the iron in intestinal lymph: (a) absorbed iron, (b) iron stores in intestine including lymph nodes and intestinal mucosa, (c) plasma iron. Following the administration of iron orally to dogs, Moore(1) found a greater increase of iron in the blood than in the lymph. Similarly, Endicott(2) recovered negligible amounts of orally administered radioactive iron in the lymph. These studies certainly seem to relegate the lymphatics to a minor role in iron absorption. It is conceivable that the iron stores of the reticuloendothelial system and the intestine(6) are in equilibrium with both the blood and interstitial fluid, in this case, lymph. The relative constancy of iron concentration in the lymph studied in these experiments is compatible with such an equilibrium as is the failure of iron concentration to keep pace with the rise in lymph volume produced by administration of 0.9% saline.

Blood plasma as the third possible source of lymph iron seems the most likely(1). The dialysis experiments point out a striking similarity between the adsorbed iron of lymph and that of plasma. From the work of Barkan(7), Laurell(8), Schade(9) and many others has evolved the concept that iron is present in plasma in combination with a specific globulin fraction, recently isolated and identified by Cohn(10). Because of this combination, serum iron is non-dialyzable at the pH of blood, but becomes dialyzable in more acid solutions(11).

Apparently a similar iron-protein linkage is present in lymph; and the protein resembles that of plasma in the range of pH over which it binds the iron firmly enough to prevent dialysis. Under the conditions of the experiments the protein is only about 60% saturated with iron.

Summary. The iron content of intestinal lymph of rats maintained on a normal diet is relatively constant over periods as long as seven days. At lymph outputs of one ml per hour, there is an hourly output of 0.5 γ of iron. With a 3- to 4-fold increase of lymph volume, iron concentration falls off and total output remains less than 1.0 γ per hour. The iron present in lymph is non-dialyzable at pH 7.0 to 4.7, but is dialyzable at pH 1.5. Added iron, up to concentrations of 48 γ per 100 ml in 2 specimens of pooled lymph, was non-dialyzable at pH 7, but all added iron in excess of this concentration was dialyzable.

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'Benemid' p-(Di-n-Propylsulfamyl)-Benzoic Acid: Lack of Effect of Aureomycin, Chloromycetin, Streptomycin and Terramycin.* (18442)

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Para-(Di-n-propylsulfamyl)-benzoic acid, 'Benemid',† increases by two to four times the penicillemia resulting from the administration of penicillin(1,2) and enhances the

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† Sharp & Dohme's trade-mark for p-(di-n-propylsulfamyl)-benzoic acid. The drug has been tentatively given the generic designation "probenecid".

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plasma concentrations of para-aminosalicylic acid (PAS)(3,4). The rapid elimination of penicillin from the body as contrasted to the much slower excretion of aureomycin, chloromycetin, streptomycin and terramycin indicates that these drugs are probably cleared by the kidneys by a different mechanism.

Because 'Benemid' has such a marked effect upon the plasma concentrations and the renal clearance of penicillin(5) by reason of its ability to suppress the tubular component of penicillin excretion, it was of interest to determine what effect, if any, the drug might have upon the plasma concentrations of aureomycin, chloromycetin, streptomycin and terramycin. Any effect on streptomycin would be of particular interest for streptomycin is administered in combination with PAS and 'Benemid' enhances the plasma concentrations of PAS. Since streptomycin has toxic properties, the incidence of toxic manifestations might be markedly increased if 'Benemid' interfered with the renal clearance of streptomycin. Should these circumstances obtain, it would be hazardous to employ 'Benemid' for its enhancement effect upon PAS when combined streptomycin and PAS therapy was being given. The following study was undertaken to clarify these points.

Subjects studied. Thirty-one individuals were studied; 6 individuals who received terramycin were healthy, adult male volunteers, the remaining 21 individuals were convalescent patients. None of the subjects of this investigation were suffering from apparent disorders of the liver, heart or kidneys.

Methods. Aureomycin and terramycin were assayed by the method described by Herrell and Heilman(6), which in this laboratory has checked well with that originally described by Dornbush(7) for aureomycin. Chloromycetin was assayed by the method of Smith and his associates(8). Penicillin was assayed by a cup-plate diffusion method described by Burke(9) employing Sarcina-lutea strain P.C.I. 1001. Streptomycin was assayed by a modification of the method of the Food and Drug Administration(10). The study was carried out in 2 parts, one with and one without the administration of 'Benemid' in conjunction with the administration of single doses of the antibiotic agents. Part I: each patient received a single dose of the respective antibiotic and thereafter blood samples were obtained at 1½, 3 and 6 hours. At least 48 hours were allowed to elapse in order to permit elimination of the antibiotic agents, a precaution necessitated because of the prolonged periods over which plasma concentrations of aureomycin and terramycin can be demonstrated following single administrations. Part II; after 48 hours the same patients received 0.5 g of 'Benemid' at 6 hourly intervals for 4 doses and were then given a fifth dose of 0.5 g of 'Benemid' in combination with the antibiotic agent under test. Thereafter, blood specimens were drawn at intervals that matched the time schedule followed in Part I.

Results. The data are presented in Fig. 1 and it is apparent that 'Benemid' had no effect on the plasma concentrations of aureomycin, chloromycetin, terramycin and streptomycin. Three patients received single doses of 250 mg of aureomycin, 3 patients received single doses of 1 g of chloromycetin, and 1 individual received 1 g of streptomycin with and without 'Benemid' and these patients showed the same lack of effect of 'Benemid', (Table I).

