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Continued Administration of Sulfathiazole on Renal and Hepatic Function in the Dog.

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Clinical experience with sulfapyridine has indicated that haematuria, associated with urolithiasis, occurs occasionally from the administration of this drug.[1, 2, 3] Molitor, Antopol and Robinson[4, 5] succeeded in demonstrating the etiological relationship between the drug and the pathological lesion under experimental laboratory conditions. In the course of our early investigations on the pharmacological properties of sulfathiazole it became evident that this compound, like sulfapyridine, could give rise to experimental urolithiasis and, as a direct result, produce varying degrees of physical irritation in the renal tracts of animals maintained on large continued doses. However, no data on the effects of sulfathiazole on kidney function are available, nor has any study of its effects on the acid-base balance, similar to that of Marshall, *et al.*,[6] on sulfanilamide, been made.

The primary purpose of this investigation has been to ascertain whether or not the continued administration of large doses of sulfathiazole would result in any significant impairment of renal function; secondarily, to determine whether or not there is any alteration of the alkali reserve during such a regime. Finally, in the light of certain of our experimental findings, it became necessary to duplicate the experimental conditions in order to study liver function.

Experimental Methods. The subjects were 3 normal, adult, female dogs trained for the necessary handling. During a preliminary control period frequent determinations were made of accepted criteria for the efficiency of kidney and liver function. The dogs then received 150 mg per kg per day of sulfathiazole for 4 days,

1 Snapper, I., Liu, S. H., and Chang, H. L., *Nederl. Tijschr. v. Geneesk.*, 1939, **23**, 4501.

2 Backhouse, T. C., *Lancet*, 1939, **2**, 736.

3 Gross, P., Cooper, F. B., and Lewis, M. L., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 448.

4 Molitor, H., and Robinson, H., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 409.

5 Antopol, W., and Robinson, H., PROC. SOC. EXP. BIOL AND MED., 1939, **40**, 428.

6 Marshall, E. K., Cutting, W. C., and Emerson, K., *J. A. M. A.*, 1938, **110**, 252.

followed by 250 mg per kg per day for 10 days.* Observations were continued for a period of several days after withdrawal of the drug in order to reëstablish normal conditions.

The drug was administered daily at 8:30 A.M., 4:30 P.M., and 11:30 P.M. in capsule form; we had previously observed that a continued blood concentration at a reasonably constant level might be maintained by dividing the daily dose in 3 equal parts and administering at the above time intervals. Exceptionally, sharp falls in the blood concentration were observed, due in all instances to repeated emesis which occasionally followed the administration of the drug. It should be pointed out at this time that the administration of doses of sulfathiazole of this order to dogs is associated with severe anorexia and it was necessary to change from the routine laboratory diet to more acceptable foods in order to avoid complicating the picture by a superimposed inanition.

Daily blood and urine (catheterized) samples were taken 3 hours and 4 hours respectively after the morning dose.

As indices of kidney function we chose the phenolsulphonphthalein excretion rate, the blood urea level, and the urea clearance, the last of which was determined by the method of Summerville, Hanzal and Goldblatt.[7] The urea clearance values reported here are the "standard clearances per square meter" calculated in the manner described by those authors. The other values described above were determined by the standard clinical methods.

Sulfathiazole concentrations in the blood and urine were determined by a modification of Marshall's method. The CO_2 and O_2 content of the blood and the O_2 capacity were determined by Van Slyke's manometric methods. The efficiency of liver function was studied by the bromsulphonphthalein excretion method.

Results. The results are presented in diagrammatic form in Fig. 1.

The blood sulfathiazole level produced by 150 mg per kg per day was approximately 8 mg per 100 cc. When the dose was increased to 250 mg per kg per day, the blood level increased to about 16 mg per 100 cc. The blood concentration persisted for about 24 hours after the cessation of medication and then rapidly fell to zero during the succeeding 24-48 hours.

* These dose levels approximate 3 and 5 times the average human therapeutic dose administered over 24 hours, and give rise to blood concentrations of from 15-20 mg per 100 cc. In our previous work on this subject we found that the maintenance of blood concentrations of this order for such a period of time was associated with urolith formation.

