relapse and, in fact, that the relapse was imminent on the day of the operation. The finding of a contemporaneous exo-erythrocytic cycle would supply a reasonable explanation of the source of the parasites producing the relapse if the interpretation of our findings given below is accepted.

Although it involves some repetition, we think it would be useful to give, in a few words, our interpretation of the findings obtained in our recent work on the exo-erythrocytic cycle in mammalian malaria.

The inoculation of sporozoites by the infected mosquito is followed by a pre-erythrocytic development in the parenchyma cells of the liver, with the ultimate production of merozoites. Many of these enter the erythrocytes to produce a parasitaemia and a clinical attack of malaria. Other merozoites enter normal liver cells and repeat the process of exo-erythrocytic schizogony. This latter process repeats itself indefinitely, irrespective of whether the erythrocytic cycle is present or is in abeyance as the result of antimalarial treatment or a naturally acquired active immunity. This active immunity is operative only against the erythrocytic parasites and destroys those merozoites liberated by the exo-erythrocytic schizonts which are destined to enter red cells. Those which enter liver cells to maintain the exo-erythrocytic cycle are protected from this immunity by their intracellular position outside the circulating blood.

If, for any reason, the active immunity of the host is impaired it no longer operates against the merozoites destined to start the erythrocytic cycle, and these enter the blood cells and initiate a clinical relapse.

The marked similarities both in erythrocytic and in pre-erythrocytic stages between *P. cynomolgi* and *P. vivax* make it reasonable to suppose that the course of events here described in the case of the former parasite will be applicable to the latter.

Until recently the fact that exo-erythrocytic development is the rule in the case of avian plasmodia, while it was not demonstrable in the case of mammalian plasmodia, tended to cause some misgiving in placing both groups in the same genus. The discovery, however, of the pre-erythrocytic cycle in simian and human plasmodia appeared to narrow the gap between the two groups, and now that the simultaneous existence of erythrocytic and exo-erythrocytic cycles has been demonstrated in a simian *Plasmodium* there seems still less justification for considering avian and mammalian plasmodia as other than very closely related.

Summary

The finding of exo-erythrocytic schizonts of *Plasmodium cynomolgi* in the liver of a monkey about three and a half months after a sporozoite-induced infection is evidence of the persistence of the exo-erythrocytic cycle after establishment of the blood infection.

Reasons are given for the assumption that this is the cycle responsible for the production of relapses.

As in earlier work in this investigation we wish to record the valuable technical assistance of our staff, Mr. W. Cooper and Mr. E. Blackie and Miss J. Stedman.

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BILHARZIAL AFFECTION OF THE URETER

A STUDY OF 110 CONSECUTIVE NECROPSIES SHOWING VESICAL BILHARZIASIS

BY

MICHAEL GELFAND, M.B., M.R.C.P., D.M.R.

Acting Government Pathologist, Southern Rhodesia
Government Medical Service

The ureter is often affected in urinary bilharziasis. The purpose of this article is therefore to report on the various lesions found in the ureter in a series of 110 consecutive necropsies on Africans held at the Salisbury Mortuary, Southern Rhodesia.

The literature would appear to stress the obstructive lesions met with in urinary schistosomiasis. As early as 1919 Fairley drew attention to the tendency of the disease to invade the lower portion of the ureter. He reported that catheterization of such a ureter may reveal a hydronephrosis that has not shown any clinical manifestations. He is one of the early workers to refer to the golf-hole appearance of the ureteric orifice, which he not infrequently found involved even in early cases. In another publication Fairley (1919b) drew attention to the obstruction occurring in a bilharzial ureter, but he also recognized the possibility of a hydronephrosis resulting from obstruction in the bladder-wall itself. In his experimental work on infected monkeys he found that the lumen of the lower third of the ureter may show dilatation and the wall considerable thickening. The dilatation results from obstruction due to thickening from the cellular infiltration of the wall in the neighbourhood of deposited ova.

