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II

PATHOLOGICAL EVIDENCE AS TO THE CAUSATION OF HÆMATURIA FOLLOWING SULPHAPYRIDINE THERAPY*

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THE recent death of a patient under treatment with sulphapyridine has provided an opportunity for investigating the excretion of this drug from the body and the cause of the hæmaturia which occasionally occurs during such treatment.

The case under review was that of a man aged 30 who was admitted to hospital with a non-specific urethritis. He was given an intensive course of sulphapyridine but after receiving 17 grams in forty hours he complained of pain in the loins and the treatment was stopped. His output of urine began to diminish and the flow eventually ceased altogether. The urine contained blood and needle-shaped crystals of acetyl sulphapyridine. On the day of the patient's death the concentration of urea in the blood rose to 300 mgm. per 100 c.c.

I propose to give only a brief summary of the post-

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mortem findings and then to describe in greater detail the microscopic appearance of such tissues as have a bearing on the subject.

The kidneys were both enlarged (right $8\frac{1}{2}$ ounces, left 9 ounces) and there were a number of subcapsular hæmorrhages on the surface. When split open the medullary regions were seen to be much congested.

The ureters were greatly dilated and contained a thick dark-brown fluid. The ureteric openings in the bladder were both blocked with "altered" blood and were surrounded by a ring of sub-epithelial hæmorrhage. Along the course of the ureters were a few small bleb-like swellings full of blood and they were present even more noticeably in the wall of the renal pelvis.

The rest of the abdominal organs were examined, but no abnormalities were found. The lungs were congested and œdematous.

Death was due to blockage of both ureters with subsequent uræmia.

We now pass to the microscopical appearances. The contents of the ureters consisted of hæmolysed blood, epithelial cells, leucocytes and blood pigment. None of the typical sulphapyridine crystals were seen, but some small crystals were present which were round or oval in shape and had a rough surface. Their size was about 30 microns.

The most noticeable feature in the sections of the kidneys were the extravasations of blood which had taken place in the medullary regions. Throughout this area multiple hæmorrhages had occurred, some being a little bigger than a glomerulus whilst others were large enough to be seen with the naked eye.

Blood was also observed tracking down towards the hilum of the kidney both inside and outside the tubules. The blood which flowed down *inside* the tubules passed into the ureters, whereas the blood that had made its way *between* the tubules tended to collect in the connective tissue surrounding the calyces and the renal pelvis.

Another point of some interest is that in almost every section of the kidney which was examined small crystals were to be found very similar in appearance to those already seen amongst the contents of the ureters.

These crystals were situated inside the tubules, in the surrounding interstitial tissue and in the hæmorrhagic

- (A) Cross-section of a crystal showing striæ radiating from the centre.
 (B) Crystal of sheaf-like form. Note the striæ radiating from the centre and the beginning of a fracture originating in the upper pole.

- (C) Two crystals in a tubule. The one on the left has not been cut and shows the rough outer surface.
 (D) A crystal is here shown completely filling a tubule.

- (E) This crystal lies on the edge of the hæmorrhage. The section has been carried only half-way through the crystal, the outer edge of which shows minute spicules.
 (F) A crystal in the process of breaking up into wedge-shaped segments. Note the thinning of the wall of the tubule at one end.

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areas. In some instances the crystals could even be seen in the process of being forced through the wall of the tubules. The size of the crystals varied between 15 and 30 microns and their shape was usually round or oval, though sometimes small projections and outgrowths gave them a more irregular appearance. Their surface was rough and often indented by deep clefts down which fractures could easily be produced by light pressure on the coverslip. Such treatment broke up the crystals into a number of sharp-pointed, wedge-shaped forms. Cross-sections showed the crystals to be very finely striated, often with the addition of minute spicules on the surface. This is well shown in Fig. E, especially if use is made of an ordinary hand lens.

There appears to have been some inflammation of the glomeruli as evidenced by the increased number of nuclei in the tufts of the kidney and the swelling of the endothelial cells lining the glomerular spaces. In some cases these were so large as to look much more like epithelial than endothelial cells. The cells lining the tubules showed signs of degeneration and the interstitial tissue of the kidney was markedly oedematous. Sections through the bleb-like swellings in the ureters and in the wall of the renal pelvis showed sub-epithelial hæmorrhage, oedema and well-marked round-cell infiltration.

