liver, then the normal turnover of plasma phospholipid phosphorus would have been increased by an additional $\frac{400}{520} \times 31$ or 24 mg per hour.‡ The results obtained here clearly demonstrate that such an increase in the turnover of plasma phospholipid P did not occur. Hence, it would appear that plasma phospholipids do not participate in the disturbance in fatty acid metabolism encountered in the diabetic state.

The view that phospholipids are concerned with fatty acid transport is widely held today. Such a function for phospholipid, however, has received no support from several types of studies carried out recently in this laboratory:

In the diabetic dog there is reason to believe that considerable amounts of fat migrate from depot to liver. Yet, as noted above, the rate of turnover of plasma phospholipid in this condition was no greater than normal.

In dogs in which the liver is excised the concentration of plasma phospholipids remains constant, and their turnover practically stops.[8] This finding and other evidence show not only that plasma phospholipids are synthesized in the liver, but that this organ is the only one concerned with their utilization. These studies thus fail to support the concept that fatty acids are transported between liver and other organs via phospholipids.

Recent unpublished observations dealing with the mechanism of action of choline[9] are also pertinent here. It was shown that choline does not affect the turnover rate of plasma phospholipids, but that it does stimulate the turnover of lecithin within the liver itself. This seems to indicate that phospholipids, while mediating the lipotropic action of choline, do not bring this about by increasing the transport of fatty acids.

Finally, mention should be made of the studies on the turnover rate of the small intestine's phospholipids in the fasted and fat-fed dog and rat.[10] Here again it appeared that phospholipids are not instrumental in the transport of fatty acids across the intestinal wall.

Summary. The rate of turnover of plasma phospholipids is not increased above normal in the diabetic state. This and other evidence reviewed here fails to support the concept that phospholipids are agents for the transport of fatty acids.

‡ In the phospholipid molecule 520 mg of fatty acids are associated with 31 mg of phosphorus.

8 Entenman, C., Chaikoff, I. L., and Zilversmit, D. B., *J. Biol. Chem.*, 1946, **166**, 15.

9 Zilversmit, D. B., Entenman, C., and Chaikoff, I. L., in press.

10 Zilversmit, D. B., Chaikoff, I. L., and Entenman, C., *J. Biol. Chem.*, 1948, **172**, 637.

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Administration of Chloromycetin to Normal Human Subjects.

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The need for information on the results of administration of Chloromycetin to normal human beings became evident shortly after the chemotherapeutic properties of this antibiotic were first noted;[1,2] this became imperative recently when an opportunity presented itself for a field trial of the drug in the treatment of patients with typhus fever.[3]

1 Smadel, J. E., and Jackson, E. B., *Science*, 1947, **106**, 418.

2 Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R., *Science*, 1947, **106**, 417.

