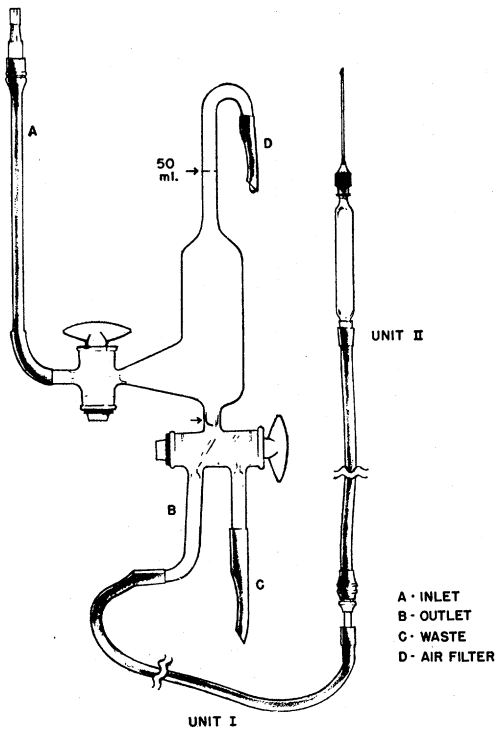

FIG. 1. Multiple sterile infusion apparatus.

The two stopcocks are greased with "high vacuum" grease supplied by Dow Corning Co. This silicon lubricant withstands temperatures over 200° C and may be repeatedly autoclaved without deterioration.

By means of this setup, the difficulty attending the sterilization of a large number of syringes was by-passed, and it was felt that the volume of injection fluid could be more accurately controlled. Using a No. 20 gauge needle, the injection time for 50 ml ranged between 4 and 5½ min. This apparatus was used successfully on over 50 subjects without a single untoward reaction.

Plasma Concentrations of *p*-Aminosalicylic Acid (PAS) Increased by *p*-(Di-*n*-propylsulfamyl)benzoic Acid

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PAS is being applied increasingly to the treatment of tuberculosis, the daily dose being 8–16 g. The amount of this dose is based on patients' ability to tolerate PAS medication, not on the belief that it represents the optimal dose; indeed, some workers believe that 20 g per day would be desirable (*3*). Therefore, an agent capable of enhancing the plasma concentrations of PAS would be worthy of attention, for although a direct relationship between plasma concentrations of PAS and therapeutic effect has not been established, this relationship, within limits, can be anticipated.

It was shown (*4*) that carinamide reduces the renal clearances of PAS to glomerular filtration rate, supposedly by inhibiting tubular excretion of PAS. But the suggestion was made that the same elevation in plasma concentrations of PAS produced by inhibiting the excretory function of the tubules would be observed if a form of PAS, less readily cleared by the renal tubules, was presented to the kidney for excretion. The concept that the catabolism (conjugation) of PAS may be altered in such a way as to slow its elimination gains support from the demonstration that carinamide acts upon an enzymatic conjugase system (*1*). A new compound *p*-(di-*n*-propylsulfamyl)benzoic acid, Benemid,[2] also has been shown to influence an enzymatic conjugation system that tentatively is regarded as related to the reversible inhibition of the excretion of penicillin and *p*-aminohippurate (*2*). The possibility that Benemid might inhibit the conjugation of PAS, and thereby retard its elimination from the body, prompted this investigation.

Seven patients with tuberculosis whose renal functions were unimpaired as determined by microscopic examination of the urine, blood urea nitrogen determinations, and phenolsulphonphthalein excretion tests were chosen for this investigation. In the fasting state, each patient was studied on three occasions: (A) after a single 4-g oral dose of PAS[3] (administered as NaPAS in aqueous solution); (B) after a 4-g oral dose of PAS and a single 2-g oral dose of Benemid; and (C) after a 4-g dose of PAS that was administered subsequent to premedication for 24 hr with 0.5 g of Benemid every 6 hr. The test doses of PAS were administered when the patients were in the fasting state, and blood samples for plasma determination of PAS were drawn at ½, 2, 4, 6, and 8 hr after administration of PAS. Plasma determinations of PAS were done by the method of Way (*5*).

The mean plasma concentrations[4] for the three periods of study were for treatment A, 1.00 mg PAS/100 ml blood; for treatment B, 1.71 mg/100 ml; and for treatment C, 2.63 mg/100 ml. These means were determined with a standard error of ±0.20 mg/100 ml, and the 95% confidence limits are ±0.44 mg/100 ml. Thus, treatment B gave significantly greater plasma concentrations of PAS than treatment A ($P < 0.05$), and treatment C gave plasma concentrations of PAS significantly

[1] The authors wish to express their thanks to Drs. Charles A. Heiken and Peter A. Theodos, chiefs of service of the Department of Chronic Diseases of the Chest, Philadelphia General Hospital, for the privilege of studying patients on their services. The technical assistance of Mrs. Alice E. Pitt is gratefully acknowledged.

[2] Benemid is Sharp and Dohme's trademark for *p*-(di-*n*-propylsulfamyl)benzoic acid. Tentatively, the compound has been given the nonproprietary chemical name "probenecid."

