THE CLINICO-PATHOLOGICAL MANIFESTATIONS OF SCHISTOSOMIASIS IN THE AFRICAN & THE INDIAN IN DURBAN

THESIS

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by

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CHAPTER I

INTRODUCTION

Schistosomiasis, or Bilharziasis, as a disease, has been recognised from the time of the Pharoahs of ancient Egypt. Shortly after the momentous discovery of the parasitic worms in man by Theodor Bilharz in 1851, Harley (1864) in South Africa demonstrated the presence of terminal-spined ova in the urine of patients around Grahamstown in the Cape, thereby showing that the disease was prevalent in South Africa. In fact the disease was encountered often enough and thought to be sufficiently serious a problem to merit a full discussion at a medical congress in Grahamstown as early as 1896 (Anon: 1934).

The investigations and discoveries concerning Bilharziasis in Europe, Egypt, Japan and South Africa were followed

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with interest by South African observers and workers who were themselves engaged on the same problems. Numerous articles in the early medical literature attest to this view. The discovery of the intermediate hosts of the schistosomes by Leiper (1915) was welcomed by an editorial in the Medical Journal of South Africa in 1916 whose concluding paragraph exhorted its readers to inform the editor of infected pools or rivers " - as a preliminary to the campaign for the eradication of the disease from the Union" (Anon, 1916).

In 1918 the Pretoria branch of the British Medical Association passed a resolution " - to bring to the notice of the M.O.H. for the Union the advisability of taking measures for dealing with the prevalence of the disease known as Bilharzia, so marked in some parts of South Africa" (Anon, 1918).

In a cursory urine-examination in some Natal Indian school children, Kay Sharp in 1925 revealed an incidence of up to 15% in some areas, demonstrating that Bilharziasis was not an uncommon infestation. The measure of concern which the medical profession had for the increasing problem of bilharziasis may be gauged from the fact that it was once again the main subject of discussion at a medical conference in South Africa in 1934.

Pijper (1934) was the first South African worker to suggest that the disease as manifest here may differ from that in Egypt. He commented that kidneys, ureters and urethras were hardly ever heavily infected and that papillomata, fistulae and carcinoma of the bladder due to bilharzia were rare and that " - the formation of strictures in the urinary organs due to bilharziasis are rather a curiosity. The harm done by urinary bilharziasis in most cases amounts to little more than a periodic loss of blood". He emphasised then that the apparent increase in the incidence of the disease might have been an impression due to the medical profession having become better informed and concluded: "Perhaps we are somewhat overdoing it, and are needlessly treating many persons".

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However, a few years later Vermooten (1937) disagreed with the view of Pijper and clinically demonstrated severe bilharzial involvement of the bladder and upper urinary tract. He was of the opinion that bilharziasis produced severe renal pathology.

This early divergence of opinion as to the clinical importance of bilharziasis has persisted to the present day and summarized succintly, though unintentionally, in the first report of the Expert Committee on Bilharziasis (Anon, 1953) as: "Infection with Schistosoma is often well tolerated and without clinical signs. However, this relative benignity appears to vary considerably from country to country without the cause of these variations being as yet thoroughly understood".

Earlier Gelfand (1950), and Symmers (1951), had cast doubt on the claims of Egyptian and South American workers of the bilharzial origin of "pipe-stem" cirrhosis of the liver and bilharzial hepatic fibrosis. Gelfand (1950) was also sceptical of the relationship between bilharziasis and carcinoma of the bladder.

The first African Conference on Bilharziasis in 1957 agreed that "there is no valid evidence of a relationship between S. haematobium infection and cancer of the urinary bladder in Africa south of the Sahara" (Anon, 1957), yet at the Second African Conference on Bilharziasis in 1960 delegates accepted that: "There is also some association between intensity of bilharzial infection and the occurrence of squamous carcinoma of the bladder" (Anon, 1960).

In 1954, Elsdon-Dew referred to Bilharziasis as "Africa's most vicious helminth enemy ..... ", but four years later (1958) doubts had crept in sufficiently for him to inquire: "Because Bilharzia puts up a 'red flag' and thus makes its presence known, is it doing more damage than the self-effacing round worms?" He wondered whether there may not have

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been more deaths due to the treatment of Bilharziasis rather than from the parasite itself (Elsdon-Dew, 1958). A further three years later he was of the opinion " - that many, if not the majority, of humans harbouring these worms suffer little, if any, disability" stating that, "were it not for these red flags flown by urinary Bilharziasis, it is not unlikely that the majority of such cases would be missed altogether" (Elsdon-Dew, 1962). Earlier Elsdon-Dew quoted Professor E.B. Adams, Professor of Medicine at Natal University, Durban, "as considering the morbidity due to Bilharzia as negligible in the African, despite an incidence of urinary and alimentary infection of well over 50%" (Adams, 1957).

Kark (1960) considered that the surgical aspects of bilharziasis constituted a serious problem in Durban and that although the disease had been regarded as benign by some, he found complications of the disease in the form of strictures and carcinoma of the bladder in an early age group. Chapman (1964) confirmed the view of Kark by his own experience and observations.

Similarly, da Azevedo et al. (1954) regarded the ill-effects of bilharziasis in Mozambique as slight, yet de Morais (Anon, 1960) a few years later demonstrated serious and numerous complications. At the Second African Conference on Bilharziasis (1960) an earlier view (Anon, 1953) was partially modified in that: "Now in 1960, it is regarded as detracting seriously from health in some countries, as an infection of moderate significance to be considered in the company of many of equal importance in others and as of minor or negligible importance in a few" (Anon, 1960).

Honey & Gelfand (1960) conceded that whereas 15-20 years ago the disease had been considered benign, clinical and pathological observations had led them to accept that Bilharziasis produced serious complications.

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From the above discussion it is apparent that in addition to regional differences, different observers in the same region, and even the same observers in the same region but at different times, hold divergent views on the morbidity and pathology produced by, and the public health importance of Bilharziasis.

The disease is important when it produces irreversible changes "which always seriously detract from the ability and health of the individual, and in addition, expose him to considerable specific risks" (Anon, 1960). A further significant observation from endemic areas has been that of an increase in the prevalence of the disease in recent years (Anon, 1961) including that in South Africa. The increase in the incidence is understandable considering that public health measures have been almost completely ineffective and inappropriate.

This failure of public health measures against Bilharziasis coupled with the recent extensive programme of new water-conservation, irrigation and hydro-electric projects in the country provides the very conditions conducive to spread of Bilharziasis and " - with every extra mile of water will go the bilharzia snail with his 'quiverful of arrows', striking man down, and to put it at its lowest, making him an uneconomic unit" (Alves, 1957).

In spite of the wide divergence of opinion as quoted above, and the threat, real or apparent, of a sudden increase in the incidence of the disease, no comprehensive investigation of Bilharziasis from the clinico-pathological aspect has been attempted in South Africa. Kisner (1952) made an admirable study of the urological aspects of the disease in the Transvaal, and more recently Schneider (1958) has investigated aspects of intestinal schistosomiasis in Natal and Transvaal.

There is a considerable amount of literature from South African contributors on isolated aspects of the disease. However, in spite of the fairly prolific literature on other

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aspects, except for the work of Pijper (1934), there is no literature on the pathology of Bilharziasis. Nor has any serious attempt been made to correlate the symptomatology and clinical stage of the disease with the pathology as demonstrable in the necropsy room and with the histopathological features.

AIMS OF THE PRESENT THESIS

The purpose of this study is to correlate these various aspects of the disease processes produced by the two types of schistosomes - S. haematobium (the vesical form) and S. mansoni (the intestinal form). Furthermore, an attempt has been made to assess the importance or otherwise of these lesions in causing morbidity and mortality in the individual. By determining the incidence of morbidity in a community it is hoped to reveal the true public health importance of the disease.

In this study the clinico-pathological and morbid-pathological manifestations of the disease as encountered in the local population are compared with that reported in other major endemic areas thereby to elucidate qualitative differences if there be any.

Kisner (1952) from the Transvaal and Honey & Gelfand (1960) from Southern Rhodesia reported certain differences in urinary tract involvement in Europeans and Africans. Kark (1960) and Chapman (1964) suggested that a racial difference exists between Africans and Indians in the presentation and complications of the disease.

Durban, situated on the east coast of Natal, lies in an endemic area for schistosomiasis, both species, S. haematobium and S. mansoni being prevalent in this region (Fig. 1). The population of Durban of over half a million is made up of Africans, Europeans and Indians, most of the latter two being of

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second and third generations in Africa. Thus there is an ideal situation for a comparative study in the different races thereby illustrating any racial differences in the disease manifestations. Though it has not been possible to investigate the European population group, a comparative study of the disease in the local African and Indian populations has been undertaken in this work.

As indicated earlier, different workers and investigators in different areas, and in the same region at different times, investigating varying aspects of the problem, arrived at different conclusions. Thus it was essential for a single investigator, sufficiently trained in the various disciplines to correlate all the investigations, to present a unitarian concept of the disease, and to attempt to explain the variance of opinions of the numerous authors.

Consequently all material presented in this study has been investigated personally. The clinical examinations, special investigations, morbid pathology and histopathology have all been personally conducted and examined in consultation with specialists in each department.