Aly Bey Ibrahim (1923) published from Egypt an important paper on bilharziasis of the ureter. In it he refers to the very serious complication of stricture of the ureter. He writes: "The disease ends in the formation of fibrous tissue, which replaces the normal coats of the ureter. This leads to contraction and narrowing or even complete obliteration of the lumen of the lower part of the ureter. Secondary to this, the upper part of the ureter and pelvis of the kidney become dilated." Dew (1923), of Egypt, infers that the ureter becomes narrowed because of fibrosis and calcification, contraction ensuing fairly early in the disease. Hydronephrosis as a result is common. Also from Egypt, Hutchison (1928) refers to an ascending pyelitis and hydronephrosis resulting from stasis of the urine, occurring because of obstruction at the lower end of the ureter. Campbell-Begg (1944), writing on schistosomiasis in South Africa, refers to the occurrence of a tight fibrous stricture of the ureter which is found only in the minority of cases. Kirkaldy-Willis (1946), working in East Africa, mentions the possibility of obstruction in the lower ends of the ureters.

Procedure

Because of the prevalence of urinary bilharziasis in Southern Rhodesia investigation into the incidence of stricture and other possible effects of the disease in the ureter was not difficult. Mashonaland, where the work was done, is a highly endemic focus for both the urinary and the intestinal forms of the disease. Bilharzial disease there is essentially a disease of childhood, acquired by exposure of children in the Native Reserves to infected waters. In fact, in some districts haematuria in a child is regarded almost as a normal phenomenon, and little notice is taken of it. By the time adult life is reached it is safe to assume that the

individual has had the disease for a number of years, and complications in the ureter can be expected.

Adults were therefore chosen for this investigation, as naturally it would take a few years for complications to arise. In all, 110 consecutive cases showing urinary bilharziasis were examined. The vast majority of these were men between 20 and 50. The technique adopted at necropsy was as follows.

After the liver had been removed each kidney was carefully taken out, together with its ureter as far as its lower third in the pelvis. The bladder was then removed below the prostate from its connexion with the urethra and carefully dissected free from the rectum and in women from the uterus. Finally, the lower third of each ureter was dissected out. In other words, the whole bladder, ureter, and kidneys were removed *in toto*. The bladder was then opened with a sharp pair of scissors through the urethral orifice, the incision being continued upwards through the anterior wall, thus exposing to view the fundus (base) and below the trigone.

After the bladder was inspected for signs of schistosomiasis the ureteric orifices were identified and a narrow probe (2 mm. in diameter) was passed up the whole length of the ureters. A stricture was considered to be probably present when a sense of obstruction, tightness, or a complete hold-up of the probe was encountered. Later it was found easier and quicker to open the ureter just below its junction with the pelvis and to pass the probe down into the bladder.

With this method a number of apparent strictures were first encountered in some cases as the probe would not pass beyond a certain point. When, however, the ureter was opened along its length from its bladder orifice to the pelvis most of these hold-ups were found to be due to sacculations, dilatations, or tiny pouch-like distortions in the wall. Only in a few cases was a true reduction in the normal lumen of the ureter demonstrable.

After each ureter was opened its inner surface was carefully inspected for bilharzial patches. In each case the circumference of the ureter was measured at about $1\frac{1}{2}$ in. (3.75 cm.) from its orifice into the bladder. It was found that the normal circumference (as determined in those free of any bilharzial disease) varied from about 5 to 11 mm., with an average of about 8 mm. This site was selected as the disease chiefly affects this portion of the ureter. Other areas were measured, depending on whether disease was found. By this means I was able to determine whether the ureter was narrowed, dilated, or unaltered.

Results

Dilatation was found in the ureter in 25 of the 110 cases, three others showed stenosis or stricture—that is, reduction in the normal circumference—one case had the lower end of a ureter blocked by a small phosphatic calculus, and in three cases both ureters were dilated because of obstruction produced at their lower ends by an infiltrating carcinoma of the bladder associated with bilharziasis.

In 16 of the 25 cases the dilatation was unilateral: in six of them the dilatation affected the whole length of the ureter, in five it was present in the middle and lower thirds, and in five only the lowest third was dilated. In nine cases the dilatation was unilateral—in two being present throughout the length, in four confined to the middle third, and in three confined to the middle and lower thirds of the ureter.

Occasionally those portions of the ureters much dilated by the disease may show one or more narrow constricting fibrous-tissue bands running horizontally, but the lumen at these points was always greater than normal. Two such cases in the above-mentioned series were encountered.

The disease in the ureter can, as a rule, be easily identified, as the patches have a distinctive colour and the mucosa is roughened as if it were sprinkled over with fine sand. The colour of the patches varies from light brown, yellowish or greenish brown, to darker brown or a dark-

brown discoloration. They have a roughened feel. In other cases tiny tubercles, like sago grains, are seen, whereas in still fewer cases flattish or even pedunculated "papillomata" are found in addition.

