ADDITIONAL MANIFESTATION OF SULPHATHIAZOLE TOXICITY* NON-CALCULOUS RENAL INSUFFICIENCY FOLLOWING THE USE OF SULPHATHIAZOLE

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'The possibility of serious renal damage resulting from sulphapyridine therapy, apart from the formation of calculi, lacks confirmation at the present time.' This statement was made by Smith, Evelyn and Nolan in 1940. A review of the literature reveals no disagreement with the above statement except for a single report of the finding of severe parenchymal damage in the kidneys of animals by Antopol and Robinson (1940). In all the reported studies and cases, whether calculous or non-calculous, anatomical changes in the kidneys were striking enough to account easily for oliguria or anuria, for hyposthenuria, and for nitrogen retention. The association of functional insufficiency and anatomical damage was obvious and direct.

The two cases to be reported here were characterized by marked evidence of renal insufficiency, i.e. oliguria and nitrogen retention, and evidence of renal irritation—the presence of albumin, casts, red blood cells, and white blood cells in the urine. However, on post-mortem examination, a striking absence of calculi and of anatomical findings in any way sufficient to account for the renal failure was noted.

Case Reports

Case 1. A. M., a three-and-a-half-months old Puerto Rican male, was admitted on November 19, 1940, because of fever, cough and nasal discharge of one week's duration. Birth had been normal and the subsequent history negative until the onset of the present illness. Physical examination revealed a moderately ill infant with a temperature of 100° F., pulse of 120, and respirations of 40 per minute. A profuse purulent nasal discharge, a markedly injected pharynx and hypertrophied and cryptic tonsils were present. Many medium and coarse musical râles were present throughout both lungs. The tympanic membranes were dull, but the landmarks were present. The urinary meatus was 2 to 3 mm. in diameter and allowed an uninterrupted flow of urine without apparent straining. The admission urine was completely negative with the exception of an occasional white blood cell. The blood count was as follows: haemoglobin 11.5 gm., red blood

cells 3,570,000, white blood cells 12,800 with 64 per cent. lymphocytes, 4 per cent. eosinophils, and 32 per cent. neutrophils. The Wassermann reaction was negative.

During the first three weeks in the hospital the course was uneventful. Persistent nasal discharge and moderate injection gave evidence of the continued mild upper respiratory infection. The temperature, for the most part, was normal and rose on several occasions for a day or less to 101° F.

On the nineteenth day in hospital there was an elevation of temperature to 104° F., an increase in upper respiratory symptoms, occasional vomiting, and the appearance of three to five yellow-green stools daily. An examination at this time revealed a bilateral purulent otitis media. After twenty-four hours a bilateral myringotomy was performed which resulted in a purulent discharge from both ears. The culture from the left ear revealed a gamma streptococcus and from the right ear a staphylococcus aureus. The stool culture was negative and the diarrhoea ceased after the myringotomy. No evidence of pneumonia was found and the blood culture was negative, but the temperature persisted at 103–104° F. Therefore, on the third day of this elevated temperature, sulphathiazole was started. An initial dose of 1.2 gm. was followed by 0.3 gm. every four hours, producing a level of 4.1 mgm. per cent. After two-and-a-half days the temperature became normal, but at this time granular casts, red blood cells, white blood cells, and albumin were noted in the urine. The non-protein nitrogen was 75 mgm. per cent. and the blood pressure rose to 126/82 mm. Hg. Fluids were forced orally and parenterally and on the following day the non-protein nitrogen dropped slightly (to 65 mgm.) although the urinary findings persisted and there seemed to be some clinical improvement. However, in twenty-four hours the non-protein nitrogen rose again and the patient expired with a non-protein nitrogen of 123 mgm., five days after the onset of abnormal urinary findings and seven-and-a-half days after the beginning of chemotherapy.

AUTOPSY FINDINGS. The kidneys were of normal size for the age. The capsule stripped readily leaving a smooth surface with a few areas of congestion. Section showed cloudy swelling and congestion but no evidence of obstruction and no haemorrhage. No calculi or crystals were present. The renal pelvis, the ureters and the bladder were entirely normal.

Other significant gross findings were as follows:

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The liver showed cloudy swellings and mild fatty changes. The small intestinal mucosa was mildly hyperaemic and oedematous. In both middle ears was about 1 c.c. of mucopurulent exudate and the right mastoid bone was necrotic. The meninges and sigmoid sinus were negative.