H I S T O R I C A L S U R V E Y

INTRODUCTION

Ancient Egyptian literature contains numerous references to haematuria and prescriptions for its treatment. One of the earliest references is in the Ebers papyrus, which has been authoritatively dated to about 1550 B.C. The Berlin Medical papyrus and the Hearst papyrus also contain references to the disease. Certain passages in these ancient manuscripts suggest that the ancient Egyptians may have discovered the worm during embalming processes and realised its relationship to haematuria (Ward, 1954).

Further evidence for the existence of Bilharziasis in ancient Egypt was provided by Sir Armund Ruffer (1910). He demonstrated the presence of bilharzial ova in the kidneys of mummies of the 18th and 20th dynasties i.e. dated about 1250-1000 B.C. To quote Ruffer (1910) : " - in the kidneys of 2 mummies of the 20th dynasty I have demonstrated in microscopic sections a large number of calcified eggs of Bilharzia haematobia, situated, for the most part, amongst the straight tubules".

INVESTIGATION OF THE LIFE CYCLE

Despite the knowledge of the disease and its association to bathing in the Nile waters, it was only in 1851 that Theodor Bilharz, Professor of Zoology in Cairo, discovered the parasite. He found the worm in the portal veins of both man and experimental animals, and called the worm distoma haematobium.

In 1864, the same year that Griesinger (1864) suggested that the life cycle of the schistosome may require an intermediate molluscan host, Harley (1864) in South Africa observed terminal-spined ova in the urine of patients complaining of

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haematuria around Grahamstown. He named the disease Bilharzia Capensis in honour of Theodor Bilharz. Harley (1864) was of the opinion that the worm required to undergo metamorphosis several times from the embryo stage before assuming the adult form. Whereas workers in Egypt had reported both lateral- and terminal-spined ova in man, Harley found only terminal-spined ova.

About this time various investigators in many countries were studying the life-cycle and seeking the intermediate hosts of the Schistosomes.

Leiper (1915) gives an admirable review of the work done on the parasite up to that date. He quotes from the text book "Entozoa", by Cobbold (1864) as suggesting that larvae, in the form of cercariea, rediae and sporocysts, would be found in certain gastropod molluscs proper.

Sonsino (1874-1885), in spite of intensive efforts, failed to find the intermediate host, although he suspected that it might have been a crustacean.

Special investigating teams from Italy, France and Austria visited Egypt between 1893-1894 and attempted unsuccessfully to elucidate the transmission <u>via</u> intermediate hosts (Leiper, 1915). Subsequently Looss (1894) formulated the hypothesis that the disease was communicable directly from man to man and in spite of scepticism from the large majority of the investigators he restated his belief in 1908.

However, Manson (1914) in his book on "Tropical Diseases" wrote: "Analogy suggests that the miracidium passes into the body of some fresh-water mollusc, crustacean or larval arthropod, there to undergo developmental changes -". Lateral-spined ova were first demonstrated by Bilharz (1851) who did not realise their significance. Sonsino (1874-1885) regarded the two species as being distinct. Manson (1893) had considered that the intestinal and vesical forms of the disease were due

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to different species and in 1902 concluded that the terminal- and lateral-spined ova came from different species. Looss (1894 and 1908) however, opposed this view. Nevertheless, Manson (1902), Castellani (1902), Martinez (1904), Letulle (1904) and Turner (1910) demonstrated a different geographical distribution (and clinical presentation) of the worms with lateral-spined ova compared to the worms with terminal-spined ova. Consequently, in 1907 Sambon created a new species Schistosoma mansoni to distinguish the worm laying lateral-spined ova from Schistosoma haematobium with terminal-spined ova. Leiper (1915), from experimental evidence, subsequently confirmed the observations of Sambon and others.

Finally in 1913, two Japanese workers, Miyairi & Suzuki (1914) using the S. japonicum species (discovered by Katsurada, 1903 and accepted as a separate species in 1904) demonstrated the life cycle and the intermediate hosts of this schistosome species. Leiper and his co-workers (1915) confirmed these findings and demonstrated conclusively the life cycle and intermediate hosts of S. haematobium and S. mansoni in Egypt. They also supported the contention of Manson as to the differences between S. mansoni and S. haematobium.

In South Africa, where the disease was known to be present, keen interest was shown in the work of Leiper and this was reported in the local journal (Anon, 1916). South African investigators had also been engaged in efforts to demonstrate the life cycle of the local type of the parasite. Harley (1871) failed to infect rabbits and mice by feeding them ova of S. haematobium. As early as 1910, Turner, in South Africa, had arrived at similar conclusions to that of Manson, claiming that post-mortem and geographical evidence supported the contention that there were two separate trematodes in the aetiology of intestinal and vesical bilharziasis.

Following the discovery of Leiper, Cawston (1916a)

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working with Warren, demonstrated cercariae in snails, Limnea natalensis, Physopsis africana and Planorbis sp. found around Durban, but none of the cercariae were of the human type. Later in the same year (1916b) he showed that Physopsis africana harboured cercariae similar to those described in Egypt. He found this type of cercariae only on Physopsis africana, although Planorbis pfeifferi also harboured cercariae but whose significance he considered doubtful.

Cawston may well be called the "South African Leiper" for, although unable to devote any considerable time to the investigation of Bilharzia due to his other duties, he nevertheless made valuable and significant contributions on the subject ranging from identification of snails and cercariae (1916a & 1916b) and trials of drug therapy (1919) to prevention and epidemiology (1948) over a period of more than thirty years (1916-1948).

Becker (1916) confirmed that Physopsis africana was the intermediate host of S. haematobium in South Africa. He failed to infect L. natalesnsis with S. haematobium. A year later (1917) he exposed guinea pigs to cercariae from infected snails and six months later recovered adult worms from their portal veins.

Annie Porter (1920a) reported that whereas P. africana was the common intermediate host of S. haematobium, this snail might also occasionally act as the host for S. mansoni. Moreover, although P. africana was the usual host of S. haematobium, in rare instances L. natalensis might also act as an intermediate host. Subsequently (1920b), in that same year, she described cercariae of S. mansoni in Planorbis pfeifferi in Natal. Cawston (1920) submitted snails of P. africana to Dr. E.C. Faust for examination and subsequently reported finding cercariae of both S. haematobium and S. mansoni thus seeming to

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confirm the findings of Porter (1920b). The claim that P. africana is capable of serving as an intermediate host of S. mansoni and that L. natalensis can transmit S. haematobium have since not been substantiated (Gelfand, 1950).

Orpen (1916) in the meantime had reported the disease from Southern Rhodesia. Prior to his paper it was thought that this part of the country was free from the disease and that infected cases came from beyond the borders. Orpen also made the observation that a greater number of ova were passed by patients following bodily exertion.

In the meantime, Iturbe & Gonzalez (1917) investigated and demonstrated the life cycle and intermediate molluscan hosts of S. mansoni in Venezuela.

Back in Egypt, Fairley (1919a) had devised a complement-fixation test to aid in the early diagnosis of the disease and also to serve as an index of the efficacy of treatment.

In the same year Christopherson & Newlove (1919) gave a detailed account of treatment with tartar emetic. The usefulness of antimoney compounds in treating bilharziasis has been since confirmed by all authors, and in South Africa Cawston (1921) reported good results with antimoney.

EARLY CONTRIBUTIONS ON THE PATHOLOGY OF BILHARZIASIS

In 1904 Symmers St. Clair noted a peculiar form of hepatic portal fibrosis associated with severe bilharzial infection in Egypt and termed it "pipe-stem cirrhosis".

Fairley (1920) observed and described the liver lesions produced experimentally in monkeys. He concluded that the liver was more severely affected by the lateral-spined ova (S. mansoni) and that the hepatic lesions progressed to the type of cirrhosis described earlier by Symmers. Furthermore, he gave detailed

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pathological descriptions of both S. haematobium and S. mansoni lesions as observed in his experimental animals.

Dew (1924) also gave a comprehensive pathological description of bilharziasis in man and confirmed the observations of Symmers and of Fairley.

Earlier (1914) Ferguson had reported that carcinoma of the urinary bladder was not an uncommon complication of bilharziasis.

Faust & Meleney (1924) described the pathological changes caused by S. japonicum in the East.

In South Africa, Mursell (1912) and Pirie & Welchman (1918-1919) first described Bilharzial appendicitis and Pirie (1924) suggested that Bilharzial appendicitis might be a peculiar manifestation of the disease confined to South Africa. He also noted the frequent association of carcinoma of the liver and bilharziasis (Pirie, 1921). He advanced the hypothesis that the high incidence of carcinoma of the liver might be due to malignancy supervening on a cirrhosis caused primarily by bilharziasis.

des Ligneris (1921) reported a case of bilharzial salpingitis and thereafter Gibson (1925) described the bilharzial lesions commonly encountered around the female genital tract. Notwithstanding the observations and deductions of these early workers in South Africa, Pijper (1934), commenting on the "Pathology of South African Bilharziasis", claimed that little or no irreversible pathology resulted from bilharzial infection. Vermooten (1937) contradicted the claims of Pijper and clinically demonstrated renal pathology, both of the bladder and upper urinary tract in the form of strictures of the ureters, hydroureters and hydronephrosis.

Despite the high incidence in Durban, Elsdon-Dew

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(1953) regarded the morbidity and mortality due to bilharziasis as being negligible.