The usual site of the disease was the lower third of the ureter. The dilatation was therefore generally found in this portion, but also not infrequently in the middle or upper third of the ureter. In some cases the dilatation was uniform throughout its length. A very important and interesting observation was that the dilatation was present only where the bilharzial disease was found. Where the ureter looked normal no dilatation could be demonstrated.

If stricture were the cause of dilatation one would naturally expect all portions of the ureter above the obstruction to be dilated, and not, as these cases showed, only at the diseased site. Further, the dilatation often varies from point to point, depending on the local effect of the disease. Thus the ureter becomes corrugated and irregular in its course. In a severe case the ureter may be thrown into folds or assume an S-shaped bend at one or other point. Therefore when a probe is passed upwards it is liable to encounter such a bend or be held up in one of the tiny pockets or corrugations, thus simulating stricture.

To determine the presence of hydronephrosis each kidney was bisected and the size of the pelvis and its calices was noted. So as to exclude urethral obstruction as a cause of hydronephrosis a curved metal sound was passed up the urethra into the bladder. In no case with hydronephrosis was such an obstruction demonstrated. In the series there were eight cases in which hydronephrosis was observed. Four of the 25 cases showing dilatation of the ureter were affected by hydronephrosis (bilateral). One of the three cases of stenosis or stricture showed hydronephrosis on the side of the narrowing (this case also showed dilatation of other parts of the ureter by the disease). All three cases of carcinoma of the bladder were associated with bilateral hydronephrosis due to obstruction of the lower portions of the ureter by the growth.

Of the three cases showing narrowing or stenosis of the lumen of the ureter two did not have any hydronephrosis, but one showed early hydronephrosis on the right side. In its upper two-thirds this ureter was dilated by disease to a circumference of 14 mm. and in its lower third to a similar extent; but in between these two dilated portions was a narrowed portion with a circumference of 8 mm., through which the probe passed easily. The left ureter was dilated by the disease in its lower third. In another of the cases accepted as stricture the probe was held up in the middle third of the left ureter. On opening this ureter a fine fibrous stricture was found. This was the only stricture which held up the probe. In the third case of stricture there was a narrowing at one point to 8 mm. in the middle third of the right ureter, with dilatation above (28 mm.) and below to 20 mm. The probe easily passed up the ureter.

One case of bilateral hydronephrosis was interesting. Although there was bilharzial disease of the bladder and ureters, the latter opened into the apex of the bladder, the orifices being only about $1\frac{1}{2}$ in. (1.25 cm.) apart. The bladder mucosa between the orifices was considerably reticulated and thickened. The ureters were markedly thickened and dilated. The intravesical parts of the ureters were dilated (14 mm. right and 11 mm. left). In this case the hydronephrosis could be explained by the congenital anomaly of the ureteric openings.

The dilatation of the particular part of the ureter affected is usually caused, so far as this study shows, by the disease itself. Owing to infiltration of the wall the affected portion dilates and rarely stenoses, as is commonly thought. As

a rule not only is the ureter dilated by the disease but there is well-marked thickening of the coats of the tube by fibrous-tissue formation. This causes the ureter, when removed, to appear somewhat rigid and elongated.

A number of the dilated portions of the ureters affected by bilharziasis were examined histologically. Ova were found not only in the submucosa but also in between the muscle bundles in the muscular layer. The ova are often seen lying together in clumps with a varying amount of fibrous-tissue and inflammatory reaction. Such fibrosis may be slight. This is in striking contrast to the pathological processes in the appendix, where tubercle formation is often observed. It seems to me, therefore, that as a result of the deposition of eggs in the muscle layers the muscle bundles are separated, atrophy ensues, and eventually dilatation sets in. The affected part of the ureter thus widens, elongates, and becomes tortuous.

The ureteric orifice may or may not show changes. In none of the cases in this series was the lumen of the orifice occluded or so narrowed as not to allow the probe to pass with ease. In many of the cases the orifice is widened, producing the golf-hole appearance. In some cases the orifice itself appears smaller than usual, whereas in others it is not easy to find owing to the surrounding disease of the bladder mucosa. In such cases passing the probe downwards in the ureter from above will assist in locating it.

Comments

My results reveal certain interesting points, and if corroborated by others might cause the present-day treatment of bilharzial ureteric disease to be reviewed.

