THE SURGICAL PATHOLOGY OF BILHARZIASIS*

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This continent of Africa is not only heir to those diseases common to man throughout the world, but serves as the repository of special parasitic diseases widespread throughout this vast land. Of these none is so prevalent, so refractory to prophylactic control and so insidious in its clinical progress as bilharziasis. It has been estimated that over 100 million human beings in Africa suffer from schistosomiasis, and if regard be given to its general and visceral effects it becomes clear that this disease provides the greatest challenge to preventive medical endeavour on this continent.

The schistosomal trio clinically important to man are *S. haematobium*, whose main habitat is in the urinary system, *S. mansoni*, which has a special predilection for the digestive system, and *S. japonicum*, which exists, with its intermediate snail-host the *Oncomelania nasophora*, in Japan, China and the Phillipines. The fresh-water snail is the essential intermediate host in the life-cycle of the schistosoma; the species *Physopsis africana* of the genus Bullinus being the main intermediate host for *S. haematobium*, whilst the *Biomphalaria pfeifferei* of the genus Planorbis is similarly the intermediate host for *S. mansoni*.

S. haematobium is rarely found outside the African continent, whilst *S. mansoni* exists not only in Egypt, East and West Africa and Madagascar alongside haematobium, but as the sole form of schistosomal infection in South America and the West Indies. Bilharzial infestation in Africa occurs in a wide belt, extending along the Nile into the Sudan, along the East coast including Eritrea and Somaliland into Uganda, Tanganyika and Kenya and spreading centrally into the Belgian Congo. The Central African Federation of the Rhodesias and Nyasaland is heavily infested, and the establishment of vast water conservation schemes and irrigation networks and its rapid industrialization will undoubtedly increase its incidence for, despite measures aimed at killing the snails in the water courses of the affected areas and early diagnosis and treatment of human victims, it is unlikely that this disease will be contained until a natural biological antagonist to the snail is found and developed. Mozambique and the Eastern half of South Africa (Transvaal and Natal) also suffer bilharzial infestation, the belt extending to the Cape. Similarly affected are portions of Nigeria, Ghana, French West Africa, Algeria, Morocco and the Middle East.

The sexually distinct, digenetic trematodes of the schistosoma family inhabit the portal system of the human victim of the disease. The 11-mm.-long male worm is shorter and broader than the female of the species and widens just caudally to its ventral suckers to form a gynaecophoric canal, within which the female is enclosed in times of sexual activity. The conjoined couple travel against the course of the portal blood stream, the terminal-spined ova of *S. haematobium* reaching the vesical plexus to be deposited in bladder

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and lower ureter, whilst the lateral-spined ova of *S. mansoni* are deposited mainly in the colon and rectum.

Many eggs are voided in the urine or faeces, and perpetuation of the life cycle becomes contingent upon their reaching the intermediate host within 24 hours. With disintegration of the chitinous shell of the ovum, its contained miracidium is released to penetrate into a snail, where it develops through the sporocyst stage into the bifid-tailed larval cercariae. The cercariae leave the snail and coming into contact with the skin or mucous membrane of man, pierce the lymphatics to reach the venous system and are thence distributed to their ultimate visceral locale.

During this 4-6 week period of migration, systemic disturbances often referred to as the Katayama syndrome are common. General ill-health, malaise and proneness to fatigue may be complained of, whilst recurrent bouts of pyrexia, urticaria, transient pulmonary infiltrations, lymphadenopathy and enlargement of liver and spleen may be manifest. Haematological examination may disclose a normochromic or hypochromic anaemia associated with an eosinophilia of the order 10-60%. At this stage a positive cercarial skin test and a positive complement fixation test may elucidate the clinical problem and permit of early commencement of a curative course of systemic antimony therapy.

THE VISCERAL LESION

I should like here to consider the irreversible effects of visceral bilharziasis and the surgical implications involved. It is as well to appreciate that apparent cure of schistosomal infestation with the trivalent antimony preparations is no guarantee that the patient who has suffered visceral ovideposition will not present, months or years later, with effects of luminal distortion or obliteration.

