care and treatment. None of these developed gas gangrene or serious sepsis.

The courage and cheerfulness of the patients were most remarkable. For example, one woman about 52 years of age, when asked how she was, said: "Oh, I've only a few cuts and scratches"; and added, "Hitler can't get me; he bombed me once before and blew the roof off my house. I was downstairs this time. My house is now down flat, and I won't be there next time he bombs it." Visitors were allowed freely, but were warned that there were to be "no tears" while in the wards.

I wish to express my thanks to the medical superintendent and his staff, and to the nursing staff, stretcher-bearers, and scouts, for their constant help and real team spirit in great emergencies.

RENAL COMPLICATIONS OF SULPHAPYRIDINE

ACCOUNT OF A CASE WHICH SHOWED GROSS HAEMATURIA AND URAEMIA

BY

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Although haematuria is generally recognized as an occasional complication of sulphapyridine treatment it is a condition which has received little attention in the literature of this country. All the information that I have been able to glean has been culled from communications published in the United States and in Canada, and from a summary of part of this transatlantic work by R. St. A. Heathcote (1940). The object of this paper is to report a case in which haematuria and uraemia occurred, and to give a general description of the renal complications of sulphapyridine (Backhouse, 1939).

Case Report

A second lieutenant aged 26 was admitted to hospital on August 26, 1940, with follicular tonsillitis. He gave a recent history of three similar attacks. There was no elevation of pulse or temperature. He was put on to sulphapyridine and given gargles of potassium chlorate. The following day he felt better and his throat was less painful. On August 28 he vomited several times and passed 10 oz. of deeply blood-stained urine. The sulphapyridine, of which he had received a total dose of 12 grammes, was stopped. He passed 1 oz. of urine during that night, and in the early morning of the 29th had a severe attack of pain in the lower abdomen, which radiated later to the penis. During the day he passed only 5 oz. of urine, which was grossly blood-stained. He continued to vomit throughout the day, and still complained of pain in the abdomen and across the lumbar region. In the evening he was very drowsy.

On August 31 an intravenous "drip" saline was started, as he was vomiting intermittently and had passed no urine for forty-eight hours. At this time his tongue was dry and furred, and occasional hiccups had begun to add to his distress. He was tender in the left iliac fossa and left costo-vertebral angle, and slightly tender in the right iliac fossa. There was no evidence of oedema. A blood count showed Hb 90%; R.B.C. 5,500,000; W.B.C. 11,250—78% polymorphs, 15% lymphocytes, 7% monocytes. During the night he became restless and delirious. The "drip" was stopped on the morning of September 1, by which time he had received 4 pints of normal saline and 2 pints of 5% glucose in normal saline. At the end of the drip his mental outlook was rational and his tongue had become moist. He was still vomiting, but less copiously and less often, and had not yet passed urine. During the afternoon another intravenous "drip" was started, 1 pint of normal saline being followed by 2 pints of 5% glucose-saline, and the same evening he passed about 1½ oz. of bloody

urine after a period of anuria lasting seventy-two hours. The specimen of urine was examined by Major C. E. van Rooyen, who reported as follows: "Specimen consists of about 1½ oz. of blood-stained urine—cloudy, dark, and with much amorphous granular sediment. Microscopical examination: Numerous R.B.C. and pus cells; no bacteria; no crystals of any sort visible." This urine was passed at 8.30 p.m. At 9 p.m. a solution of 4.28% sodium sulphate was substituted for the glucose-saline, and at 9.45 p.m. a further 6 oz. of urine was passed. By the following morning the patient had passed 82 oz. of urine. The "drip" was continued till the morning of September 3, by which time 8 pints of saline and glucose and 2 pints of sodium sulphate solution had been given. From now on his condition rapidly improved and gave rise to no further anxiety. On September 11 a centrifuged deposit of urine showed W.B.C. (average 20 per field), R.B.C. (average 6 per field), 4 epithelial casts, and 1 hyaline cast.