While stricture or stenosis of the ureter is encountered at necropsy, this finding is very much less common than I originally expected. Gelfand (1947) reported a series of 100 consecutive necropsy cases affected by vesical bilharziasis and found only one stricture but many dilated ureters. In one of the three cases showing stenosis in this second series hydronephrosis was present. I do not state that stricture or stenosis is not serious and does not occur in practice or that cases of hydronephrosis due to it are not found. I have seen such cases, but I consider that they are comparatively rare.

My experience goes to show that dilatation of the ureter by the disease is far more common than stenosis or stricture. Such dilatation is usually associated with thickening of the wall of the ureter, which also becomes elongated and tortuous. This effect is usually well demonstrated radiologically. The functions of such a ureter will become impaired, peristalsis will be diminished or lost, and hence urine would not be properly propelled towards the bladder. As a result stasis will follow, and with it some degree of hydronephrosis. This may not be the only explanation of hydronephrosis in cases showing only dilatation of the ureters. Another possible explanation for some of these cases may be a reflux of urine up an incompetent ureteric orifice during micturition, when the bladder actively contracts. Owing to the dilatation produced by the disease the sphincteric function of the intravesical portion of the ureter is lost or impaired. The hydronephrosis due to such loss of sphincteric function probably explains some of the cases of hydronephrosis seen in prostatic disease (Hughes, 1946).

The ureter when it dilates also lengthens and "unfolds" itself. This "unfolding" may cause the ureter in the particular portion affected to assume an S-shaped curve or bend, thus simulating stricture. This was seen in one of the 25 cases reported with dilatation of the ureter. The right ureteric orifice protruded about 2 mm. beyond the

bladder mucosa. The orifice itself was dilated (6 mm.). The tube could be passed neither from below nor from above, and a stricture was held to be responsible for this. However, on opening the ureter the intravesical portion was dilated owing to disease, its circumference being 11 mm. as compared with 8 mm. on the opposite side. The intravesical portion of the ureter had elongated and hence its orifice protruded beyond the bladder mucosa; the rest of it had become "folded," so to speak, upon itself, causing an obstruction.

Recently Dr. N. Barlow, of the Southern Rhodesia Government Medical Service, was able to demonstrate such a reflux in one of my ward cases. The patient, an African male, passed ova of *Schistosoma haematobium* in his urine, and an intravenous pyelogram revealed a well-marked dilatation of the lower end of the right ureter. Dr. Barlow filled the bladder with "uropac" and then instructed the patient to empty his bladder. An x-ray film taken before and after micturition revealed that some of the dye had passed up the ureter from the bladder. In this case there was no evidence of a hydronephrosis on the affected side.

Summary

A series of 110 consecutive necropsies were performed on African adults found to have bilharzial disease of the bladder.

In 25 cases the ureters were dilated by the disease.

Stenosis or stricture of the ureter was found in three cases.

Hydronephrosis was found in three cases showing dilatation of the ureters and in one of the cases affected by stenosis of the ureter.

Possible explanations for the hydronephrosis in the presence of dilated ureters are advanced.

I would like to express my thanks to Dr. R. M. Morris, Medical Director of Southern Rhodesia, for permission to carry out this investigation and to publish my findings. Dr. Graham White rendered invaluable assistance in the mortuary.

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Dr. Evang, Chief Medical Officer of the Norwegian Public Health Service, has recently been advocating health passports for all. Often, when questioned by his doctor, the patient recalls a tuberculin test but cannot say whether it was positive or negative; his blood pressure was measured recently but he does not know what it was; he has undergone an abdominal operation but is blissfully ignorant of what it revealed. In the autumn of 1946, Dr. Evang set up a committee to study the whole problem of health passports. A year later this committee reported, and the type of health passport it recommends is issued as a supplement to the May 1 issue of *Tidsskrift for Den Norske Lægeforening*. It is a modest 16-page booklet measuring about 6 inches by 4 (15 by 10 cm.). Dr. Evang's committee recommends the issue of this booklet to everyone on leaving school. It is not necessary to provide a similar document for children because their ailments are recorded by the school medical service. The booklet provides a record of diseases in the family and of such children's diseases as whooping-cough. In it are also to be recorded height and weight; blood and urine tests; examinations of the eyes and ears; vaccinations against smallpox, diphtheria, tuberculosis (B.C.G.), and other diseases; tuberculin tests and radiological examinations of the lungs; doctors' reports and hospital records with the name and address of the hospital and the nature of the disease for which treatment was given. Disabilities due to disease or injury are also to be entered in this miniature medical biography.