In 1948 Botha de Meillon (1948) commented that insufficient investigations had been conducted on the bionomics and distribution of Bilharzia and that the behaviour of snail vectors was still based on the earlier works of Cawston & Porter. The same criticism may in fact be said to apply to the pathology. Except for the contributions of the earlier workers already mentioned, and Pijper (1934) in particular, little attention has been directed towards the human pathology produced by the bilharzial infections in South Africa.

More recently Lurie & de Meillon (1952 & 1956), Bersohn & Lurie (1953) and Lurie (1953) have reported on some aspects of experimental bilharziasis in animals but a wide hiatus still exists in the understanding of the human pathology in South Africa.

MORE RECENT SOUTH AFRICAN CONTRIBUTIONS ON THE PATHOLOGY OF BILHARZIASIS

Cawston (1942) suggested that immunity may be acquired by the death of worms *in vivo* caused by treatment. He also made the observation that school children largely harboured male worms causing slight hepatic enlargement and a rise in the eosinophil count.

Botha de Meillon (1948) was of the opinion that the incidence of *S. mansoni* was definitely increasing in South Africa. Numerous investigators reported a high incidence of vesical bilharzia.

Dormer (1942) investigated African school children in Durban and revealed an incidence of up to 39% in some areas. In 1958 Freedman & Elsdon-Dew reported an incidence of 46.8%

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in African boys and 20.2% in girls in Durban. Annecke et al. (1955) found an incidence of up to 60% in some areas of the Transvaal. Furthermore, they considered treatment in the absence of effective public health measures of doubtful significance in the control of the disease. Earlier Cluver (1934) had suggested that an attack of Bilharzia by mass treatment should be instituted.

Although Monnig (1934) had doubted the occurrence of zoonosis, Pitchford (1959) in humans found an infection rate as high as 23% with S. bovis and/or S. mattheei (cattle and sheep schistosome) and in 1961 suggested the possibility of hybridization between man and cattle schistosomes.

Gelfand (1950) made a valuable contribution from neighbouring Southern Rhodesia by discussing the various aspects of the Bilharzial problem as present in that country. Kisner (1952) reported on the urological manifestations of S. haematobium from the Transvaal and Schneider (1958) has recently discussed some of the problems of intestinal bilharziasis in Transvaal and Natal.

Marcks (1956) discussed the surgical aspects of bilharziasis in Southern Rhodesia, and from a review of the literature, these appear to differ in some respects from those described by Kark (1960) and Chapman (1964).

Numerous authors have made significant contributions on various aspects of the disease in South Africa. Annecke & Peacock (1951), Botha de Meillon (1948), Pitchford (1954), Botha de Meillon et al. (1953) and Alves (1957) have reported on the epidemiological significance of the disease.

Lurie (1953), Brink et al. (1959 & 1961), Walker et al. (1954) and Gerritsen et al. (1953) have discussed some of the clinical aspects whilst Schneider (1964) reviewed the therapy of Bilharziasis.

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The surgical management of the complication of Bilharziasis has received attention from Marcks (1956), Kark (1960), Kisner (1964) and Chapman (1964).

Charlewood et al. (1949) and Boulle and Notelowitz (1964) described the gynaecological manifestations of bilharzia whilst Lurie & de Meillon (1952 & 1956), Bersohn & Lurie (1953), and Gillman, T. (1957) have investigated the lesions produced experimentally in animals.

The important and outstanding contributions of the Nelspruit Bilharzial Field Unit under the directorship of Dr. R.J. Pitchford towards an understanding of the bionomics, ecology, distribution and epidemiology of Bilharzia, particularly in the Transvaal, but also in Swaziland, Bechuanaland and Basutoland, deserve special mention.

CHAPTER II

SCHISTOSOMES AND THEIR INTERMEDIATE HOSTS

THE LIFE CYCLE OF THE SCHISTOSOMES

In South Africa man is the definitive host of S. haematobium and S. mansoni. The adult worms of S. haematobium chiefly inhabit the pelvi-vesical venous plexuses, whilst those of S. mansoni are found in the portal vein and tributaries of the superior and inferior mesenteric veins (Leiper, 1915; Fairley, 1920; Dew, 1923).

The mature adult male and female lie in intimate association, with the female occupying the gynaecophoric canal of the male. When the female is gravid, having been fertilised by the male, she temporarily leaves the gynaecophoric canal and migrates to the smallest venules against the bloodstream to deposit her ova. As she deposits her ovum, the female retracts in the direction of the blood flow. When laid, the ovum is immature, containing yolk granules only (Faust, 1924). But, by the time the ova are evacuated by the host, they contain a fully developed motile miracidium (Faust, 1924).

The ovum of S. mansoni (Fig. 3) differs from that of S. haematobium (Fig. 2) in that it possesses a prominent lateral spine in contrast to the terminal spine of S. haematobium. The ovum of S. mansoni is slightly larger, (155 microns x 66 microns) than S. haematobium ova, measuring 143 microns x 60 microns (Belding, 1952).

Initially it was believed that the ovum escaped from the venule by engaging the spine to breach the vascular wall (Fairley, 1920). Shaw & Ghareeb (1938) rejected this theory

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and Heinz (1964) observed that the apparently deficient spine of S. japonicum ova did not in any way hinder their escape from the vessel. He suggested, like Shaw & Ghareeb, that this seemed unlikely to be a mechanism of the ovum's passage through the vessel. A more likely mode of the passage of the ova may be described as not an escape at all, but its extrusion from the vessel by a combination of factors. The ovum comes to lie against the vascular endothelium to which it becomes adherent. There is then an overgrowth of vascular endothelium over the ovum thus excluding it from the circulation. Its subsequent escape is facilitated by the secretion of enzymes by the miracidium and the local inflammatory reaction stimulated by the presence of the ovum (Dew, 1923; Fairley, 1937; Koppisch, 1943; Faust, 1946).

Embolization of minute terminal venules by ova with subsequent rupture, together with the muscular activity and contractions of hollow viscera, like the bladder and bowel, must all aid in expelling the ova from the venules.

The capacity for egg production varies with the schistosome species, S. japonicum having the greatest capacity, S. mansoni the least and S. haematobium occupying an intermediate position. Leiper (1915) claimed that S. mansoni lays one ovum at a time whilst Fairley (1920), though agreeing with Leiper, stated that he had observed as many as six ova in a small segment of a venule, presumably deposited by one adult female. He also showed that the S. haematobium female had a much larger uterus and therefore greater capacity for storage of ova. He claimed that he had observed as many as 50 ova in the uterus of one S. haematobium adult female. Belding (1952) quotes the following uterine features of the three species:

S. mansoni : short uterus occupying the anterior half of the body, with a capacity for from 1 to 4 ova only;

S. haematobium/...

S. haematobium : long, voluminous uterus occupying the posterior half of the body with a capacity for from 20 to 30 ova;

S. japonicum : long uterus occupying the mid-position of the body with a capacity for from 50 to 300 ova.

Numerous authors have remarked on the wide variability of the egg output by patients with bilharziasis. Orpen (1916) first noted the varying numbers of ova excreted by the same individual over several months, even when untreated. He also observed that egg output increased following bodily exertion. Bennie (1949); Gerritsen et al. (1953) and Stimmel & Scott (1956) demonstrated the wide variations in the total egg output during a single day by the same person. Bennie (1949) and Stimmel & Scott (1956) emphasised that, contrary to accepted belief, the early afternoon specimen of urine contained more ova than the early morning specimen of urine. The more recent observations of Jordan (1960) and Onori (1962) confirm the diurnal variations in egg output. Moore & Sandground (1956) have estimated that approximately 80% of ova produced by S. mansoni are retained in the tissues of hamster. Prata (1957) demonstrated that only 18% of S. mansoni eggs reach the fourth stage of development and that of this number, a certain proportion are non-viable. Kloetzel (1963) estimated that due to this factor, only infections with over 200 flukes are detected by routine stool examination.

From the moment that the ovum is deposited in the venule, it has a life span and viability of approximately 21 days (Vogel, 1942).

Although the larval form is fully developed within the ovum whilst still in the host, the miracidium only hatches when the ovum is shed in water with a salinity of less than 0.7% NaCl and at an optimum temperature of between 25^{o} to 31^{o}C

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(Magath & Mathieson, 1946). Under optimum conditions, the ovum imbibes water, the shell ruptures and the miracidium swims rapidly away (Goodliffe et al., 1948; Standen, 1951). The miracidium is positively phototactic and negatively thermotactic (Standen, 1951). From the time that they hatch, miracidia remain infective to the snail host for about 20 hours (Belding, 1952). Experimental evidence suggests that the miracidium locates the snail host by a chemotactic mechanism - the miracidium being attracted by some substance either secreted or excreted by the snail (Davenport et al., 1962). Other workers (Eli Chernin & Dunavan, 1962) could find no positive behaviour by the miracidium and believed that the discovery of the snail host was fortuitous.

Whereas man is the principal definitive host of the human schistosome, the snail is the exclusive intermediate host, and a suitable molluscan host is necessary for each species of schistosome (Leiper, 1915). Thus, unless the miracidium finds a suitable molluscan host within 20 - 24 hours, it dies (Schreiber & Schubert, 1949). The miracidium burrows its way through the soft tissues of the host and proceeds to the liver or digestive gland to become converted to the primary sporocyst. The primary sporocyst gives rise to the secondary daughter spotocysts wherein develop the typical fork-tailed, non-eyed cercariae lacking a pharynx, as described by Leiper (1915). The parasite's stages of development within the snail often produces severe damage to this host, sufficiently in many cases, to cause its death. About half the infected snails die within four weeks after the first shedding of cercariae (Schrieber et al., 1949).