Ovideposition initiates a constant pathological pattern, details and variations depending upon the intensity and duration of the infection. Though ova are generally deposited in the submucous and subserous layers, no visceral layer is immune from its effects. The ova initiate an inflammatory foreign-body reaction, resulting in intense engorgement of the surrounding capillaries and causing local oedema and hyperaemia. The cellular response is not long delayed and focal aggregations of lymphocytes, monocytes and eosinophils collect round each ovum. Though the arrangement of the cells is irregular at first, they soon form a concentric ring round the ovum with the eosinophils retaining prominence. The hyperaemia gradually resolves, the capillaries undergoing endarteritic changes. Central necrosis follows, the ova becoming unrecognizable or undergoing hyalinization and calcification. Large multinucleated giant cells make their appearance, their nuclei having an irregular distribution throughout the cellular protoplasm. This basic cellular reaction results in the formation of bilharzial tubercles due to conglomeration of these microscopic complexes. Fibrosis and calcification of these localized tubercles provide the 'sandy patch' appearance so pathognomonic of the visceral lesion. Coalescence of many tubercles gives rise to a large avascular mass, comparable to the gumma of syphilis or the tuberculoma of Koch's bacillus, so that this bilharzial granuloma may well be referred to as a bilharzioma.

The tendency for mucous membranes to form projections in response to irritation is well known, and this tendency is well exemplified in the papillary formations which develop in the urinary and alimentary tracts in response to continued irritation by bilharzial ova. These papillary projections may bleed or ulcerate, ulceration sometimes extending to produce sinuses and fistulae.

The round-cell infiltration earlier described is soon followed by the appearance of fibroblasts, which lay down a fine fibrous reticulum that rapidly matures and, involving all the coats of the affected viscus, may cause partial or total obliteration of its lumen. Deposition of calcium, though variable in degree, may be a very prominent feature.

THE URINARY SYSTEM

The Bladder

The urinary tract is peculiarly susceptible to ovideposition by *S. haematobium*. The vesical irritant sets up a local inflammatory reaction which may be visualized early in the disease, at a stage when microscopic examination of the urine will show it to be teeming with terminal-spined ova and red cells, cystoscopic examination of the bladder then disclosing an intense hyperaemia and oedema of the periureteric vesical mucosa. In the course of the subsequent 6 weeks greyish tubercles become discernible on the trigone of the bladder and around the ureteric orifices, a fine zone of hyperaemia often still persisting round some of the tubercles. Urinary microscopy, at this stage, often fails to disclose ova, though leucocytes and pus cells may be present. Cystoscopic biopsy of a tubercle will permit histological confirmation of the diagnosis. Though haematuria, dysuria or the effects of superposed cystitis may be the presenting features, prolonged lassitude, backache or a persistent eosinophilia may often be the only clinical indication of bilharzial infestation, cystoscopy being necessary to demonstrate the presence of vesical ovideposition. Blockage of the vesical submucous glands consequent upon the inflammatory reaction results in the formation of pale bullous cysts, which are seen at cystoscopy to be arranged focally or in clusters. Occasionally the appearance is that of cystitis cystica.

Cystoscopic control during systemic antimony therapy permits assessment of the degree of local response and assurance that the lesions are reversible. After completion of treatment the affected vesical mucosa bears a permanent golden-yellow punctate appearance due to the deposition of cholesterol esters in the healed and fibrosed follicles.

With progression of the bilharzial cystitis, the vesical epithelium becomes heaped up into papillary projections by the vascular granulation tissue which develops. It is, I believe, wrong to refer to these papillary masses as papillomata, for these masses are neither neoplastic nor do they have the malignant propensities of true papillomata. They respond extremely well to a combination of systemic therapy and local fulguration, so that the term papillary bilharzioma adequately defines the inflammatory nature of the lesion.

Ulceration of the bladder, although not usually a prominent feature, may extend widely and deeply to penetrate adjacent structures. As malignant vesical ulceration may co-exist with bilharzial cystitis, it is wise to perform histological study of a biopsy of the ulcer before commencing systemic treatment. Massive vesical ovideposition may result in a chronic interstitial cystitis, producing a small contracted bladder and corresponding back pressure effects.