7 Summerville, W. W., Hanzal, R. F., and Goldblatt, H., *Am. J. Physiol.*, 1932, **102**, 1.

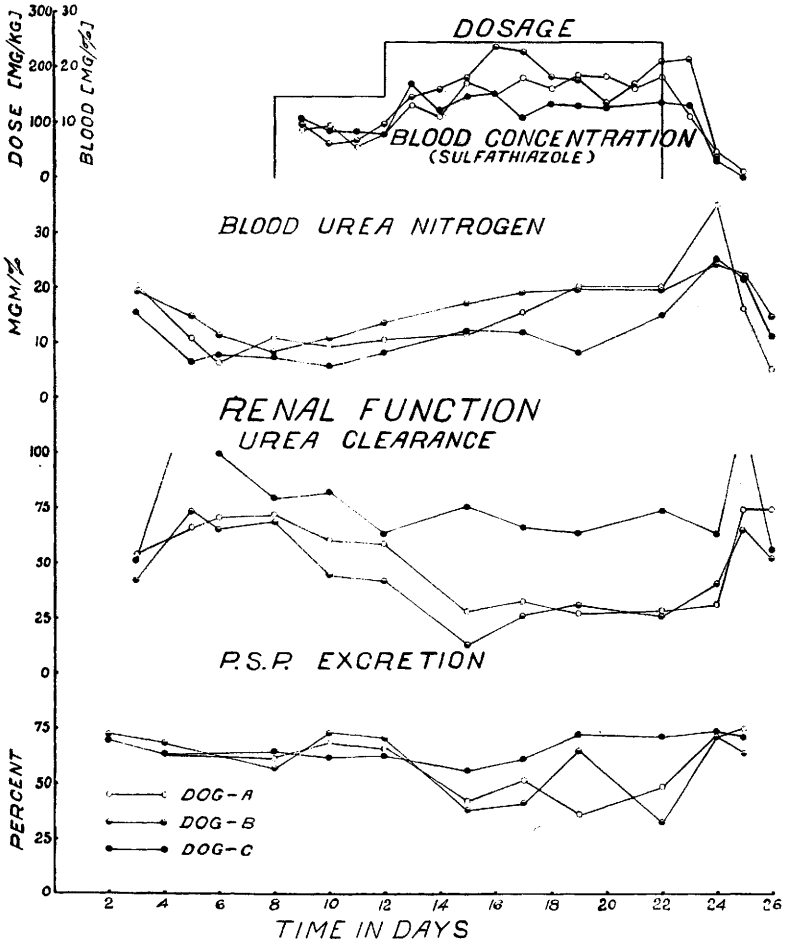

FIG. 1.

In the period prior to medication the blood urea nitrogen averaged about 10 mg per 100 cc. This value began to rise slowly but steadily throughout the entire period of medication, finally reaching a level of about 18 mg per 100 cc at the time the drug was withdrawn. However, all observations made during this period were within the established normal values. A sudden rapid rise occurred in the post-medication period to a mean value of about 30 mg per 100 cc after which there was an extremely rapid fall to the pre-medication level.

With respect to urea clearance, 2 cases must be distinguished. Prior to medication, Dogs A and B showed a urea clearance of about 70. With the beginning of medication they immediately began to

fall off until they reached a new level of about 30. With the cessation of medication, the urea clearances of both dogs rapidly returned to their normal levels. On the other hand, Dog C, which was more erratic and occasionally showed extremely high levels, had apparently reached a static urea clearance of about 85 and fell off only very slightly during the medication period. This animal appeared to tolerate sulfathiazole better than the other 2 in all respects. This difference in behavior was not the result of faulty absorption of the drug from the gastrointestinal tract, for the blood sulfathiazole concentration in this animal was of the same order as that of the others.

All 3 animals showed P.S.P. excretion values in excess of 60% within 2 hours during the premedication period. During medication the excretion values of Dogs A and B fell to a level as low as 40%, but returned to a normal level rapidly after medication ceased. The P.S.P. excretion for Dog C was analogous to the urea clearance for this animal in that normal values were maintained throughout.

During the course of medication, frequent urinalyses were made. Both occult and frank blood and traces of albumin appeared coincidentally in the later stages of medication in all dogs. Glycosuria was never observed. As soon as the dose level reached 250 mg per kg per day, large quantities of crystalline sulfathiazole appeared in the urine. The terminal portions of the catheter specimens contained dense clouds of these crystals. Such crystals often appeared as accretions about the urethral meatus. Cystoscopic examination was carried out on the twelfth day of medication and revealed an acute inflammatory reaction of the vesical mucosa of sufficient intensity to obscure all landmarks. In spite of this, the animals appeared to be in no discomfort and the cystitis and urethritis was never sufficiently severe to interfere with the passage of the catheter.

Daily determinations of O_2 capacity, O_2 and CO_2 content failed to reveal any variations beyond the expected daily fluctuations, indicating that no significant quantity of abnormal haemoglobin pigments is formed as a result of the administration of this drug and that there is no primary CO_2 deficit of the type associated with the administration of sulfanilamide.[8] It should be noted, however, that the dose of sulfathiazole administered in this experiment is less than half the amount of sulfanilamide required to produce acidosis.

Periodic examination of the blood picture throughout the course of the experiment failed to reveal any significant changes.

[8] McChesney, E. W., Marshall, I. H., and Sprague, K. D., *J. Lab. and Clin. Med.*, in press.

Discussion. An examination of the data shows that the administration of doses of sulfathiazole of this order is capable of producing moderate interference with the efficiency of renal function. Such changes are reversible since there is an immediate resumption of normal renal efficiency on withdrawal of the drug. It seems likely that impairment of renal efficiency is primarily due to physical blocking of the renal tract resulting from the accumulation of this poorly soluble drug, rather than to any toxic effect of the drug on the renal tissue. If the latter were the case, one would not expect to find such prompt recovery on discontinuance of medication.

An interesting phenomenon brought out in this study is the sudden sharp rise in the urea nitrogen content of the blood associated with a simultaneous rise in the urea clearance level soon after cessation of medication. While we do not entirely understand this phenomenon, there is a strong suggestion that the animals were in a state of positive nitrogen balance during the phase of maintained sulfathiazole blood concentration, and this increase was associated with a flushing out of the retained nitrogen. It occurred to us that some impairment of hepatic function resulting in the storage of amino nitrogen might have caused this phenomenon; accordingly, we repeated the experimental conditions on the same animals and observed the efficiency of liver function by means of the bromsulphonphthalein excretion test. Repeated tests indicated that no significant retention of the dye occurred under the experimental conditions established. While it must be recognized that this is not a crucial test of the deamination function, it does indicate that liver function was not impaired. Obviously, this phenomenon deserves further study.

Conclusions. 1. The continued administration of sulfathiazole to dogs over a period of 10 days in doses of 250 mg per kg per day produces slight impairment of renal function as evidenced by elevation of the blood urea nitrogen level, and diminution in the urea clearance and P.S.P. excretion. 2. This impairment of function is reversible and normal values are reëstablished within 48 hours after the withdrawal of the drug. 3. Doses of this order have no demonstrable effect on O_2 capacity, O_2 and CO_2 content. 4. Doses of this order have no demonstrable effect on liver function as indicated by the rate of excretion of bromsulphonphthalein.