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Perirenal Hemorrhage in Ureter Ligated Dogs Receiving Phthalylsulfathiazole.

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Reports of toxic manifestations following the administration of succinylsulfathiazole or phthalylsulfathiazole are infrequent and are considered to be of little consequence. In the course of some experiments on the treatment of experimental uremia[1] it was noted that the combination of ureter ligation in dogs and the oral administration of phthalylsulfathiazole resulted in hemorrhage beneath the fascial sheath covering the perirenal fat. Further studies were done in an attempt to discover the cause of this bleeding. The results of these studies are reported here.

Procedure. The animals used were mongrel dogs weighing 6 to 14 kg. Six test animals received 0.5 to 0.75 g/kg/day of phthalylsulfathiazole in oral divided doses for 3-6 days before the ureters were ligated and thereafter until the death of the animal. In addition, the ureters of 6 control dogs were ligated; the operation in both cases was done under ether anesthesia with morphine-atropine premedication, except Dogs 6, 7, and 9 which were anesthetized with pentobarbital sodium (30 mg/kg). The ureters were located and doubly ligated with silk about one cm from their entrance into the bladder. The animals were observed until their death.

In 4 of the test animals, (No. 8, 10, 11 and 12) blood sulfathiazole levels* were determined within 24 hours prior to death according to the method of Bratton and Marshall.[2] Serial blood phenol determinations, according to the method of Bernhart and Schneider,[3] were done in some of the test and control animals to follow the course of the uremia. In 3 dogs receiving the phthalylsulfathiazole (No. 10, 11 and 12) daily, pre- and post-operative prothrombin times according to the method of Quick,[4] red blood cell and platelet counts, and bleeding, clotting, and clot retraction times were done. Autopsies were done on all animals as soon after death as possible.

Results. All animals in which there was evidence that urine flow had been reestablished were omitted from the series. The significant pathologic findings are recorded in Table I. Of the 6 ureter ligated animals receiving phthalylsulfathiazole, 4 had gross hemorrhage beneath the perirenal sheath (Fig. 1), and of these, 3 had free blood in the abdomen. Of the remaining two test animals, one had a marked increase in vascularity of the perirenal sheath with a small amount of perirenal hemorrhage, and the other animal had a moderate increase in perirenal vascularity without perirenal hemorrhage.

Four of the control animals, without sulfonamide administration, showed moderately increased perirenal vascularity at autopsy, but none showed perirenal sheath hemorrhage. One had a small amount of old hemolyzed blood in the abdomen, but since this could not be attributed to a perirenal lesion it was thought to be due to the operative procedure.

Of the 3 test animals in which hematologic studies were done, one showed perirenal sheath hemorrhage and free blood in the abdomen, one showed a marked increase in perirenal vascularity without hemorrhage, and one showed a moderately increased perirenal vascularity. None of these animals showed any

1 Wallace, S. L., Little, J. M., and Bobb, J. R. R., in preparation.

* We are indebted to the staff of the Clinical Chemistry Laboratory for the sulfathiazole determinations reported in this paper.

2 Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

3 Bernhart, F. W., and Schneider, R. W., *Am. J. Med. Sci.*, 1943, **205**, 636.

4 Kracke, R. R., *Diseases of the Blood*, 2nd Ed., J. B. Lippincott Co., Philadelphia, 1941.

TABLE I

Dog No.	Pathologic findings: Increased vascularity of perirenal sheath	Hemorrhage beneath perirenal sheath	Free blood in abdomen	Capsular hemorrhage	Kidney substance hemorrhage
		Control			
1	Moderate	None	None	None	None
2	"	"	"	"	"
3	"	"	"	"	"
4	None	"	Yes*	"	"
5	Moderate	"	None	"	"
6	None	"	"	"	"
		Test			
7	**	Yes	None	None	None
8	**	"	Yes	"	"
9	**	"	"	"	"
10	**	"	"	"	"
11	Marked	Small amt	None	"	"
12	Moderate	None	"	Punctate	"

* This animal had 50-75 cc of old, hemolyzed blood in its abdomen with no observable origin. There were no changes in the perirenal tissues.

** Because of the perirenal sheath hemorrhage in these animals, it was not possible to determine if they had increased vascularity of the sheath.

hematologic abnormalities either pre- or post-operatively. In addition, none of the test animals during life or at autopsy showed any evidence of hemorrhage in any other tissue that was not also seen in the control animals. All animals showed punctate subendocardial hemorrhage on the valves and ventricular wall.