Microscopically the renal glomeruli were entirely normal, containing normal quantities of blood, no leucocytes or increased number of nuclei. The tubules showed pronounced epithelial degeneration with granulation and hyaline droplet degeneration of many cells, but no necrosis. Many tubules contained foamy or granular, very slightly basophilic material which was not calcium. The endothelium of many small vessels was swollen and a few contained small clusters of white blood cells. No thrombi were present. Frozen sections of unfixed tissue showed no evidence of crystal formation on direct and polariscopic examination. There were no other microscopic findings of note except that the mucosal stroma of the ileum was considerably thickened by an infiltration of lymphocytes, plasma cells, and a few neutrophils. The glands were compressed and scarcely secreting. Some of them contained some nuclear detritus.

Case 2. W. S., a five-months-old male infant, was admitted on November 26, 1940, because of diarrhoea, vomiting, and fever of one day's duration. The birth and development had been normal. One day before admission there was sudden onset of fever, the infant vomited three or four times, and passed eleven or twelve watery green stools without blood in twenty-four hours. There was no previous upper respiratory infection or any change in the formula. The physical examination revealed an acutely ill child with a temperature of 101°F. , a pulse of 160 and Kussmaul respirations of 40 per minute. The fontanelle was sunken, the skin turgor only fair, and the child appeared moderately dehydrated. The physical examination was otherwise negative: there was no evidence of an upper respiratory or ear infection.

The urine on admission was completely normal, with no albumin and a negative microscopic examination. Blood count showed evidence of haemococoncentration with 16 gm. of haemoglobin; 7,200,000 red blood cells; 16,000 white blood cells, and 32 per cent. polymorphonuclears. The CO_2 -combining power was 20 volumes per cent. Two successive stool cultures were negative for typhoid, salmonella, and dysentery bacteria. The Mantoux test was negative.

Parenteral fluids were administered and later a protein milk formula was given. After three or four days, paregoric and bismuth subcarbonate were added. The diarrhoea decreased to five or seven stools daily and the CO_2 -combining power rose. Hydration improved greatly and the general condition was fair. On the third hospital day an upper respiratory infection developed and on the fifth day early signs of pneumonia were detected. These signs were corroborated by x-ray, and sulphathiazole was therefore started. 'Gag' culture revealed only streptococci and the blood culture was negative. An initial dose of 1 gm. of sulphathiazole, followed by 0.25 gm. every six hours, was given. After thirty-six hours during which a total of 2.25 gm. was given and the temperature dropped to normal, the sulphathiazole was discontinued because the

urine showed a trace of albumin, occasional granular casts, 3 to 10 red cells and 5 to 12 white blood cells per high power field. At this time a sclerematous condition of the skin of the entire trunk and extremities developed, which in from one to two days progressed to a firm induration. The non-protein nitrogen was 151 mgm. Total proteins were 5.2 gm. Although serial x-ray films showed partial clearing of the pulmonary consolidation, the infant's condition gradually grew worse, oliguria developed and, in spite of a continuous intravenous infusion of glucose in distilled water and a blood transfusion, the non-protein nitrogen rose to 164 mgm. and the creatinine to 7.0 mgm. per cent. The patient expired five days after the onset of the urinary symptoms, six-and-a-half days after sulphathiazole had been started, and on the eleventh day in hospital.

AUTOPSY FINDINGS. Autopsy revealed kidneys that were moderately swollen. The capsule stripped easily leaving a smooth surface. Section revealed the appearance of cloudy swelling and in addition several small (1 mm.) haemorrhagic spots in the medullary portion of the collecting tubules. No petechiae were observed in the cortex. The pelves, ureters, and bladder showed a pale, smooth mucosa. They were of normal volume. No calculi or crystals were noted. The skin and subcutaneous tissue, especially over the lower abdomen and thighs, had a remarkably thickened appearance varying from $1\frac{1}{2}$ to $2\frac{1}{2}$ cm. in thickness. The subcutaneous fat was white, hard, and had the feel of beef suet. The lungs showed several grayish patches of consolidation most marked in the right upper lobe. The stomach and small intestine showed discolouration interpreted as autolytic.