[3] Supplied through the courtesy of Sharp and Dohme, Inc., in the form of Propasa, an effervescent tablet of PAS that permits formation of NaPAS immediately prior to administration of the drug.

[4] The ½- and 2-hr plasma concentrations were eliminated from the statistical analysis because these samples were drawn during the period required for PAS from the single oral dose to be absorbed and distributed in the body fluids.

greater than treatment B ($P < 0.01$). The results are presented in Fig. 1.

A single 2-g dose of Benemid (treatment B) elevates by 1.6 to 2.1 times the plasma concentrations of PAS observed 4, 6, and 8 hr after a single 4-g dose of PAS. A daily dose of 2 g of Benemid administered in 0.5-g doses every 6 hr (treatment C) elevates by 2.3 to 4.1 times the plasma concentrations of PAS observed at the same time intervals after 4 g of PAS.

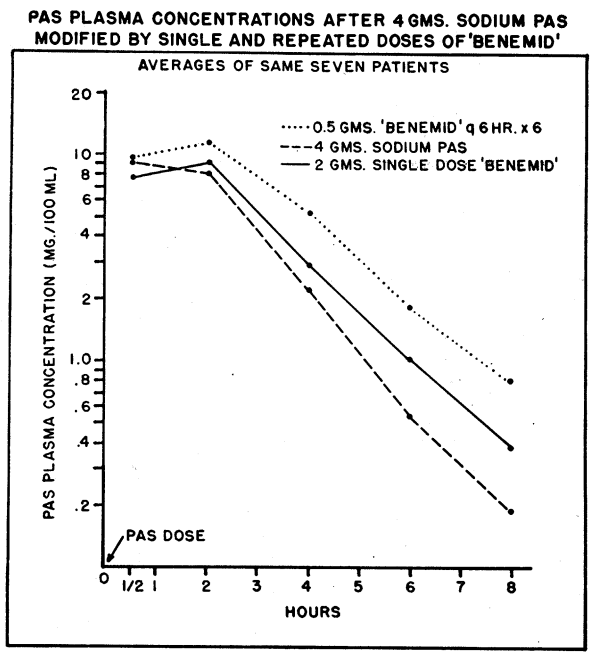

FIG. 1.

Because of the stability of Benemid and the absence of a free amine group in its structure, noninterference of the compound with the Way method might be anticipated. Repeated tests have shown that Benemid does not give a color reaction when samples were analyzed by the Way procedure.

Benemid, a crystalline white powder, is nearly insoluble in water.[5] Initially the drug is tasteless but a bitter taste is noted occasionally, which is then displaced by a pleasant aftertaste. The drug is absorbed rapidly from the gastrointestinal tract, and, after a single oral dose administered to dogs, it can be demonstrated in the plasma for as long as 36 hr. Nearly 75% of the drug is bound to plasma proteins and it is excreted in the urine almost entirely in conjugated form, probably as a glucuronide. Both acute and chronic toxicity studies in mice and dogs have shown a high therapeutic index for Benemid (*4*). Benemid has been administered daily to human patients for 3 weeks without any observed toxicity.

PAS is conjugated before excretion, and, of the total amount of PAS excreted in the urine, "approximately 59% is AcPASA, 18% is PASA, 13% is *p*-aminosalicyluric acid and the remainder represents one free amine and one conjugated amine which are highly water soluble" (*5*). It is suggested that Benemid inhibits the conjugation of PAS so that the drug is presented to the kidney for excretion in a form that is less rapidly excreted than are the conjugates of PAS. An adequate dose of Benemid in combination with PAS would be expected to result in more prolonged and higher plasma concentrations of PAS, and on the basis of the observations here reported, the plasma concentrations of PAS are enhanced two to four times. Therefore, Benemid may extend and greatly increase the efficacy of PAS in the treatment of tuberculosis.

[5] The chemistry of this substance and related substances will be published by Miller, Zeigler, and Sprague.

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The Composition of Meconium: Isolation of Blood-Group-Specific Polysaccharides. Abnormal Composition of Meconium in Meconium Ileus

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Meconium, the first intestinal discharge of the newborn, differs in appearance and properties from the stools of later life. It represents material accumulated during fetal life and is free of bacteria or their breakdown products. In the human infant it is blackish-green, odorless, has a viscid, sticky consistency, and varies in amount from 60 to 200 g. It is first demonstrable during the fifth month of gestation. Generally it is considered to be an accumulation of debris consisting of desquamated cells of the alimentary tract and skin, lanugo hairs, fatty material from the vernix caseosa, amniotic fluid, and various intestinal secretions. Its color is thought to be due to bile pigments (*12*). In a pathologic condition called "meconium ileus" (*8*), the amount of meconium is greater and its consistency even more viscid than is normal. This disorder is thought to represent the earliest and most severe form of cystic fibrosis of the pancreas, a disease characterized by diminution or absence of pancreatic enzymes. Neither normal nor abnormal meconium has as yet been studied by modern methods.

Analysis of meconium. In Table 1 is listed the composition of a pooled sample of normal meconium, as well as that of a specimen obtained from an infant with meconium ileus. Considering first the normal meconium, it may be seen that, as compared with adult stools, the