Vesical and, occasionally, ureteric calcification follow heavy local infestation. The calcification is mainly confined

to the submucous and muscular layers and, being arranged concentrically, provides a radiological similarity to a foetal head *in utero*. Phosphatic incrustation of the bladder mucosa may occur as a result of secondary infection with urea-splitting organisms.

If one takes into consideration the fact that bilharziasis in the Salisbury region affects 10% of the European population and 80% of the Bantu community, and if cognisance is taken of the fact that the African presents with far-advanced pathological sequelae in his urinary tract, it would be anticipated that urinary calculi would occur frequently in the African. Yet amongst 66,842 consecutive African hospital admissions between March 1949 and March 1955, there were only 14 cases with urinary calculi, an incidence of 0·02%. Amongst 28,547 consecutive European hospital admissions during this same period there were 84 cases with urinary calculi, an incidence of 0·28%. It may be recalled that when McCarrison investigated the cause of the high incidence of urinary calculi in Southern India, he demonstrated that a high dietary calcium and low vitamin-A content were the most important aetiological factors. It is, therefore, interesting to find that an analysis by Fox of the African dietary showed it to be low in calcium content and variable in vitamin-A content, and to provide an acid ash residue.

It is, accordingly, not illogical to infer that urinary stagnation and sepsis is less important in the pathogenesis of urinary calculi than maintenance of an acid pH in the urine and a low calcium excretion.

There has been much difference of opinion regarding the aetiological relationship between bilharzial infestation and carcinogenesis and my own view is that bilharzial ova do not exert a focal carcinogenic effect, despite the fact that chronic bilharzial cystitis and vesical carcinoma not infrequently co-exist. If bilharzial ova could exert a focal carcinogenic effect it would surely exert this effect in other organs where ovideposition is common. Similarly it might be anticipated that vesical carcinoma due to bilharzial irritation would be a squamous-cell type, yet the usual pattern of carcinoma, in the cases I have studied, has been of an anaplastic cellular type. I have also observed that the maximal cellular proliferation and anaplasia often occurs where ova are absent or exist in minimal concentration, so that the impression is obtained that the fibrosis induced by the ova keeps at bay the cellular advance. Recent studies of tryptophane metabolism has suggested that excretion of unconjugated hydroxy-anthranilic acid in the urine may initiate vesical malignancy and similar studies in patients with chronic vesical bilharziasis may serve a useful purpose.

The Ureter

Ovideposition in the lower ureter is followed by an inflammatory response which, as elsewhere, is characterized by early infiltration by monocytes, lymphocytes and eosinophils. The cellular infiltration and vascular granulation tissue which develops causes a disintegration of the muscle layers, with vacuolation and hyalinization of the muscle fibres. Fibroblastic activity follows and the ensuing ureteric ulceration and fibrosis leads to varying degrees of cicatrization, stricture and obliteration of the affected portion of the ureteric lumen. Back pressure, and secondary infection produces varying degrees of hydronephrosis, pyonephrosis or ascending pyelonephritis.

I have indicated above that the earliest vesical involvement occurs in the periureteric region, and it may accordingly be anticipated that cicatrization and fibrosis at the ureteric orifice would result in stricture or obliteration of that orifice. This not infrequently occurs, but occasionally the traction effects of peri-ureteric fibrosis results in the production of a gaping 'golf-hole' ureteric orifice not unlike that seen in tuberculosis. Such an orifice may exist unilaterally or bilaterally, or may be associated with stenosis of the contralateral side. The resultant incompetence of the ureterovesical mechanism will permit reflux of urine up the ureter and augmented by superposed sepsis gives rise, in progressive manner, to one form of bilharzial mega-ureter and hydronephrosis.

Intrinsic ureteric lesions are generally confined to the lower one-third of the ureter, though concomitant strictures may exist more proximally, and the degree of pathological change will determine whether ureteric stricture or ureterectasia will occur. By ureterectasia I mean a primary focal dilatation in the lower ureter, unassociated with distal obstruction or uretero-vesical incompetence. It is a lesion which is caused by the constant stress imposed by the propulsion of urine on an area weakened by fibrous-tissue replacement of the destroyed contractile muscle layer. This localized dilatation results in varying degrees of neuromuscular incoordination in the ureteric propulsive effort, and progressive dilatation occurs in a cephalad direction. Whether ureteric stricture or ureterectasia will develop in a case of bilharzial ureteritis depends on the degree of destruction of the muscle layer and the quality and quantity of the fibroblastic reaction.