The average post-operative survival time of the animals receiving phthalylsulfathiazole was 79 hours with a range of from 54 to 118 hours. The average post-operative survival time of the control animals was 72 hours, with a range of from 37 to 109 hours. The post-operative course in the two groups was essentially the same, except that some of the animals subsequently showing free blood in the abdomen died more acutely, presumably of shock.

There was no significant difference in the blood phenol levels before death in the two series of animals. The blood sulfathiazole levels taken before death averaged 2.9 mg %, with a range of 2.5 to 3.4 mg %. The combined form of sulfathiazole averaged 0.1 mg %.

Discussion. The principal difference between the control and test groups of animals was the presence of hemorrhage beneath the perirenal sheath and free blood in the peritoneal cavity in the test group. We have found in other experiments (unpublished) that such hemorrhage does not occur with phthalylsulfathiazole administration to normal dogs, to dogs subjected to bilateral nephrectomy, or to dogs with ureter ligation in which the urine flow is reestablished. Therefore the responsible factors involved in producing the hemorrhage are the administration of phthalylsulfathiazole and the presence of ureteral obstruction with intact kidneys. Neither factor alone is sufficient.

The hemorrhage could be due either to hematologic changes or to vascular changes or to a combination of the two. The complete absence of abnormal hematologic findings suggests that vascular abnormalities are responsible. It appears that the increased perirenal vascularity accompanying ureteral ligation is a predisposing factor for hemorrhage upon phthalylsulfathiazole administration, but the nature of the highly localized vascular changes is unknown.

Winternitz and Katzenstein,[5] in a review of the experimental pathology of ureteral obstruction, report that at autopsy the kidney capsular vessels were prominent and congested and that the surface of the kidney in many

[5] Winternitz, M. C., and Katzenstein, R., *Yale J. Biol. and Med.*, 1940, **13**, 15.