COMMENTS

Several points of interest arise from the foregoing observations. What, for instance, caused the blockage of the ureters? Where was the chief site of the hæmorrhage, and could the crystals described have been the cause of it? Lastly, what is the composition of these crystals?

Contrary to the findings of some other observers, there were no concretions blocking the ureteric orifices in this case. The ureters, as they passed through the wall of the bladder, were markedly narrowed owing to the extensive sub-epithelial hæmorrhages in this region. This narrowing of the terminal part of the ureter added to the sludge-like condition of the blood descending from the kidney amply accounts for the blockage of these passages.

The chief site of the hæmorrhage was in the central medullary regions of the kidneys. That the crystals

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were the cause of the hæmorrhage is supported by the evidence of a number of the histological sections. These showed the crystals passing through the tubular walls and damaging the blood capillaries in the process.

The small sub-epithelial hæmorrhages in the walls of the ureters were probably caused by the crystals which had had an uninterrupted journey through the kidneys and were on their way to the bladder.

The sub-capsular hæmorrhages were undoubtedly a toxic manifestation.

With regard to the composition of the crystals there are three main forms described as appearing in the urine of patients receiving sulphapyridine: (1) Lenticular-shaped crystals; (2) sheaves of needle-like crystals; (3) wedge-shaped, striated crystals.

Backhouse has stated that the lenticular form is the one most usually seen. In one case he found that after a day or so the lenticular form was replaced by an occasional needle sheaf. He also points out that the urine was often passed clear but deposited these crystals on standing. O'Meara made similar observations and noticed that as the number of crystals decreased there was a relative increase in the needle sheaves. Smith, Evelyn and Nolan noticed amorphous, spherical aggregates in addition to the sheaf-like type of crystal. Plummer and McLellan describe a wedge-shaped striated variation.

The crystal I have described does not correspond with any of these forms though Fig. B has some resemblance to a sheaf of very tightly-packed needles. We have seen, however, that the sulphapyridine appears in at least three types and that a patient's urine may contain crystals of more than one of them. In the case under review needle-sheaf crystals did appear in the early stages of the treatment and it seems highly probable that the minute crystals herein described supply yet another variation of this substance. It would besides be reasonable to expect a crystal formed in the confined space of a renal tubule to differ both in size and structure from one precipitated in the urine "on standing," or even in the comparatively roomy and commodious renal pelvis.

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III

SOME FACTORS AFFECTING THE
DEVELOPMENT OF IMMUNITY IN
EXPERIMENTAL RABBIT-SYPHILIS

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THE object of this paper is to bring to notice some hitherto unpublished experiments to see if simultaneous inoculation of a rabbit with a few strains of *S. pallida* and the consequent provocation of a large reaction in the first instance would make the animal resistant to superinoculation with other strains, in other words, develop a pan-immunity as contrasted with a mono-immunity. Before, however, dealing with these experiments, which I carried out in 1930-32 in the Bacteriological Department of the Reichsgesundheitsamt, Berlin-Dahlem, it seems appropriate to summarize existing knowledge on some factors affecting the acquisition of immunity in experimental syphilis of the rabbit.

In the investigation of experimental rabbit-syphilis two questions are of outstanding interest. (a) Is there any "true" immunity? and (b) are the immunological conditions in the syphilitic rabbit essentially different from those in the syphilitic patient? As regards the first question, the majority of investigators [Chesney and Kemp (1924), Chesney (1926, 1930), Manteufel and Worms (1927), Uhlenhuth and Grossmann (1927, 1928), Breinl and Wagner (1929), Manteufel and Herzberg (1933), Breinl (1935), Tani and Aikawa (1936), (1940), Vászárhelyi (1936)] hold that the syphilitic rabbit acquires a "true" immunity, that is one which does not necessarily depend on the persistence of *S. pallida* in the body, but remains after disappearance of this organism. Whether the syphilitic rabbit acquires a pan-immunity such as is said to