Bilharzial mega-ureter and hydronephrosis may thus follow ureteric stricture confined to the orifice or to the pelvic ureter; it may be a sequel of ureterectasia or of ureteric calcification; it may result from uretero-vesical incompetence, or it may be caused by back pressure from a small-capacity bladder.

Assessment of the extent of structural and functional disturbance in the urinary system naturally requires a comprehensive investigation. Urinalysis will disclose the presence or absence of active bilharzial infection, as well as the nature and drug sensitivity of any secondary infecting agents. Cystoscopy is necessary to assess the extent of vesical involvement and to gauge the degree of ureteric implication, appropriate instrumentation being carried out at this time. Biopsy of any suspicious area is performed, whilst the intravenous injection of 0·4% indigo carmine permits an immediate assessment of renal function.

Radiological examination is never omitted, straight X-ray of the abdomen and intravenous and retrograde pyelography demonstrating the architectural pattern of the diseased urinary tract. Cystography permits evaluation of the degree of uretero-vesical incompetence and reveals the presence of ureteric reflux.

Estimation of the blood non-protein nitrogen and blood urea provide a satisfactory guide to the functional efficiency of the kidneys.

The aim of surgical treatment is to provide the greatest degree of relief from the irreversible effects of urinary bilharziasis. Naturally, active bilharzial infection must receive an effective course of antimony therapy before any operative manoeuvres are commenced, whilst appropriate control of secondary urinary infection will often prevent or hold in check progressive structural changes.

Cystoscopic meatotomy of the stenosed or cicatrized ureteric orifice, followed by regular bougie dilatation, may confer great benefit on the patient, whilst ureteric bouginage often controls stricture of the lower ureter and prevents back-pressure effects. Bouginage, however, is useless in ureterectasia, so that an early decision should be made to resect this segment of ureter if recurrent sepsis or back-pressure effects ensue. Similarly, ureteric resection is carried out if a stricture is impassable or repeated dilatations prove ineffectual. After resection of several inches of lower ureter I have always found it possible to perform a uretero-cysto-neostomy, but should excessive tension prevent anastomosis it is well to be prepared to bridge the gap with a length of ileum. Transplantation of the ureters into the pelvic colon would be indicated if a completely disorganized bladder with internal or external fistulae existed, whilst ileocystoplasty may permit an increase in bladder capacity where this is desirable. Nephrectomy or nephro-ureterectomy may have to be performed on its merits, but one must be absolutely certain that the contralateral kidney is not affected by progressive disease. Nephrostomy or pyelostomy may be a necessary preliminary manoeuvre to improve the function of the kidney on that side before excision of the strictured distal ureter can be considered.

THE ALIMENTARY SYSTEM

Bilharzial Appendicitis

The appendix is one of the organs that frequently suffers the deposition of bilharzial ova. It is interesting to note that in 92% of appendiceal bilharziasis, the *S. haematobium* is the infecting agent and this, no doubt, explains the not infrequent association of a mixed urinary and appendicular clinical pattern. From clinical, operative and pathological assessment of this condition it has become clear that the relationship between the appendix and bilharzial infection may take 2 forms:

1. Appendiceal bilharziasis. Ovideposition occurs in the appendix, as it may also in the gall-bladder, pancreas or other viscera, and undergoes the natural healing process without involvement of the lumen or the development of a granuloma.

2. Bilharzial Appendicitis. This is a true clinico-pathological entity which results from partial or total obliteration of the lumen. The obstructive effect of partial obliteration of the lumen not infrequently predisposes to the complication of acute pyogenic appendicitis with abscess formation, gangrene, perforation and peritonitis.

Ovideposition results in the customary cellular response; at laparotomy tubercles are visible to the naked eye on the serosal aspect of the appendix and may also be seen in the meso-appendix, on the caecum, and on adjacent viscera, viz. bladder, uterus, tubes and ovaries. Extension and conglomeration of submucous lesions leads to the destruction of lymphoid follicles and their replacement by fibrous tissue, with distortion, narrowing or obliteration of the lumen. Ulceration of the mucosa is often in evidence, while superposed pyogenic infection, acute or subacute, may occur distal to the luminal distortion.