The cercariae migrate through the tissues of the snail and escape into the water (Leiper, 1915). The period of development in the snail from the time the miracidium enters the snail to the time the cercariae leave the snail is approximately 27 days (Belding, 1952). A snail can shed up to 700 cercariae

per/...

per day (Schreiber et al., 1949). The phototactic cercariae usually emerge during the day (Kuntz, 1947). Cercariae are actively motile, swimming backwards with the aid of their forked tails. These cercariae remain infective for a period of up to 2 days (Belding, 1952). Cercariae are highly susceptible to acids, antiseptics, chlorine and high temperatures. Moreover, they are phototrophic, thermotropic and generally, though not in all strains, negatively geotropic (Standen, 1950).

When man comes into contact with infected water, the cercariae penetrate the skin by means of anterior spines and lytic substances secreted by the cercariae (Stirewalt, 1956; Standen, 1953).

Penetration is accomplished within 10 - 15 minutes, the tail being either shed during the act (Belding, 1952; Faust & Russell, 1964), or shed in the skin shortly after penetration (Standen, 1953). From their point of entry into the skin - they lose their identity as cercariae and are thereafter referred to as schistosomulae (Faust & Meleney, 1924).

The schistosomulae (metacercariae) then travel via the veins and probably via the lymphatics (Leiper, 1915; Fairley, 1920; Koppisch, 1943; Standen, 1953) to enter the general venous circulation and the lungs.

There appears to be some controversy as to the subsequent path of the schistosomulae to the liver. Narabayashi (1917) described their migration along bronchi and blood vessels to the lung hilus and thence, via the anterior mediastinum and through the diaphragm, to the liver and the portal vessels.

Miyagawa & Takemoto (1921) however, traced the more plausible route via the pulmonary circulation to the left side of the heart, subsequently to be distributed through the systemic circulation to all regions. Only those schistosomulae entering the mesenteric system finally reach the portal vessels.

This/...

This view was supported by Koppisch (1943) and Faust & Meleney (1924). From the time of penetration, schistosomulae may pass through the circulation several times before finally arriving in the portal vein (Koppisch, 1943).

Having reached the portal vein, the schistosomulae which have till now remained quiescent, rapidly mature and differentiate into their respective sexes (Leiper, 1915).

When fully developed the paired worms, with the female residing in the gynaecophoric canal of the male, migrate against the blood stream to their sites of ova deposition (Leiper, 1915).

The incubation period in man, from the time of penetration of the cercariae to the time of egg deposition varies from 30-45 days for S. mansoni and 25-60 days for S. haematobium (Fairley, 1920; Dew, 1923). In an experimental infection with S. haematobium in a human volunteer, ova, after the primary infection, were first observed in the seminal fluid on the 77th day and in the urine on the 106th day (Barlow & Meleney, 1949).

Adult schitosomes have a long productive life. Fairley (1931) quotes a case report of a patient who became infected with S. haematobium in South Africa, and returned to England where he died 28 years later from carcinoma of the bladder. Non-viable ova of S. haematobium were present in his urine. Wallerstein (1949) cited an example of a Puerto Rican woman who had resided in a non-endemic area - New York State - for 29 years and presented with a rectal polyp and bleeding. The polyp proved to be bilharzial in aetiology in which were present numerous ova of S. mansoni. Berberian et al. (1953) reported recovering ova of S. haematobium and S. mansoni from a patient who had been away from an endemic area for at least 26 years and who fairly accurately dated his probable infection back 40 years previously. He also cites Christorpherson (1924) who described

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a patient passing viable ova of S. haematobium in his urine 28 years after his return to England from South Africa where he had been infected.

SCHISTOSOME COMPLEXES, ZOONOSIS AND INFRA-SPECIFIC TAXONOMY

Some interesting facts and hypotheses relating to the infection of man by animal schistosomes (zoonosis); to animals acting as reservoirs of human schistosomes and to subspecies differences, not only in the schistosomes but in their intermediate molluscan hosts, have recently been proposed. These are of immense import not only in the epidemiological field but also in so far as they may influence regional manifestations of the disease. Consequently, although beyond the scope of the present investigation, the literature on this aspect is briefly reviewed and the significance of some of the observations discussed. S. japonicum is confined to the East, and though similar trends in investigation have been reported, this review is confined to the African species.

SCHISTOSOME COMPLEXES

The schistosomes affecting man in Africa have been generally accepted as belonging to two species: S. haematobium with the terminal-spined ova and S. mansoni with the lateral-spined ova.

However, Cawston (1921) reported finding ova in the urine of a patient indistinguishable from those of S. bovis, the cattle schistosome described much earlier by Sonsoni (1876) in Egypt. Not long after this, Veglia and Le Roux (1929) also from South Africa, described a new schistosome which they had discovered in sheep and named it S. mattheei. Although Lane (1936) and Van den Berghe (1937) questioned the validity of

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this distinction, Alves (1949) and later Schwetz (1951) provided further evidence in support of the claim of Veglia & Le Roux (1929).

S. bovis is the cattle schistosome, infecting ungulates from Egypt and East Africa. Teesdale & Nelson (1958) reported widespread cattle infection with S. bovis in Kenya. However, they claim never to have seen the parasite in man (Nelson et al., 1962).

Further south, in Central Africa and in South Africa, it is claimed that S. bovis (Sonsino, 1876) is represented by S. mattheei (Veglia & Le Roux, 1929). Pitchford (1961) demonstrated many natural definitive hosts for the latter parasite, and had earlier (1959b) reported that infection of man in some areas of the Transvaal by this type of schistosome was as high as 40%. This is in marked contrast to the observations of Nelson et al. (1962) on the behaviour of S. bovis. Pitchford (1959b) had noted however that infection with S. mattheei was always associated with either S. mansoni or S. haematobium infections and was never a pure infection (Figs. 5 & 7).

Earlier, Fisher (1934), working in the Stanleyville area of the Congo, reported the discovery of yet another terminal-spined schistosome morphologically not unlike S. bovis and S. mattheei and called it S. intercalatum. However, whereas S. bovis and S. mattheei are primarily animal parasites, Fisher (1934) reported that S. intercalatum was primarily a parasite of man and that this schistosome had not been observed in animals. Moreover, although the ova possessed a terminal spine, this schistosome gave rise to intestinal symptoms of bilharzia whereas S. haematobium, which was also prevalent in this region, produced vesical symptoms.

Schwetz (1951) noted that although there were some

morphological/...

morphological similarities and a common snail host (Physopsis) there were sufficient important differences, both morphological and biological, to regard S. haematobium, S. mattheei, S. bovis and S. intercalatum as separate species.

Similarly S. mansoni was regarded as the sole representative of the schistosomes with lateral-spined ova in Africa until Brumpt (1931) described lateral-spined ova which he recovered from wild rodents. He called this schistosome S. rodhaini. This was subsequently confirmed by Schwetz & Stijns (1951). Schwetz (1953) himself described yet another lateral-spined ova-producing schistosome and called it S. mansoni var: rodentorum. However, Le Roux (1954) reported that ova produced by hybrids of S. mansoni and S. rodhaini were identical to that of S. mansoni var: rodentorum. Teesdale & Nelson (1958) supported this view. Subsequently, Pitchford (1961) claimed that hybridization also occurred between S. haematobium and S. mattheei.

ZOONOSIS

There appears to be some confusion over the usage of the term "zoonosis". The World Health Organisation (Anon, 1959) defines it as "those diseases and infections naturally transmitted between vertebrate animals and man". Nelson (1960) proposed stricter limitations and suggested various categories and subdivisions. However, the simple definition of Heisch (1956) - "infections of man naturally acquired from other vertebrates" - adequately describes the term and it is in this context that the term "zoonosis" is used in this discussion.

Whereas S. mattheei and S. bovis have been reported as infecting man, S. rodhaini is not known to infect man. As both S. mattheei and S. bovis are primarily animal parasites, infections with these parasites in man may be regarded as

examples/...

examples of zoonosis. It has been recognised, too, that cercariae of some animal and avian schistosomes are responsible for cercarial dermatitis in Africa, Asia and the Americas, but that in man the cercariae never develop into adults (Kuntz, 1955).

The problems of zoonosis have not as yet been properly assessed. Although the general concensus of opinion at the present stage of our knowledge appears to be that zoonosis is not a serious problem (Kuntz, 1955; Le Roux, 1961; Nelson, 1960; Nelson et al., 1962), the high incidence of S. mattheei in humans as reported by Pitchford (1959b) cannot be discounted.

Nelson (1962) suggested that zoonosis may, in fact, confer some beneficial effects on man. He concluded: "The partial immunization of men through the agency of non-pathogenic schistosomes may be of considerable significance in the epidemiology of bilharziasis".

ANIMAL RESERVOIRS OF HUMAN SCHISTOSOMES

Numerous authors have reported recovering ova of human schistosomes from animal sources. This raises the problem of the role of these lower animals as reservoirs of human bilharzia and their capability of maintaining the propagation of the parasite in the absence of the definitive human host (Kuntz & Malakatis, 1955; Miller, 1959; Pitchford, 1959a; Nelson et al., 1962; Amberson & Schwarz, 1953).

