stupefied preparatory to an operation. Frogs are of course easily anesthetized either in cracked ice or in ice and water (Parker and Scatterty[4]), and lizards may be chilled with cracked ice (Parker[5]). Thus far we have treated only cold-blooded vertebrates, but Pfeiffer[6] has applied the method to newly-born rats. For some time after birth the young rat fails to maintain a high, constant temperature. During this period Pfeiffer found that it could be chilled in an electric refrigerator and after it had become motionless it could be satisfactorily operated upon on a bed of ice. On warming such a rat, it again became active and was received by its mother. This procedure appears to have been first used by Wiesner.[7]

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Relation of Concentrations of Free to Conjugated Sulfapyridine in the Blood of Patients.

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In the course of a clinical investigation of the use of sulfapyridine in the treatment of pneumonia[1] and other conditions, we were considerably interested in the practical problem of dosage in relation to the level of the drug obtained in the blood. Patients were given varying amounts of the drug according to weight, 1 or 1.5 grams per lb per 24 hr, in order to study their blood levels and to compare the influence of various levels on therapeutic response. Six hundred and fourteen determinations* were made of free sulfapyridine content of the blood of 126 children. On the basis of the findings of these determinations we concluded, as will be reported elsewhere, that *groups* of patients of various ages, receiving equivalent amounts of sulfapyridine according to their weights have, on the average, approx-

4 Parker, G. H., and Scatterty, L. E., *J. Cell. Comp. Physiol.*, 1937, **9**, 297.

5 Parker, G. H., *J. Exp. Biol.*, 1938, **15**, 48.

6 Pfeiffer, C. A., *Am. J. Anat.*, 1936, **58**, 195.

7 Wiesner, B. P., *J. Obst. Gynæcol. Brit. Empire*, 1934, **41**, 867.

* Marshall's method adapted for use with the Evelyn colorimeter was used in making the determinations.

Merck and Co. kindly furnished the sulfapyridine (Dagenan).

1 Wilson, A. T., Spreen, A. H., Cooper, M. L., Stevenson, F. E., Cullen, G. E., and Mitchell, A. G., *J. A. M. A.*, 1939, **112**, 1435.

imately the same levels of free drug in the blood; but that the individual patients constituting these groups vary widely in their levels so that it becomes necessary to adjust the dosage of any given case to reach the level desired.

Many factors were considered in possible explanation of this individual variability. It seemed probable that differences in absorption of the drug, in fluid turn-over, in the acid-base reaction of the gastro-enteric tract, in the power to conjugate the drug, and in the occurrence of vomiting and diarrhea all contributed their share in producing this variation.

It has been suggested[2] that patients vary in their ability to conjugate sulfapyridine, and that this variation might be a major factor in accounting for differences in level of the free drug from patient to patient. If this were true, then it would follow that the total drug levels should be constant, relatively speaking, for the various patients, and that those who conjugated a large part of the drug would have levels of the free drug lower to that extent, while those who conjugated little of the drug would have correspondingly higher free drug levels. That this is not correct is shown by the findings in 100 determinations of free and total sulfapyridine levels on the blood of 26 of our patients. There was indeed greater variation in the total drug levels of these patients (3.5 to 28.5 mg per 100 cc of blood) than there was in their free drug levels (1.4 to 17.4).

We observed a marked tendency for the level of acetylsulfpyridine in the blood of patients receiving varying amounts of sulfapyridine to be around 2 to 3 mg per 100 cc regardless of the level of the total or of the free drug in their blood. This was seen to be true of almost all patients except for a few of those having unusually high total drug levels. Three of these showed occasional samples with levels of 6 to 8 mg per 100 cc and, in the one case, of 11 mg per 100 cc. This case with the highest level shown on the chart had only one sample analyzed. The accompanying diagram, in which the patients have been arranged in order of the average of their total sulfapyridine blood levels, illustrates this point. We have considered the possible rôle of the relative insolubility of acetylsulfpyridine in the blood, the possibility of a variable renal clearance, and the possibility of a definitely limited ability to produce the conjugated drug in explanation of this phenomenon, but the explanation is not immediately apparent. It is possible that the sudden rise in conjugated drug content of the blood with increasing dosage may serve as a warning of danger, particularly since the acetylated compound has been

2 Meakins, J. C., and Hanson, F. R., *Canad. M. A. J.*, 1939, **40**, 333.

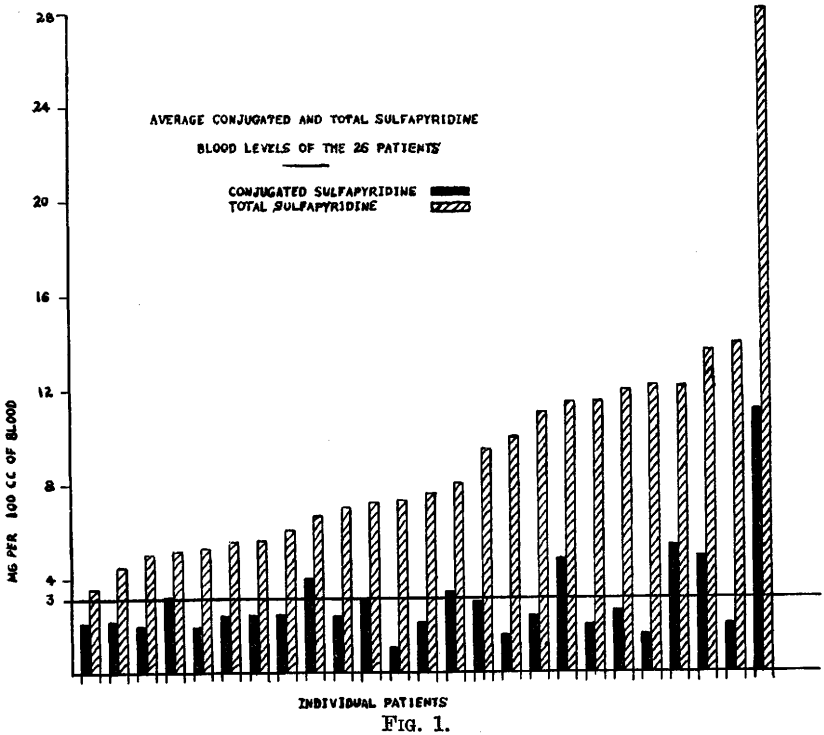

FIG. 1.

This diagram shows that the average blood levels of conjugated sulfapyridine tend to remain below 3 mg per 100 cc, independently of the amount of free and total drug present, except in a few cases with high total levels.

shown to be potentially harmful both from direct toxic action[3] and from its precipitation in crystalline form in the ureters.[4]

Conclusion. Patients show wide variation in blood content of free and total sulfapyridine when receiving standard dosage by weight, but the conjugated drug in most cases is present in about 2 to 3 mg concentration per 100 cc blood. However, in a few instances, patients with high levels of free sulfapyridine depart from this tendency, and have high conjugated drug content in the blood.

[3] Marshall, E. K., Bratton, A. C., and Litchfield, J. T., *Science*, 1938, **88**, 599.

[4] Antopol, W., and Robinson, H., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 428; Gross, P., Cooper, F. B., and Lewis, M. L., *ibid.*, 1939, **40**, 448.