Progression of the fibro-cellular reaction in the serous and subserous coats may result in the formation of a large granulomatous mass attached to the appendix, or the appendix may be incorporated in the granulomatous process, resulting in a mass 3-4 cm. in diameter.

The pathological technique in the demonstration of visceral schistosomiasis requires some mention. Examination of the appropriate tissue or organ will, in a high proportion of cases, demonstrate not only the characteristic fibro-cellular reaction to the ova, but will also permit recognition of hyalinized, fibrosed or calcified degenerate ova. To permit recognition of ova in all cases, however, it is necessary to digest the organ in 10% caustic potash at 60°C for 10 hours before examining the residue for ova.

There is little need to recount the well-known clinical features of chronic appendicitis. Suffice it to state that the patient may present with chronic appendicular dyspepsia, with persistent pain in the right iliac fossa, or with the features of acute appendicitis. Special mention, however, needs to be made of the not infrequent association of diarrhoea and the occasional manifestation of melaena with the appendicular syndrome, for these features may cause diagnostic difficulties. Other causes of these latter symptoms must, of course, be excluded. Appendicectomy performed for the relief of appendicular dysfunction in these cases also cures the episodic bouts of diarrhoea and melaena, pathological examination demonstrating the bilharzial involvement of the appendix.

Bilharzial Colitis and Proctitis

S. mansoni has a great predilection for the part of the alimentary system that is drained by the inferior mesenteric vein. The earliest changes visualized sigmoidoscopically are those of a congested haemorrhagic mucosa which bleeds rather readily. Shallow rounded or oval ulcers surrounded by normal intervening mucosa may be seen and biopsy of these areas invariably permits identification of the causative ova, even on occasions when stool examinations are negative. Bilharzial colitis or proctitis is a potent source of diarrhoea, which may be very severe, with pus and blood in the stools, if ulceration of the bowel is very extensive. Proliferative fibro-cellular changes may give rise to pseudo-polypi not unlike those seen in ulcerative colitis, but there are no indications that these lesions are premalignant. A bilharzial granuloma of the rectum may attain a large size, making its clinical differentiation from carcinoma almost impossible. Histological examination of a biopsy specimen with demonstration of ova, and the therapeutic response to systemic therapy naturally solves the diagnostic problem. Similarly the presence of ulcerative or proliferative peri-anal or perineal lesions, occurring in people coming from bilharzia-infested countries, should suggest a bilharzial origin.

Genital Bilharziasis

Though minor evidence of ovideposition is often encountered in the tubes, ovaries and broad ligaments, occasionally frank pathological sequelae may develop in vulva, vagina, cervix or tubes. Chronic bilharzial salpingitis may present as a paratubal granuloma or tubo-ovarian mass which is clinically palpable, or it may cause symptoms because of partial or total obliteration of a tubal lumen. Submucous ovideposition may lead to a progressive disorganization of the mucosal, muscular and serosal layers with narrowing or obliteration of one or both lumina. Naturally, sterility results when both tubes are completely obliterated, but partial obliteration of a tube by bilharzial fibrosis may predispose to ectopic gestation. Bilharzial involvement of the vagina and cervix not infrequently occurs in the African, the present-

ing leucorrhoea reflecting either an area of hyperaemia, an ulcer, or a papillary bilharzioma. A proliferative lesion of the cervix may very readily be mistaken for carcinoma. Lesions of the vulva may manifest themselves either as an exuberant granuloma or as an area of ulceration involving the vestibule or clitoris. Diagnosis naturally depends on the finding of ova in the scrapings or section.

It is a well-known fact that one of the earliest clinical manifestations of urinary tuberculosis in the male is a tuberculous epididymitis. In great contrast to this, however, is the relative rarity of male genital bilharziasis. Nevertheless, bilharzial disease of testicle, cord, prostate, seminal vesicles and urethra do occasionally occur, and the possibility of such lesions should always be kept in mind.

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