Pitchford (1959a) reported a high incidence of natural infections in the rodents Mastomys and Otomys both with S. mansoni and S. haematobium, and reported later (1962) that the incidence varied greatly in the same region at different times. He explained that this seasonal variation was due to the short life span of the rodent and the inability of these rodents to

maintain/...

maintain the life cycle of the human schistosomes in the absence of contact with human hosts. Miller (1960) and Nelson (1960) both reported high incidences (varying between 40-60% at the highest) of natural infection with S. mansoni in baboons of East Africa. There was a much lower incidence of natural infection with S. haematobium. There are numerous reports on susceptibility in laboratory animals to schistosome infections. However, Martins (1958) has emphasised that susceptibility in the laboratory animal does not necessarily prove that these animals are good natural hosts.

The epidemiological significance of natural infections of human schistosomes in non-human hosts has not been fully investigated. However, the problem is not yet regarded of serious import in Africa (Kuntz, 1955; Nelson, 1960; Nelson et al., 1962 and Pitchford, 1962).

Barbosa (1962) commented that although S. mansoni appeared to be infective to a much wider host group, he was of the opinion that animal reservoirs did not, as yet present a serious problem in South America. It has been shown too, that S. japonicum in the Orient, is naturally infectious to a wide variety of animal hosts as well as man (De Witt, 1954, Hsu et al., 1958; Kuntz, 1955).

There appears then, to be a differing width of host spectrum in the three major schistosomes of man:

S. haematobium appears to be host-specific to man;
S. mansoni, only slightly less host specific, whilst
S. japonicum is almost non-specific.

It has been suggested that S. japonicum is in fact, primarily an animal schistisome which has recently, in the evolutionary cycle, begun to adapt itself to the human host (Elsdon-Dew, 1962; Hairston, 1962).

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The wider range of definitive hosts utilised by S. mansoni and especially S. japonicum, together with evidence of the existence of different strains of intermediate hosts, may be indicative of marked infra-specific differentiation. This may be a probable factor related to the more severe pathology produced in man by these schistosomes compared with the more host specific S. haematobium.

INFRA-SPECIFIC TAXONOMY

Leiper (1915) demonstrated the need for suitable molluscan intermediate hosts for survival of the schistosome species, and, in fact, the geographical distribution of the disease is limited by, and dependent on, the availability of suitable molluscan hosts.

The genera of molluscs that are generally accepted as acting as intermediate hosts of the principal schistosome species parasitic in man are as follows:

S. japonicum	- Oncomelania sp.
S. mansoni	- Biomphalaria sp.
	Australorbis sp.
	Tropicorbis sp.
S. haematobium	- Bulinus (Physopsis) sp.

Cram (1953) suggested that Biomphalaria sp. was the established host for S. mansoni in Africa, whilst Australorbis sp. was a more recent host and that S. mansoni was still in the process of adaptation to the most recent host - Tropicorbis sp. Hubendick (1955), however, was of the opinion that these three so-called genera were in fact a single genus.

The fact that each species of schistosome is adapted to a particular genus of molluscan intermediate host has long been recognised. It has only more recently become apparent that

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this adaptation extends to a specificity to local strains of schistosomes and snails. Numerous investigators have reported failure in attempts to infect local, apparently susceptible molluscan hosts with miracidia obtained from a different geographic region. This apparent strain difference of schistosomes is not peculiar to any particular species but embraces all the schistosome species (Le Roux, 1958; Cowper, 1953; Files & Cram, 1949; Barbosa & Barreto, 1960; Nelson, 1960 and Wright, 1962).

It will be remembered that Harley (1864) named the South African schistosome Bilharzia capensis. However, this was not due to known schistosome species differences, but merely on account of the geographical location. Le Roux (1958) however has demonstrated morphological differences in the adult worms and ova of this variety as compared to S. haematobium in Egypt. Furthermore he failed to infect snails of the B. truncatus group with miracidia obtained from South Africa - the usual host being B. africana. Le Roux (1958) therefore stated : "these results have induced the deduction that the common parasite of urinary bilharziasis in Southern Africa must be accepted as a species distinct from S. haematobium (Bilharz, 1852)". Wright (1962) subsequently supported the claims of Le Roux (1958).

Wright (1960) had proposed that "speciation in the digenetic trematodes is often based on parallel evolution of the flukes with their molluscan rather than their definitive hosts". In addition to morphological differences in strains of B. truncatus in the same area, Wright (1962) also reported physiological variations by demonstrating "differences in the chromatographic pattern and fluorescent substances in the body surface mucus". He suggested then (1962) that differences in regional schistosomes of the same species were due to an alteration of physiology rather than of morphology.

Wright (1962) raised another interesting point by

suggesting/...

suggesting that: "Although proof is not yet available it seems likely that this dichotomy (between S. haematobium and S. capense is the exact parallel of that between the two common African schistosomes of cattle, with S. mattheei developing in snails of the africanus complex and S. bovis which uses the truncatus group".

Nelson et al. (1962) on the other hand considered that there were insufficient grounds for regarding the parasite with terminal-spined ova in South Africa as a separate species from S. haematobium.

Being cognizant of these observations various authors have suggested that in fact there are two major Bilharzial complexes in Africa : (Amberson & Schwarz, 1953; Le Roux, 1958; Nelson et al., 1962; Kuntz, 1955) :

(1) S. haematobium complex with terminal-spined ova, which includes:
S. haematobium (Bilharz, 1852)
S. capense (Harley, 1864)
S. bovis (Sonsino, 1876)
S. intercalatum (Fisher, 1934)
S. mattheei (Veglia & Le Roux, 1929); and

(2) S. mansoni complex with lateral-spined ova, which includes:
S. mansoni (Sambon, 1907)
S. rodhaini (Brumpt, 1931)
S. mansoni var: rodentorum (Schwetz, 1953).

Le Roux (1958) went further and proposed separate genera with the common schistosome of man in three separate genera : Schistosoma, Afrobilharzia and Sinobilharzia. This complex subdivison has generally not been welcomed (Nelson et al., 1962).

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THE INTERMEDIATE HOSTS OF HUMAN SCHISTOSOMES IN NATAL

Five actual or potential intermediate hosts are believed to be present in Natal (Brown, 1964). These are :

Bulinus (Physopsis) africanus (Krauss)
Bulinus (P.) globosus (Morelet)
Bulinus (Bulinus) sp.
Biomphalaria pfeifferi (Krauss)
B. angulosa (Mandahl-Barth)

Three of these are probably of little importance. Bulinus (P.) globosus has so far been found in a limited locality on the Makatini flats of North-Eastern Natal. B. (P.) globosus from these areas appears to be quite distinct from B. (P.) africanus. Both species are known to occur in Mozambique and North Eastern Transvaal and are regarded as probably equally suitable intermediate hosts of S. haematobium (Brown, 1964).

Biomphalaria angulosa has been recorded near Durban by Mandahl-Barth (1958). This species is otherwise known from only a few localities in East Africa and its susceptibility to Schistosoma has been investigated only in Tanganiyika where it was found to act as an intermediate host of S. mansoni (Sturrock, 1963).

Although the presence of a Bulinus (Bulinus) sp. capable of transmitting S. haematobium has not been reported from Natal, its presence may be suspected as a form of Bulinus (B), susceptible to S. haematobium has been reported from Nelspruit in the North Eastern Transvaal by Schutte & Frank (1964).

The transmission of Schistosomiasis in Natal thus depends almost entirely on Bulinus (P.) africanus (S. haematobium) and Biomphalaria pfeifferi (S. mansoni).

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From the map (Fig. 1) it is apparent that B. africanus has the widest range extending to the foothills of the Drakensberg mountains in Northern Natal. Biomphalaria pfeifferi, however, is restricted to a relatively narrow coastal belt. Dr. Brown (1964) observed that the range of both species extends less far from the coast in the southern part than in the northern area. He suggested that, although there is no experimental evidence to support this conclusion, the varying temperature conditions, from North to South and from East to West may be responsible for this distribution.

DISCUSSION

It is obvious that the problems confronting the epidemiologist are by no means simple. The significance of the above findings are profound from an epidemiological point of view.

The host parasite specificity of local regional strains, if as exclusive as suggested, is a reassuring discovery, especially in this jet age of travel and constant human population migrations. It would be comforting to know that carriers of the disease from one area cannot infect potential snail hosts of another due to the inherent selectivity of the schistosome species.

It is tempting to suggest, as a corollary to the foregoing, that inherent in the infra-specific differences of the species may be modifications in the manner of expression of the disease processes as evidenced in the definitive host. Indeed Pirie (1924) inadvertently raised this very problem by suggesting that bilharzial appendicitis was a disease peculiar to the South African type of bilharziasis. He quoted Milton (1921) as describing differences in the local manifestations of Bilharzia as compared to those seen in Egypt.

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As mentioned earlier, many investigators have been aware of the apparent variability of the pathology produced by presumably the same parasite in different geographical regions. Various explanations have been advanced to explain this apparent discrepancy and one which has been advocated, rather hesitantly, has been the possibility of strain differences of the parasites. Perhaps this may eventually provide an adequate explanation for the apparent variability of disease patterns in different regions.

The discovery of possible animal reservoirs of human schistosomes and the possible role of animals in the spread of the disease raises alarming problems for the epidemiologist. If the natural infection of animals by human schistosomes is as high in other areas and in different animals as revealed by Pitchford (1962) to be true in some areas in the Transvaal, and Nelson (1960) in East Africa, then it raises almost insurmountable barriers in public health schemes.