In Fig. 2 are presented the average fractional 24-hour urinary recoveries of

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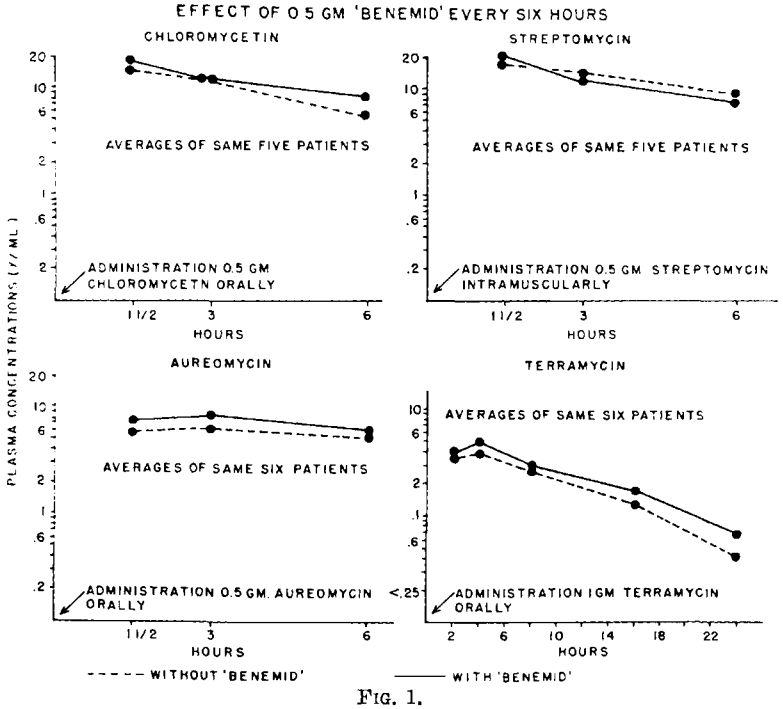

FIG. 1.

terramycin in six individuals. The recovery was 25% of the administered dose when terramycin was given either alone or in combination with 'Benemid'. The fractional urinary recoveries indicate that 'Benemid' not only did not quantitatively alter the recovery but did not influence the pattern of excretion of terramycin.

Discussion. Penicillin is cleared by the kidneys at a rate approximating renal plasma flow(11-13), and consequently penicillin disappears rapidly from the blood following single intramuscular injections of penicillin in aqueous solution. The rates at which aureomycin, chloromycetin, terramycin and streptomycin disappear from the plasma following the administration of single doses are much slower than for penicillin and differences in the renal elimination of these antibiotic agents are implied. It has been reported that the plasma concentrations of aureomycin were enhanced by the administration of carinamide(14), but this observation has not been confirmed in our hands. Carinamide and 'Benemid' are thought to act in the same manner(15), and as here reported 'Benemid' exerts no significant influence on the plasma concentrations of aureomycin. 'Benemid' plasma concentrations were determined on the specimens drawn for assay of antibiotic content and in all patients the 'Benemid' concentrations ranged between 5 and 10 mg per 100 ml of plasma, concentrations that have, without exception, increased penicillin plasma concentrations by 2 to 4 times(2).

Conclusion. Nine patients who received aureomycin, 9 patients who received chloramphenicol, 7 patients who received streptomycin and 6 patients who received terramycin failed to show any influence of p-(di-n-propylsulfamyl)-benzoic acid, 'Benemid', ad-

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TABLE I. Plasma Concentrations of Aureomycin, Chloromycetin, and Streptomycin With and Without 'Benemid'.

Patient	Age	'Benemid'*	Plasma conc.—mcg per ml (hr after dose) 1½	3	6
		Aureomycin—.25 g			
E	49	0	2	4	2
		+	4	2	2
A	36	0	2	2	2
		+	4	4	4
F	37	0	2	3	4
		+	4	4	4
		Streptomycin—1 g			
JP	22	0	26.6	21.5	7.3
		+	25	23.8	10

Chloromycetin—1 g

Patient	Age	'Benemid'	Plasma conc.—mcg/ml (hr after dose) ½	1½	2	3	4	6
S	69	0	7.5	15		7.5		
		+	7.5	15		22.6		
J	39	0	22.6		30		30	15
		+	30		30		30	22.6
JF	22	0	30		30		22.6	15
		+	30		45		45	30

ministered orally every 6 hours in a dose of 0.5 g on the plasma concentrations of the respective antibiotic agents. The failure of 'Benemid' to increase the plasma concentrations of streptomycin indicates that 'Benemid' may be administered safely to patients who are receiving streptomycin in conjunction with PAS.

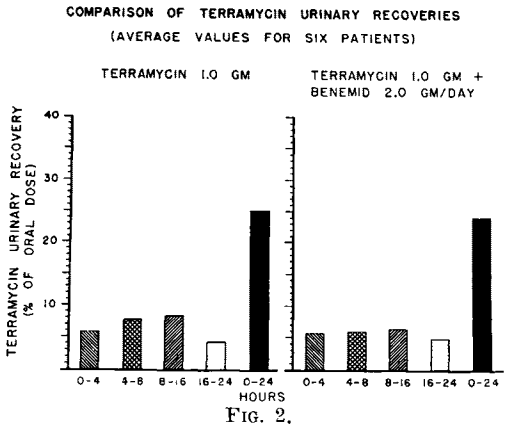

FIG. 2.

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