On September 17 an excretory pyelogram revealed no abnormality of outline or function. Tonsillectomy was performed by Major E. A. M. Connal on September 23, and the patient was discharged from hospital on October 4.

Incidence of Renal Complications

Plummer and Ensworth (1939) reported 4 cases of gross haematuria and 1 of microscopical haematuria in 323 patients treated with sulphapyridine. They also observed a mild degree of blood nitrogen retention in 3 patients who showed no haematuria. These authors maintain that in their experience of the toxic effects of sulphapyridine "those involving the kidneys and ureters have been the most disturbing." Duncan Graham of Toronto and his co-workers (1939) observed 4 cases of gross haematuria in 50 patients, Smith and Needles (1939) 1 case among 50; while Tsao, McCracken, Chen, Kuo, and Dale (1939) have reported 5 cases of gross haematuria in a series of 40 patients, but attribute this high incidence to the poor nutrition, dehydration, and avitaminosis which were features of most of their patients. Tsao's patients were children attending a hospital which admits only sick refugee Chinese. In the case of almost all the patients in these various series pneumonia had been the primary disease for which the sulphapyridine was given. My colleague Captain J. A. Scott (personal communication) has noted a case of gross haematuria among 74 patients treated with sulphapyridine for gonorrhoea.

We know from the work of Antopol and Robinson (1939) and of Gross, Cooper, and Lewis (1939) that urinary calculi composed of acetyl-sulphapyridine (64.1%) and sulphapyridine (6.4%) can be produced experimentally in monkeys, rabbits, and rats by the oral administration of large amounts of the drug; and two small stones of acetyl-sulphapyridine were found by Plummer and Ensworth at necropsy in the kidney of a woman who over a period of three months had received 540 grammes of sulphapyridine on account of a subacute bacterial endocarditis. It is important to bear in mind, however, that massive doses of the drug are not essential to effect its precipitation in the urinary tract. Plummer and McLellan (1940) found the crystals in the bladder of a man aged 46 who developed pain in the left flank and haematuria after 11 grammes, and in the case described above only 12 grammes had been given. Nor does this precipitation depend upon a high level of the blood sulphapyridine. In fact, in Plummer and McLellan's case the level was too low to be read.

Nature of the Renal Lesion

In their experimental animals Antopol and Robinson found changes ranging from a simple calculous pyelitis and ureteritis to a marked pyelonephritis. Tsao has reported the post-mortem appearances in a boy aged 8 who had died of uraemia after receiving 7.78 grammes of

sulphapyridine. The pelves and ureters were dilated and their mucosae thickened, congested, and haemorrhagic; the bladder contained a small amount of grey sandy particles, and both ureters were blocked by concretions at their entrance into the bladder. Unfortunately the sand-like material was lost in the fluids and could not therefore be examined for sulphapyridine. Stryker (1940) had the opportunity of examining at necropsy the renal lesion in a child of 5 months who had died of pneumococcal meningitis and had developed gross haematuria after 44.2 grammes of sulphapyridine, administered over a period of four weeks. In this case the mucosa of the urinary tract appeared normal. In the calices and pelves of both kidneys a small amount of yellowish-white gravel was found, and four calculi were isolated from the pelvis of the right kidney. Here, as in Tsao's case, there was an accumulation of gravel in both ureters, mostly at the entrance of the ureters into the bladder. Microscopically the kidneys showed dilatation of the cortical tubules and glomerular spaces due to precipitation within the tubules of concretions of varying structure—namely, sharp-edged basophilic crystals, amorphous basophilic debris, and discoid bodies of homogeneous material.