Three important factors tend to minimise the importance of animals to serve as reservoirs of human schistosomes and consequently as a potential source of infection to man:

(1) The inability of animals, in the absence of the human host, to perpetuate the life cycle of the human schistosomes;
(2) The short life-span of rodents and other smaller animals known to be naturally infected with human schistosomes. Nature thus interferes with the life cycle of the schistosomes and also eliminates the "carrier" state; and
(3) Simians, which would be the most suitable hosts after man, and therefore the greatest threat, do not usually inhabit the same areas as humans, and certainly not in any density.

The problem of zoonosis, with the probable exception of S. mattheei in the Transvaal (Pitchford, 1959b), has been shown to be of little importance medically. In fact, it would appear that man, by acquiring infections from animal sources,

may/...

may benefit by building up an immunity to the more pathogenic human schistosomes (Nelson *et al.*, 1962; Le Roux, 1961). The importance of zoonosis, may, in fact, lie in the zoo-prophylaxis which it may confer on man. The possibility of utilising animal strains to immunise man either directly (by exposing him to the non-pathogenic animal strains) or indirectly (by innoculations) is only recently receiving attention (Kagan, 1953; Meleney & Moore, 1954; Hunter *et al.*, 1961; Smithers, 1962).

SUMMARY

The life history, host specificity and infra-specific taxonomy of the human schistosomes has been described and the problems of zoonosis and animal reservoirs of human schistosomes have been briefly discussed.

The geographical distribution of the intermediate molluscan hosts of **S.** haematobium (B. (P.) africanus) and S. *mansoni* (Biomphalaria pfeifferi) in Natal has been illustrated.

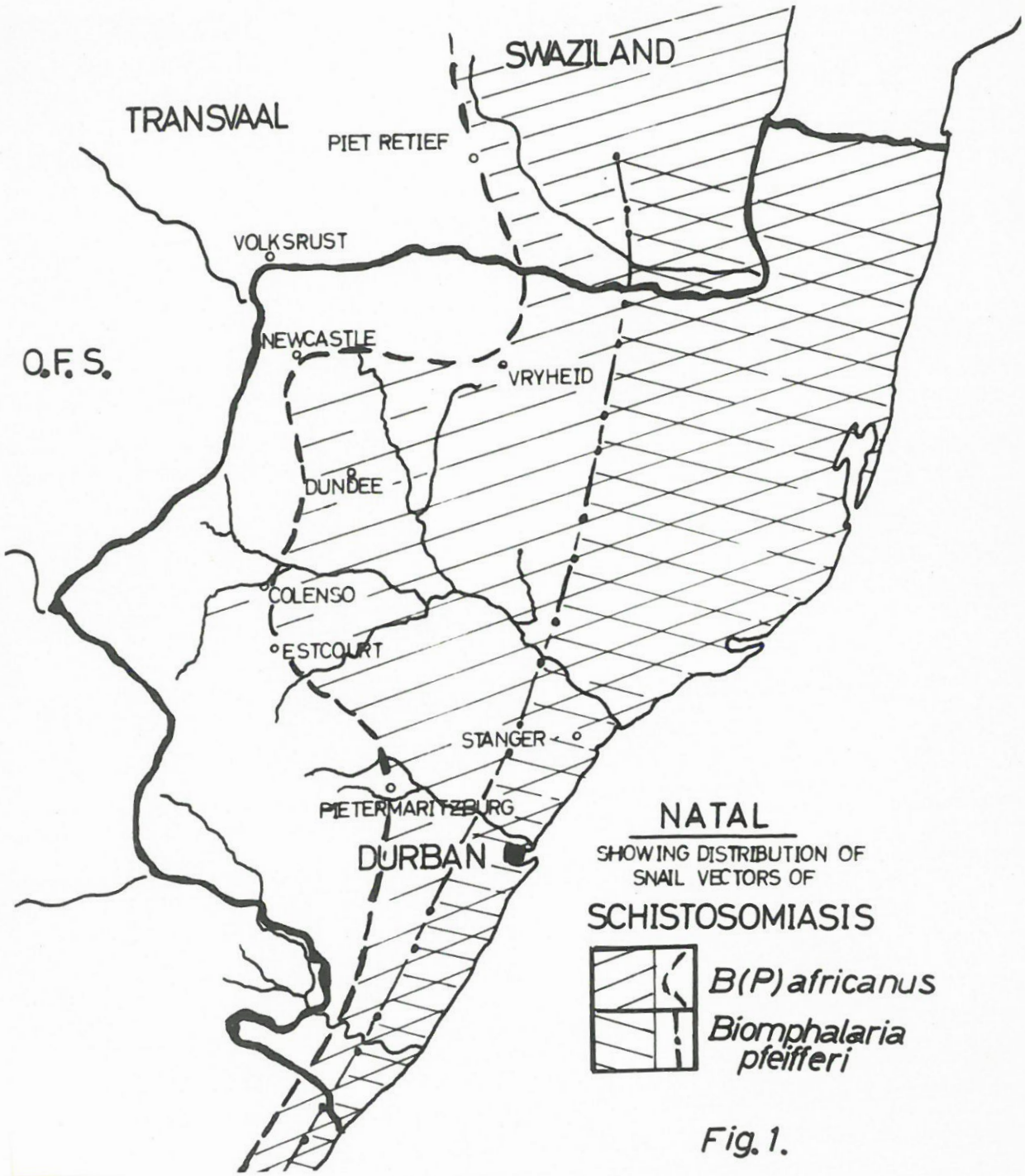
SWAZILAND
TRANSVAAL
PIET RETIEF
VOLKSRUST
NEWCASTLE
O.F.S.
VRYHEID
DUNDEE
COLENSO
ESTCOURT
STANGER
PIETERMARITZBURG
DURBAN
NATAL
SHOWING DISTRIBUTION OF
SNAIL VECTORS OF
SCHISTOSOMIASIS
B(P) africanus
Biomphalaria pfeifferi

Fig. 1.

CHAPTER III

INCIDENCE OF SCHISTOSOMIASIS IN DURBAN

INTRODUCTION

The World Health Organisation reviewing the problem of bilharziasis commented that: "In recent years the prevalence of bilharziasis has shown an increase - an increase that is largely of man's own making, because, by the construction of dams, irrigation systems and other water conservation works in his attempts to relieve the problem of feeding the world's ever growing population, he is creating the very conditions that favour the spread of the disease" (Anon: 1961).

For a proper perspective of the epidemiological problems involved, it is desirable that the true incidence of the disease in a particular locality or population be first ascertained. Whereas, in theory, this would appear to be a simple matter, in practice various problems make anything more than a rough assessment an almost impossible task.

The difficulties arise both from the parasite-snail and the parasite-host relationship.

(a) The snail-host - parasite relationship:

The maintenance and spread of bilharziasis in an area depends on the availability of the appropriate species of snails. The changing ecological pattern in an area from season to season and over years will influence, not only the snail population, but also their receptivity to, and consequent maintenance of, the schistosome infection. The proximity of humans, the source of infection to the

snails/...

snails, will also influence the infectivity rates of the snails. These factors together with malacological and other problems, have already been discussed in an earlier chapter.

(b) The human-host - parasite relationship:

The Expert Committee on Bilharziasis (Anon: 1953) stated that: "The human infection rate would appear, a priori, to be a reliable indication of the parasite incidence". They noted, however, that difficulties of interpretation may arise, which they considered were due to four causes:

(i) Uncertainty as to the place where the disease was contracted;
(ii) Variations of the rates from one place to another;
(iii) Variations of the rates from one year to another; and
(iv) Variations of rates according to age, sex, ethnic group and occupation.

To these may be added:

(v) Accessibility of medical services to potentially infected population groups; and
(vi) The reliability of the diagnostic tests used.

It is not within the scope of the present work to examine all the problems detailed.

The demonstration of schistosome ova, by whatever means, establishes the diagnosis. However, failure to recover ova does not exclude the probability of an infection. To circumvent this uncertainty a variety of techniques, including the indrect approach through immunology, concentration and other techniques on the excreta, and the recovery of ova from tissues

have/...

have been employed in the diagnosis of Bilharziasis.

DIAGNOSTIC METHODS

A. IMMUNOLOGICAL TESTS

Since Fairley (1919a) described a complement-fixation reaction in Bilharziasis, numerous immunological tests have been devised and though none were used in the present investigation, a brief review of the essential literature follows.

(1) The Intra-dermal test (I.D. Test)

Fairley & Williams (1923) first described the I.D. test wherein a characteristic wheal was produced after an intradermal injection of antigen. The antigen used by subsequent workers varied from extracts of snail livers (Ramsay, 1934) to purified extracts of adult schistosomes (Sadun, Lin & Walton, 1959). Although a useful tool, the I.D. test has various limitations:

(a) The I.D. test remains positive for a variable period of time after the active infection has been cured (Gelfand, 1950; Manson-Bahr, 1958).

(b) The test is more specific in adults than children (Lurie, de Meillon & Eiselen, 1953) and in men than in women (Kagan, Pellgrino & Memoria, 1961).

(c) Some workers have reported a fairly high proportion of false negatives (Morales & Maldonado, 1946; Latty et al., 1954).

In view of the relatively easy field application of this test, further studies, using a variety of antigens, are being carried out in various parts of the world under the auspices of the World Health Organisation.