Microscopic examination of the kidneys showed glomeruli well filled with blood, in some cases actually distended with blood. No leucocytes were present in the tufts or increased nuclei. The capsular spaces were of normal size and contained no exudate. The tubular epithelium was swollen and granular but not necrotic. Occasional tubules contained eosinophilic casts and granular debris. There were several large and some small interstitial haemorrhages in the medulla, pushing the tubules and blood vessels aside. Several thin-walled veins and their branches in the medulla contained completely or partially occlusive thrombi adherent to their wall. These consisted of heavy threads of fibrin between which were granular detritus, and masses of red blood cells, some showing haemolysis. With scarlet-R stain many tubules, both convoluted and collecting, contained collections of tiny fat droplets slightly in excess of normal. Unfortunately frozen sections were not performed until the tissue had been in 10 per cent. formalin solution for twelve hours, and although no microscopic crystals were found, there is a possibility of their dissolution. The sections of the skin showed a normal epidermis, the dermis appearing thickened by dense collagen. Although hair follicles were present, no sebaceous glands were seen. Sweat glands lay within the corium and appeared compressed. The subcutaneous fat layer was unusually wide and uniform. No inflammatory changes were present.

Discussion

Two cases are described: one, that of a three-and-a-half months and the other that of a five-

months old child, who upon treatment with sulphathiazole for an infection developed evidence of renal irritation, oliguria, and azotaemia. Since the infectious processes were limited and definitely not accountable for the deaths by themselves, it seems likely that the chief factor in the fatal outcome was the suppression of renal function. Although renal toxic degenerative changes were present at autopsy in both cases, they were not more severe than in the average infectious disease not attended by renal insufficiency (Kannerstein, 1942). No calculi or even crystals of acetyl-sulphathiazole were found in either case. In the second case, the presence of a few small haemorrhages and the failure to examine frozen sections of the kidney microscopically for crystals until after immersion in an aqueous solution may lead to questioning of the absence of crystals. However, the mere presence of a few microscopic crystals is certainly not a valid reason for renal insufficiency, especially when there was no evidence of obstruction. In short, the anatomical findings were entirely inadequate to explain the uraemia. It may be argued that the uraemia in these cases was pre- or extra-renal. There is no way of indisputably proving that this was not so; however, it seems very unlikely. In the second case, although initial dehydration was present, it was overcome long before the development of azotaemia, which increased progressively in spite of parenteral administration of large amounts of fluid. In the first case, dehydration was never a factor.

As mentioned above there have been practically no reports on renal insufficiency in humans as a result of sulphathiazole, in the absence of calculous obstruction. Antopol and Robinson (1940) from their work on animals suggested the 'possibility . . . that the drug may first produce parenchymal damage and subsequent to this, the acetylated compound is precipitated from the solution.' They also found that even when a dose insufficient to cause calculus formation was given, the kidneys still revealed the same degenerative glomerular and tubular changes. These changes were severe and

included the presence of eosinophilic globoid bodies in the tubules, a coagulum in the loops of Henle and, in some cases, cuboid anuclear cytoplasm covering Bowman's capsule. One of the cases reported by Antopol (1940) reveals anatomic renal lesions in the absence of calculi or crystals in a middle-aged man who died of bronchopneumonia after two days of sulphapyridine therapy. Rake, Van Dyke, and Corwin (1940) noted that in the case of rats on sulphapyridine and mice on sulphathiazole there appears to be a primary damage to glomeruli and cells of convoluted tubules distinct from the changes due to the mechanical effects of the crystals. These changes were chiefly tubular necrosis and degeneration, collapse and destruction of tubules, and glomerular scarring. Although the above investigators suggest the possibility of anatomical renal damage due to sulphathiazole in the absence of obstruction, no previous reports of impairment of renal function without anatomical changes as a result of this drug have been found.* These cases are, therefore, reported as probable examples of the latter effect, in the hope that this will stimulate additional evidence for or against it, as well as an increase in caution in the use of the drug.

Summary

Two cases are presented which, during treatment with sulphathiazole, developed evidence of renal irritation, oliguria, and azotaemia from which they died. These disturbances were not accompanied by the formation of calculi or anatomic changes sufficient to account for them. It is suggested that this is a toxic manifestation of sulphathiazole causing a change in function rather than structure of the nephron.

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* Since compiling this report two similar cases in adults were presented at conferences of the Mt. Sinai Hospital of New York City in February and April, 1941.

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