Diagnosis

When haematuria is observed in a patient to whom sulphapyridine is being administered it must always be borne in mind that the drug may be responsible, and the urine should be examined for crystals. The crystals are elongated and sharp, and occur in clusters grouped at one end and radiating at the other. They are well shown in a photograph reproduced in Plummer and McLellan's paper. It is worth noting that in Captain Scott's case the crystals could not be identified in the centrifuged deposit of the urine, but they could be seen clinging in abundance to the sides of the glass vessel and showed the typical structure under the microscope. The crystals were washed off the sides of the vessel, tested chemically, and identified as sulphapyridine by Miss Gilchrist of the biochemical department of the Royal Infirmary, Edinburgh. Unless concretions of acetyl-sulphapyridine are present in large quantities they are readily redissolved and cannot be identified in the urine. Southworth and Cooke (1939), for example, found them in the urine of only 1 of 3 patients who developed haematuria after sulphapyridine. Occasionally renal calculi of acetyl-sulphapyridine may be demonstrated as negative shadows in excretory or instrumental pyelograms (Plummer and McLellan, 1940). In spite of the sulphur-containing radical the stones themselves are not opaque to x rays. In the absence of crystals it may be difficult, and at times even impossible, to determine at the onset whether the haematuria should be attributed to the sulphapyridine or whether it is a symptom of an acute nephritis, since many of the patients under treatment with the drug are victims of acute infections in which nephritis is known to occur as a complication. If the bleeding is due to acute nephritis numerous casts in the urine or oedema or shivering attacks will eventually point the diagnosis. These symptoms are no more characteristic of renal damage due to sulphapyridine than they are of aseptic calculous pyelitis and ureteritis in general. Furthermore, the haematuria due to sulphapyridine is often accompanied by renal pain or colic which is far more severe than the lumbar pain that is an occasional feature of acute nephritis.

Occasionally pain precedes the appearance of haematuria, and Southworth and Cooke (1939) describe a case in which the possibility of an acute appendicitis was seriously debated. The patient was a girl of 17 who developed a transient attack of pain in the right lower quadrant of the abdomen two days after she had been

started on a course of sulphapyridine for a respiratory condition. On the following day the pain recurred and was accompanied by burning pain on micturition. Tenderness was most marked over McBurney's point. Owing to the onset of gross haematuria and the fact that her abdominal tenderness extended up to the right costo-vertebral angle, conservative treatment was decided on, and the sulphapyridine, of which she had received 10.5 grammes, was stopped. Her symptoms subsided rapidly.

Treatment

As a rule the symptoms of haematuria and renal colic disappear within twenty-four hours when sulphapyridine is withheld and fluids are forced. In the event of signs of nitrogen retention 5% glucose or 4.28% sodium sulphate solution should be administered by the intravenous "drip" method. If anuria develops and persists in spite of these measures, cystoscopy and ureteric catheterization or, if need be, renal pyelotomy, as suggested by Tsao, deserve consideration owing to the tendency for plugs of concretion to block the orifices of the bladder. This was not carried out in the case I have described, as it was not until the patient had recovered that I had the opportunity of perusing the relevant literature and of learning something of the nature of the condition.

I wish to acknowledge my thanks to Colonel J. M. Mackinnon for permission to publish this record, and to Major C. E. van Rooyen for his friendly co-operation. My grateful thanks are also due to Major Ian Murray for much helpful discussion during its preparation.

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EXPERIENCES IN TREATMENT OF PERIPHERAL NERVE INJURIES WITH AMNIOPLASTIN

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For some time efforts have been directed towards finding a substance which would isolate a damaged structure by preventing it adhering to its surroundings and which by ultimately becoming absorbed would leave the structure concerned quite free. Wilder Penfield and his associates (Chao *et al.*, 1940) experimented on cats by placing various membranous materials between the scarified cerebral cortex and a flap of overlying soft parts. They found that of the materials used the best was a prepared form of human amniotic membrane which they called amnioplastin. This was absorbed in about three weeks, leaving the cortex free from adhesion.

Following Penfield's report it appeared that this substance would be useful in the surgery of peripheral nerves as well as in that of the central nervous system. Having had some experience of it in eight intracranial cases in which it was used to prevent meningo-cerebral adhesions, and having noted the frequency with which peripheral