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(2) The Complement-Fixation Test (C.F.T.)

The Complement-Fixation Test was first employed by Fairley (1919a). With modifications (chiefly in the use of more purified antigens) the test is to-day considered about 75-95% reliable (Schofield, 1959; Chaffee et al., 1954; Mao, 1958). Schofield (1959) demonstrated that the test was more accurate in the diagnosis of infections of less than 3 years duration and became gradually less reliable as the duration of the infection increased. de Meillon & Hollingham (1958) noted that the test remained positive for at least four months after apparent clinical cure.

(3) The Precipitin Test

Oliver-Gonzalez & Pratt (1944) employed the precipitin test with some success in the diagnosis of bilharziasis.

(4) The Circumoval Precipitin Test (C.O.P.)

This test was originally described by Oliver-Gonzalez (1954). Since then Oliver-Gonzalez et al. (1955a) have reported that the test was species-specific for the schistosomes. They also noted (1955b) that, unlike the C.F.T., the C.O.P. test was more reliable in the chronic stage than in the earlier acute stages of the disease. However, Newsome (1958) demonstrated that the claim for species specificity of the test was incorrect.

(5) Cercarien-Hüllen Reaktion (C.H.R.)

The test was described by Vogel & Minning (1949). Meleney & Moore (1954) noted that amongst other disadvantages, it was neither stage- nor species-specific.

(6)/...

(6) Cercarial Agglutination Test (C.A.T. & the Miracidial Immobilization Test (M.I.T.)

Liu & Bang (1950) described the C.A.T. and Oliver-Gonzalez et al. (1955a) claimed that the test was more specific in recent than late infections. Senterfit (1953) devised the M.I.T. - based on a similar technique as the C.A.T.

(7) Haemagglutination Test

Kagan & Oliver-Gonzalez (1955 & 1958) have more recently employed the haemagglutination test in the diagnosis of bilharziasis. They have noted that the results are of doubtful significance and concluded that further studies are desirable.

(8) Slide Flocculation Test

Anderson (1960) recently employed the slide flocculation test with considerable success.

Jachowski & Anderson (1961) evaluated the above serological tests in S. mansoni infection and indicated the frequency of false negative results (Table I).

TABLE I/...

TABLE I+

SEROLOGICAL DIAGNOSIS OF S. MANSONI

TEST	% FALSE NEGATIVE	ANTIGEN
Concurrent stool examination	20.5	-
Composite stool data*	12.3	-
C.F.T.	2.1	Adult
C.F.T.	3.3	Cercarial
Slide Flocculation Test	3.9	Cercarial
C.O.P.	13.2	Ova
I.D.	32.3	Adult
I.D. test	19.5	Cercarial
I.D. test	66.0	Ova

* Correlation of numerous stool examinations and previous hospital records of stool examination.

\+ Abstracted from Jachowski & Anderson (1961).

From Table I it would seem that, despite its disadvantages, the C.F.T. is the most reliable of the immunodiagnostic methods yet devised. The slide flocculation test needs fuller evaluation.

(9) Fluorescent-Antibody Test

Sadun, Williams & Anderson (1960 & 1962) have recently applied the Fluorescent Antibody test (F.A. Test) in the immuno-diagnosis of bilharziasis. However, due to technical difficulties it has only a limited role in epidemiological surveys.

From this brief review of diagnostic techniques it

becomes/...

becomes apparent that as yet there is no simple and infallible immunological procedure.

B. RECOVERY OF EGGS

(1) From Excreta

In the acute symptomatic phase of an established infection, there is seldom difficulty in demonstrating ova either in the urine (S. haematobium) or in the stool (S. mansoni).

In the chronic phase of the disease, the discovery of eggs in the excreta is more difficult. Consequently diagnosis based on this procedure will be less reliable, and epidemiological studies, based on urine or stool examination may give an erroneously low result. Despite these objections, the simplicity of these techniques has led most workers to use the examination of excreta in prevalence studies.

(2) Rectal Snip Method

A major advance in the accuracy of diagnosis in S. mansoni infections was the introduction of the rectal snip technique. Ottolina & Antencio (1943) and Ottolina (1947) were the first to demonstrate the superiority of this method over stool examination in the diagnosis of S. mansoni infections. Hernandez-Morales & Maldonado (1946) confirmed these findings. Subsequently Gelfand (1950), Pitchford (1954) and Eastman-Nagle (1956), amongst others, used the procedure in Southern Africa. They noted that such biopsy also revealed a high proportion of infections with S. haematobium. Nonetheless, the obvious practical difficulties restrict its extensive use in field surveys.

(3) Tissue Digestion

Ferguson (1913) had earlier recommended a method particularly

suitable/...

suitable for determining the incidence rates at autopsy. This entailed the digestion of the tissue in 10% Caustic potash and microscopical examination of the residue. Theoretically this method should detect 100% of infections but the limitations are obvious. The method is not only restricted to autopsy surveys but is particularly time-consuming.

Gelfand (1950) in Rhodesia employed the procedure in a large series of autopsy cases and confirmed its value. Where the examination of excreta had revealed an incidence of approximately 20%, the autopsy digestion technique revealed over 80%.

INCIDENCE IN SOME AFRICAN COUNTRIES

The more recent reports of the incidence of bilharziasis (S. haematobium and S. mansoni) in some African countries are briefly reviewed for comparison with the present surveys undertaken in Durban.

EGYPT

It has been estimated that between 50-60% of the rural population of Egypt are infected with bilharzia (Mousa, 1962). Khalil (1928) reported that the incidence of S. haematobium was 38.9% and that of S. mansoni 52.6%. Shaw & Ghareeb (1938) were of the opinion that at least 60-70% of the Egyptian population harboured schistosomes. Hashem (1961) reported that in a post-mortem survey in 1947 he found an overall incidence of 40% whilst in 1961, in a similar survey, he noted that the incidence of bilharziasis was 38%. Mousa (1962) reported that in Egypt the highest incidence of bilharziasis was in the 2nd decade and thereafter declined considerably (Table II).

TABLE II/...

TABLE II

AGE INCIDENCE OF BILHARZIA IN EGYPT*

Age	% Incidence
2 - 4	17
5 - 9	47
10 - 14	60
>50 years	20

* Abstracted from Mousa (1962)

Manson-Bahr (1958) was of the opinion that the incidence in Egypt and the Nile delta was approximately 100%.

GHANA

Colbourne et al. (1950) reported that the incidence of S. haematobium in school children from the Kwansakron Colony (Ghana) was 9.1% whilst Harris (1951) reported that in Adeiso Colony the incidence of S. haematobium in school children was 85.3%. McCullough (1956) reporting from yet another area found an incidence of 41.1% in school children. Edington (1957) correlated the results of urine and stool examinations in hospital patients and noted that from these records the incidence of S. haematobium varied from 2% - 37.8% and that of S. mansoni from 0 - 10.2%, depending on the locality. Thus it would appear that bilharziasis has a focal endemic distribution in Ghana.

TANGANYIKA

McLean et al. (1958) reported that both S. haematobium and S. mansoni were prevalent over large areas of Tanganyika. In an area investigated they noted that the incidence of S. haematobium was 38.8% whilst that of S. mansoni was extremely low (only 7/900 stools showing S. mansoni ova).

UGANDA/...

UGANDA

Blair (1956) reported that bilharziasis had a scattered focal distribution in Uganda. On a single urine examination the highest incidence of S. haematobium was approximately 8% amongst school children. He noted, however, that whereas, in 1945, the incidence of S. mansoni amongst school children of a West Nile province of Uganda was 12%, in 1950, he found no less than 54% harbouring S. mansoni, whilst in some areas the incidence of S. mansoni infestations was as high as 88%. Nelson (1958) surveyed the same area for S. mansoni by single stool examination and reported a range of incidence of from 0.8 - 40.5%. He was of the opinion, however, that the "probable" incidence lay between 2% - 90% in this area - confirming the view that S. mansoni is the commoner infection in this area of Uganda.

THE RHODESIAS

Gelfand (1950) from Central Africa, employing the digestion technique in a large series of autopsies reported that the overall incidence of bilharziasis in the African was 82%; the incidence of S. haematobium being 72% and that of S. mansoni 30%. In a separate clinical study, he reported that the incidence of S. haematobium by urine examination was only 6.6% and that of S. mansoni by stool examination 9%. Alves (1958) from Southern Rhodesia reported that the incidence of S. haematobium in autopsies (employing the digestion technique) was 86.5%. He noted that, "In S. Rhodesia light infections are common and it is probable that gross damage is seldom produced by the disease".

MOZAMBIQUE

de Morais (1956, 1957) demonstrated a focal endemic distribution in Mozambique. Alves (1957) examined urine

specimens/...

specimens from 15,000 school children in Mozambique between 1952 and 1956, and found that 66% were infected with S. haematobium. He noted, too, that in adults over 30 years old, the incidence was 37%. Prates & Gillman (1959) reported the incidence of S. haematobium as established histologically in 478 consecutive autopsies (Table III).

TABLE III

INCIDENCE OF BILHARZIASIS (S. HAEMATOBIUM) AS ESTABLISHED BY HISTOLOGY IN 478 POST MORTEMS IN MOZAMBIQUE*

AGE IN YEARS:	% INCIDENCE	
	MALES	FEMALES
0 - 10	11.8	18.9
10 - 20	60.7	50.0
20 - 30	69.5	71.4
30 - 40	82.1	68.0
40 - 50	72.0	48.0
50 - 60	60.0	57.9
60+	60.6	56.5

* Abstracted from Prates & Gillman (1959).