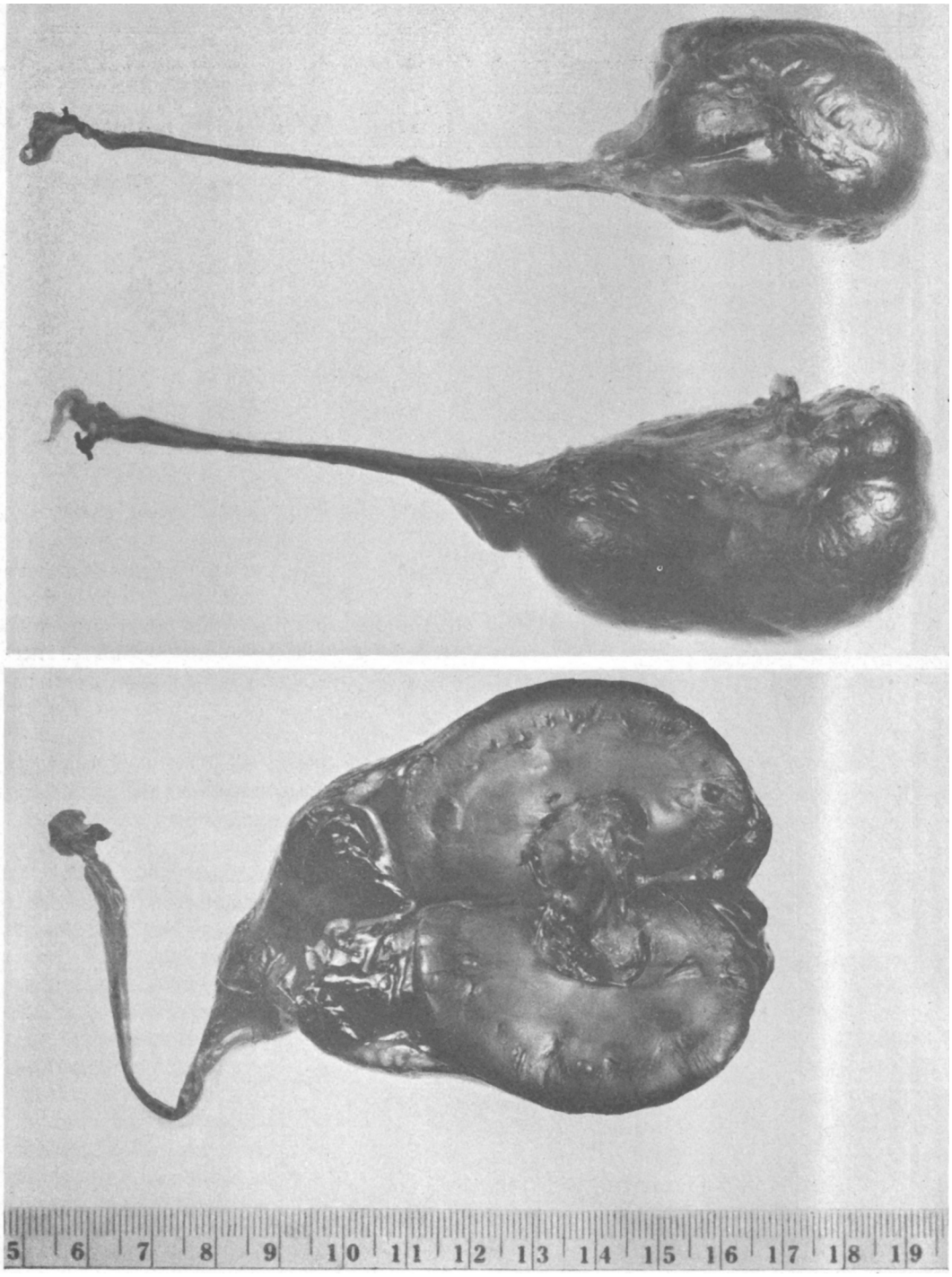

Fig. 1.
Hemorrhage beneath the fascial sheath covering the perirenal fat in ureter ligated dogs which received phthalylsulfathiazole.

cases was covered with a dark red friable exudate which usually extended into the surrounding perirenal adipose tissue. In none of their animals was perirenal hemorrhage reported. There was also no mention of such hemorrhage after ureteral ligation in the report of Harrison and Mason.[6]

Mattis, Benson and Koelle[7] reported that in one experiment they gave 1.0 g/kg of phthalylsulfathiazole intraperitoneally daily for 6 days to a monkey. The animal died on the sixth day with severe abdominal pain, hematuria, crystalluria, nausea, vomiting, weakness, and diarrhea. Autopsy showed extensive crystalline deposits in the renal parenchyma and pelvis and a marked recent bloody exudation in the peritoneal cavity. No mention was made of perirenal hemorrhage, but it is possible that the bloody exudate found represented such a hemorrhage since the animal had renal obstruction due to sulfonamide crystals. With this possible exception, the experimental[7,8] and clinical[9-13] administration of phthalylsulfathiazole has not been shown to cause bleeding in any tissue. Poth[9] quotes Allen to the effect that one-fifth of his patients with carcinoma of the colon had increased bleeding on treatment with succinylsulfathiazole, but he reported that this did not occur following phthalylsulfathiazole.

The observations reported here suggest that the clinical administration of phthalylsulfathiazole should be avoided in the presence of diminished renal function due to ureteral obstruction.

Summary. The ureters were ligated in 6 dogs, and phthalylsulfathiazole was administered orally in doses of 0.5 to 0.75 g/kg/day for 3-6 days pre-operatively and post-operatively until death. Two of these animals showed at autopsy an increased vascularity of the fascial sheath covering the perirenal fat, 5 animals showed perirenal sheath hemorrhage, and 3 animals had fresh free blood in the abdominal cavity.

The ureters were ligated in 6 control dogs, and they received no phthalylsulfathiazole. Four of these animals showed at autopsy an increased vascularity of the perirenal sheath. None of the animals showed perirenal hemorrhage.

It was found that both ureter ligation and phthalylsulfathiazole administration are necessary for production of the perirenal lesions. It appears that the perirenal hemorrhage is due to vascular changes since no abnormalities in prothrombin time, bleeding, clotting, and clot retraction time, red blood cell counts or platelet counts were demonstrated. The average total blood sulfathiazole concentration at the time of death in the test animals was 2.9 mg %.

[6] Harrison, T. R., and Mason, M. F., *Medicine*, 1937, **16**, 1.

[7] Mattis, P. A., Benson, W. M., and Koelle, E. S., *J. Pharm. and Exp. Therap.*, 1944, **81**, 116.

[8] Poth, E. J., and Ross, C. A., *Texas Rep. Biol. and Med.*, 1943, **1**, 345.

[9] Poth, E. J., *Surgery*, 1945, **17**, 773.

[10] Poth, E. J., *Texas Rep. Biol. and Med.*, 1946, **4**, 68.

[11] Streicher, M. H., *J. A. M. A.*, 1945, **129**, 1080.

[12] Angelo, G., *Am. J. Surg.*, 1945, **70**, 354.

[13] Bargen, J. A., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 85.