with use in these conditions.

To enlist your aid in ending the over-prescribing of this drug, the Food and Drug Administration asks that you carefully study the following "box warning" the substance of which has been and will continue to be part of the recently revised labeling of this drug:

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

***Precautions:* It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.**

To clarify further the status of this drug in the therapy of infectious disease, the indications for use have been stated in the recently revised labeling as follows:

INDICATIONS: IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. ACUTE INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF *SALMONELLA TYPHI*

   Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".

2. SERIOUS INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS IN ACCORDANCE WITH THE CONCEPTS EXPRESSED ABOVE:
   a. *Salmonella* species
   b. *H. influenzae*, specifically meningeal infections
   c. Rickettsia
   d. Lymphogranuloma-psittacosis group
   e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections
   f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. CYSTIC FIBROSIS REGIMENS

* In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

The revised labeling suggests that patients being treated with chloramphenicol be hospitalized where indicated to facilitate observation during therapy. It also includes cautionary information regarding use in pregnancy and lactation, and the listing of leukemia as an additional adverse reaction. An estimate of the incidence of fatal aplastic anemia is included based on a report to the California State Assembly and Senate by the California Medical Association and State Department of Public Health, January 1, 1967.

The revision of the labeling of chloramphenicol was approved by a special committee of experts in hematology, infectious diseases and other medical fields convened by the Food and Drug Administration on February 26, 1968. A copy of the revised labeling is enclosed for your attention.

To assist us in further evaluation of this problem, the Food and Drug Administration requests that you report to us any adverse reactions associated with the use of chloramphenicol. A facsimile of our Drug Experience Report (FD 1639) is reproduced on the reverse side for your information. If you wish a supply, please write to the Food and Drug Administration, Bureau of Medicine, Washington, D.C. 20204.

Sincerely yours,

James L. Goddard, M.D.
Commissioner of Food and Drugs

Enclosure:
Revised Labeling

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

BUDGET BUREAU NO. 57-R0004
Approval Expires December 31, 1970

DATE SENT TO FDA (Mo, day, yr)

1 ☐ INITIAL REPORT ☐ FOLLOW UP REPORT

2 PATIENT INITIALS AND IDENTIFICATION NUMBER

3 ACCESSION NO. (For FDA use only)

SECTION I. BASIC REACTION DATA

4. SEX ☐ M ☐ F

5. HEIGHT (ins.) WEIGHT (lbs.)

6. DATE OF BIRTH (mo / day / yr)

7. ORIGIN ☐ CAUC ☐ NEGRO ☐ ORIENTAL ☐ AMERICAN INDIAN ☐ OTHER

8. DATE OF REACTION ONSET (mo / day / yr)

9. SOURCE OF REPORT (Mfg. Hospital, etc)(Name of reporting Physician is optional.)

10. ADDRESS OF SOURCE (Give Street, City, State, and Zip Code.)

11. DESCRIBE SUSPECTED ADVERSE REACTION(S) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(S) INVOLVED

12. OUTCOME OF REACTION TO DATE
- ☐ ALIVE WITH SEQUELAE
- ☐ RECOVERED
- ☐ STILL UNDER TREATMENT
- ☐ DIED (Give date and cause)

13. LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer; List NDA or IND No.)

NAME OF DRUGS TRADE (Generic)	MANUFACTURERS CONTROL NO.	DOSAGE FORM (tab, cap, etc.)	TOTAL DAILY DOSE	ROUTE (po, im, iv, etc.)	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG

SECTION II. IMPORTANT MODIFYING DATA

15. SUBSTANTIATING LABORATORY STUDIES (Clinical Laboratory, Autopsy, X-Ray, etc.)
CLINICAL LAB: ☐ DONE ☐ ATTACHED ☐ NOT DONE
BIOPSY/AUTOPSY: ☐ DONE ☐ ATTACHED ☐ NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS (Include household products, industrial and agricultural chemicals)

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY

PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND ☐ YES ☐ NO

18. (a) IF FEMALE GRAVIDITY ☐☐ PARITY ☐☐ (b) IF PREGNANT WEEKS OF GESTATION ☐☐

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ YES ☐ NO

FOR FDA USE ONLY

FOR MFG USE ONLY

22. REACTION FACTORS (Check all applicable boxes)
☐ DECOMPOSITION OF DRUG ☐ INTERACTION OF TWO OR MORE DRUGS ☐ DRUG NOT USED ACCORDING TO LABELING ☐ DRUG OUTDATED
☐ DRUG MISUSED BY PATIENT ☐ OVERDOSAGE ☐ DRUG MISLABELED ☐ CONTAMINATION OF DRUG ☐ OTHER DRUG MISUSE (Specify)

FORM FD-1639 (Rev 8/67)

Use additional sheet if necessary.

PACKAGE INSERT FOR CHLORAMPHENICOL

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

***Precautions:* It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.**

DESCRIPTION: Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see "Indications" section).

ACTIONS AND PHARMACOLOGY: In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae.* It is particularly active against Salmonella typhi and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8-14 mcg./ml. over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68 percent to a high of 99 percent over a three-day period. From 8 to 12 percent of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS: IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. ACUTE INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF *SALMONELLA TYPHI*

   Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".

   * In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

2. SERIOUS INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS IN ACCORDANCE WITH THE CONCEPTS EXPRESSED ABOVE:
   a. *Salmonella* species
   b. *H. influenzae,* specifically meningeal infections
   c. Rickettsia
   d. Lymphogranuloma-psittacosis group
   e. Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. CYSTIC FIBROSIS REGIMENS

CONTRAINDICATIONS: Chloramphenicol is contraindicated in individuals with a history or previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

PRECAUTIONS:

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS:

1. **Blood Dyscrasias**
The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol.
An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.
A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.
An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.
In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.
There are reports of aplastic anemia terminating in leukemia attributed to chloramphenicol.
Paroxysmal nocturnal hemoglobinuria has also been reported.

2. **Gastrointestinal Reactions**
Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. **Neurotoxic Reactions**
Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. **Hypersensitivity Reactions**
Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. **"Gray Syndrome"**
Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
(a) abdominal distension with or without emesis;
(b) progressive pallid cyanosis;
(c) vasomotor collapse, frequently accompanied by irregular respiration;
(d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS

The majority of micro-organisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over most of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will usually achieve and sustain levels of this magnitude.
Except in certain circumstances (e.g., premature and newborn infants and individuals with impairment of hepatic or renal function) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Close observation of the patient should be maintained and in the event of any adverse reactions, dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

Adults—Adults should receive 50 mg./kg./day (approximately one 250 mg. capsule per each 10 lbs. body weight) in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under "Newborn Infants.") Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children—Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants—(See section titled "Gray Syndrome" under "Adverse Reactions.") A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.
When these functions are immature, (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes—In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

○