3 Smadel, J. E., León, A. P., Ley, H. L., Jr., and Varela, G., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 12.

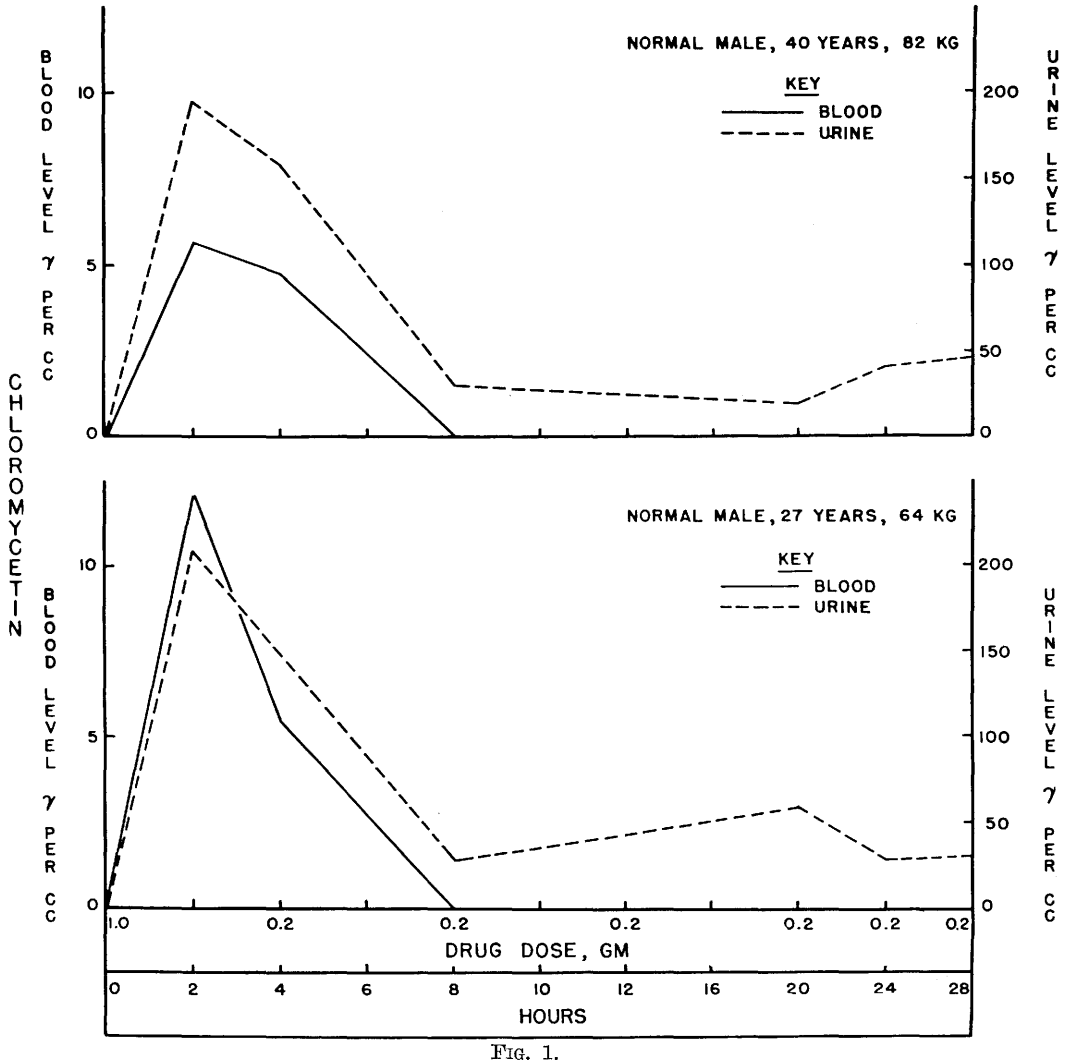

FIG. 1.

The present report summarizes the observations on three volunteers who were treated with Chloromycetin.

Materials and Methods. The oral route was selected for administration of Chloromycetin to volunteers not only because of its great convenience but also because of experimental evidence which indicated that the drug was effective by this route in treating infected mice.[1] Tablets containing 0.1 g amounts of crystalline Chloromycetin were supplied for the trial by the Research Laboratories of Parke, Davis and Company.

Levels of Chloromycetin in blood and urine were determined in samples collected at intervals throughout the study.* A modification of the method of Joslyn and Galbraith[4] which employs inhibition of growth of *Shigella paradysenteriae* (*Sonne*) was used for these microbiological assays. Blood and urine specimens taken for such assays were obtained in the following sequence: the patient voided, was bled, and then the urine sample for assay was collected within a few minutes. In addi-

* The authors wish to thank Miss A. B. Cruise who assisted with the Chloromycetin assays.

[4] Joslyn, D. A., and Galbraith, M., personal communication, 24 October, 1947.

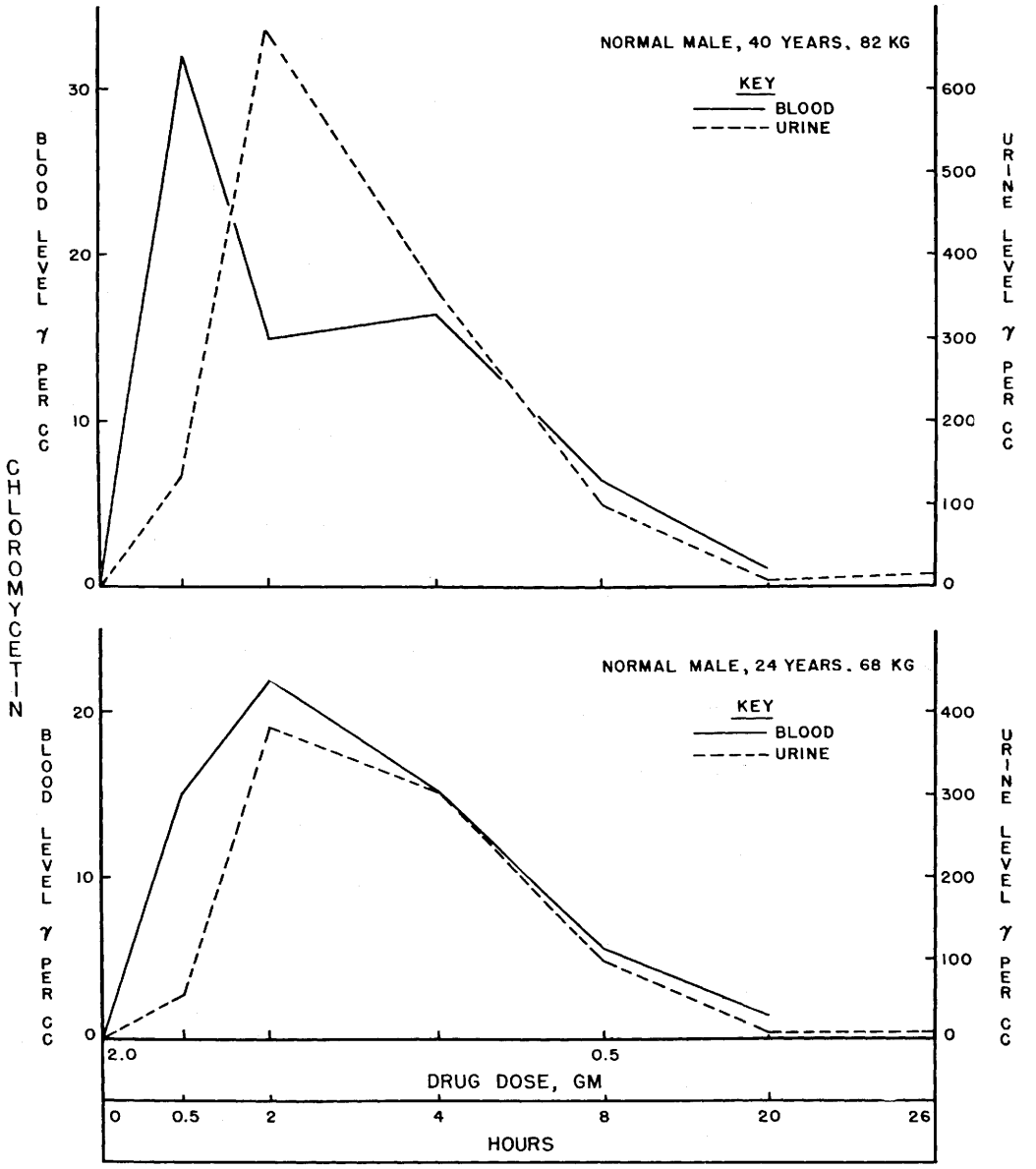

FIG. 2.

tion, urine was collected for 24-hour periods in order to permit estimation of the total daily urinary excretion of Chloromycetin. The hemoglobin levels, red and white blood cell counts, and differential leukocyte counts were obtained by the usual clinical laboratory methods.

Results. In the first test 2 normal male subjects received a prolonged course of Chloromycetin beginning with a single dose of 1.0 g which was followed by 1.0 g daily for 10 days; the latter was given in divided doses of 0.2 g every 4 hours except at 4:00 a. m. In a second test one of the volunteers from the first experiment and another subject received an initial dose of 2.0 g followed in 8 hours by a single 0.5 g dose.

Values for the levels of Chloromycetin in the blood and urine of the volunteers in the first test are given for the early portion of

the course of treatment in Fig. 1. The peak values for both blood and urine were recorded for the first specimen collected after the initial dose, *i.e.*, at 2 hours. Subsequently, the blood levels steadily fell in both subjects and detectable amounts of drug were not demonstrable at 8 hours or thereafter. The urine levels of drug were approximately 200 γ/cc at 2 hours; they fell to approximately 50 γ/cc at 8 hours and remained at about that level for the next 10 days of treatment. During and immediately following the test no significant changes occurred in the blood of either subject as revealed by determination of hemoglobin, erythrocytes and leukocytes and by examination of blood smears. Urinalysis on the third day of therapy showed no abnormalities.

Data on the volunteers who received an initial dose of 2.0 g of Chloromycetin plus 0.5 g 8 hours later are given in Fig. 2. Relatively high levels of drug were found in the blood of both volunteers only 30 minutes after the antibiotic was first given by mouth; furthermore, at this time drug was already present in the urine in appreciable amounts. The blood levels were still well above 10 γ/cc at 2 hours and were above 5 γ/cc at the end of 8 hours. Urine levels were at their maxima at 2 hours reaching values of 670 and 380 γ/cc, respectively, in the subjects. The amounts diminished rapidly in successive samples and dropped to about 10 γ/cc at 8 hours.

Approximately 10% of the total amount of Chloromycetin given daily was recovered in an active form in the urine of both groups of volunteers.

No symptoms or signs of toxic effects attributable to the drug were observed by the 3 volunteer physicians either during the treatment or subsequently.

Conclusion. These limited trials indicate that Chloromycetin can be given orally to normal adult males in single doses of 2.0 g, or in daily doses of 1.0 g for 10 days without untoward reactions. The presence of appreciable amounts of drug in the blood and urine of volunteers 30 minutes after oral administration of Chloromycetin indicates that the antibiotic is absorbed rapidly from the gastrointestinal tract of man. Excretion or inactivation of the drug occurs rather rapidly, hence, in order to maintain appreciable levels of the antibiotic in the blood, frequent administration of the drug is indicated.

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Chloromycetin in the Treatment of Patients with Typhus Fever.

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Recent reports indicate that Chloromycetin is effective in the treatment of experimental infections caused by *R. prowazeki*[1,2] and *R. mooseri* as well as other rickettsial and viral agents.[2] Data reported elsewhere[3] show that Chloromycetin can be given to normal men without untoward effects and that the levels of drug in the blood and urine of treated persons can be followed. This paper summarizes the information gained from the study of a small group of patients with typhus fever who were treated with Chloromycetin.

Materials and Methods. The patients studied in the current investigation were hos-

1 Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R., *Science*, 1947, **106**, 417.

2 Smadel, J. E., and Jackson, E. B., *Science*, 1947, **106**, 418.

3 Ley, H. L., Jr., Smadel, J. E., and Crocker, T. T., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 9.