They commented that the highest incidence was in the age group 31 - 40 years.

INCIDENCE IN SOUTHERN AFRICA

Various workers have reported on the incidence of bilharziasis in Southern Africa.

SWAZILAND/...

SWAZILAND

Eastman-Nagle (1956) by urine examinations found an incidence of 42% for S. haematobium in Swaziland; whilst employing the rectal-snip technique he obtained an incidence ranging from 28% to 41% for S. haematobium and from 3% to 13% for S. mansoni. He commented on the geographical distribution noting that while S. haematobium was common in the midland and lowveld areas, S. mansoni was restricted almost entirely to the lowveld area. Pitchford (1958a) also using the rectal-snip method showed that the incidence of S. haematobium varied from 3% in the highveld to 65% in the lowveld. He also quoted the earlier findings of the survey conducted by the Swazi Health Department, who, by a single urine examination, found that the incidence of S. haematobium varied from 3% to 75% and that of S. mansoni (rectal biopsy survey) from 0% to 49%.

BASUTOLAND AND BECHUANALAND

Pitchford (1958b) reported that bilharizasis was rare in Basutoland whilst there were endemic foci in Bechuanaland (1958c). Employing the rectal-biopsy technique he demonstrated that in some of these areas the incidence of S. haematobium was as high was 65%.

TRANSVAAL

By examining a single urine specimen van Wezel (1951) demonstrated incidences of S. haematobium in African school children ranging from 42% (Northern Transvaal) to 47% (Eastern Transvaal). The highest incidence in European school children in the same areas was 14%. Annecke & Peacock (1951) in an extensive single-urine survey of the Transvaal confirmed the high prevalence (4% - 55%) in African children. In an earlier survey in 1937-38 they had found incidences of over 80% in the

African/...

African school children of some areas. de Meillon & Lurie (1953) surveyed African and European school children around Johannesburg and reported that in contrast to the lowveld areas, the incidence of S. haematobium was not remarkably high - being 10% in European and 20% in African school children between 10-16 years old.

Higginson & de Meillon (1955) employing the digestion technique at autopsy, showed that the incidence of S. haematobium was 22% and of S. mansoni 4.6%. Pitchford (1954) combining rectal biopsy with urine and stool examinations, noted that, in the Eastern Transvaal, rectal biopsy revealed S. haematobium in 80% whilst urine examination gave 60%. Comparing 2 areas, he showed that while the incidence of S. mansoni in Africans in the reserves was 41.9%, the Africans in European farming areas showed an incidence of 77.6%. This surprisingly high incidence of S. mansoni was apparent from stool examination.

The high incidence of S. mansoni infections in the Transvaal lowveld was confirmed by the findings of Azar et al. (1958) who, by the rectal-snip method, found that 61% of African school children had S. mansoni infection. Of these children 92% had S. haematobium infection on urine examination.

Schneider (1958) by the rectal-snip method found the incidence of S. mansoni to be 32.7% in parts of the Transvaal.

From these observations, it is apparent that bilharziasis (both S. haematobium and S. mansoni) is endemic in the Transvaal and in the neighbouring countries of Swaziland, Mozambique and Rhodesia.

It is interesting to note the high incidence of S. mansoni in the Eastern Transvaal and Swaziland lowlands.

PAST REPORTS OF INCIDENCE IN NATAL

As the Province of Natal has a topographical pattern

similar/...

similar to that of Transvaal and Swaziland - highveld, midveld and lowveld, the distribution of bilharziasis in Natal would be expected to follow similar trends. No adequate overall survey of Natal has as yet been conducted.

Kay-Sharp (1921-23) examined urine samples from Indian school children from the Natal coastal regions and reported the following incidence rates: Stanger 13.3; St. Aidan (Durban) 7.0; Depot Road (Durban) 3.1; Umgeni (Durban) 10.0%. Dormer (1948) exmained African school children on the Natal coast and reported that overall, 10.5% had active bilharzia. The highest incidence was recorded in a school in the Umkomaas area (39.6%).

Freedman & Elsdon-Dew (1958) from a single urine examination revealed an infection rate of over 50% in African boys between 10 and 15 years old in Durban. Elsdon-Dew (1962) believed that these figures were too low and that the probable incidence was nearer 100%.

Stools examined from hospital patients with dysentery revealed ova of S. mansoni in 0.8% of Africans and 1.4% of Indians (Elsdon-Dew, 1947). In a further study of intestinal parasites in different African socio-economic groups in Durban, Elsdon-Dew (1953 & 1958) demonstrated an incidence of S. mansoni of up to 1.8%.

Bates & Alberto (1952) from Durban reported on the incidence of S. mansoni as found in routine stool examinations of hospital patients : Europeans 1%; Africans 1% and Indians 3%. Employing rectal biopsy, Schneider (1958) reported that the incidence of S. mansoni in African and Indian hospital patients (King George V Hospital, Durban) was 11% and 15% respectively. Powell et al. (1961) noted that the incidence of S. mansoni infections in Africans with acute amoebic dysentery was 3%; in bacillary dysentery 8% and in a control group 2%.

PRESENT/...

PRESENT STUDY

The aim of the present study was to assess the incidence of Bilharziasis in the African and Indian population in and around Durban.

The incidence was assessed in 3 groups:

(1) in autopsy material
(2) in school children
(3) in hospital out-patients.

The author believes that correlation of the results of three differing approaches would give a better estimate of the incidence in the area.

1. INCIDENCE IN AUTOPSY MATERIAL

Materials & Methods

The bladder and rectum were removed from autopsies performed on the age group 2-65 years at the King Edward VIII Hospital during the year 1963. The majority (700) of these were routine hospital examinations, and the remaining 200 were medico-legal autopsies on unnatural deaths. The inclusion of the latter group may offset the "selection" inherent in hospital material.

The race and sex distribution is shown in Table IV.

TABLE IV/...

TABLE IV

SEX & RACE OF AUTOPSIES EXAMINED

RACE	MALE	FEMALE	TOTAL
AFRICAN	492	330	823
INDIAN	52	25	77
TOTAL	545	355	900

The bladder and rectum were subjected to three methods of examination:

(1) The direct "squash"-slide method

Fresh snips of tissue from both bladder or rectal mucosa were each crushed between two microscope slides.

(2) Histology

A specimen from the bladder and one from the rectum were taken separately, fixed in formol-saline, sectioned and stained by H & E.

(3) Digestion Technique

Twenty Grams each of the remainder of the bladder and of the rectum were digested overnight in 10% caustic potash at 60^{o}C and the centrifuged deposit examined the following morning. A quantitative measure of the egg load was determined by calculating the number of eggs per gram of tissue digested.

Results

Relative/...

Relative Efficiency of 3 Methods

The relative efficiency of the three methods employed may be gauged from Table V.

TABLE V

INCIDENCE OF BILHARZIASIS AS DETERMINED BY THREE DIFFERENT METHODS IN 900 AUTOPSIES

METHOD	BLADDER		RECTUM		COMPOSITE*	
	No. +	%+	No. +	%+	No. +	%+
SNIP	217	24	165	18	268	30
HISTOLOGY	185	21	98	11	211	23
DIGESTION	237	26	178	20	277	31

* Positive result either from rectum or bladder and combining S. haematobium and S. mansoni.

The Digestion method gave the best results thus confirming the findings of previous workers (Gelfand, 1950; Alves, 1958). Moreover, it has the added advantage that the egg-load of the tissue can be determined.

The "snip" method gave results not very different from those of the digestion technique. It has the advantages of being both an extremely simple procedure and by far the least time-consuming. However, no quantitative analysis of the egg load is possible.

The histological technique is the least efficient. The sample is, of course, minute (approximately 5 mgm. as against 20 gm. for digestion). Moreover, it is difficult to identify the species of ova in sections. Histology does however reveal the

nature/...

nature of the lesion.

Incidence of Different Schistosomes:

The overall results are shown in Table VI.

TABLE VI

OVERALL INCIDENCE OF S. HAEMATOBIUM, S. MANSONI & S. MATTHEEI AS DETERMINED BY TWO METHODS IN 900 AUTOPSIES*:

TYPE	SNIP		DIGESTION	
	NO.	%	NO.	%
S. haematobium	231	26	249	28
S. mansoni (total)	58	6	58	6
S. mansoni (pure)	37	4	28	3
S. mansoni & S. haematobium (double)	21	2	30	3
S. mattheei	7	1	20	2
Total +ve (all types)	268	30	277	31

* Combining Rectal & Vesical results.

From Table VI it is seen that the overall incidence of schistosomiasis in the Durban and district Indian and African populations was 31%. 28% had S. haematobium infections, 6% had S. mansoni infections and 3% had both S. mansoni and S. haematobium. Only 2% had S. mattheei infections and these were always associated with S. haematobium.

Age, Sex & Race Incidence

The incidence of all types of bilharziasis according to the Race, Sex and Age is tabulated in Table VII, Table VIII, Table IX and Table X.

TABLE VII/...

TABLE VII

AGE INCIDENCE OF BILHARZIASIS IN 494 - AFRICAN MALE AUTOPSIES

AGES	TOTAL IN AGE GROUP		+ SH		+ SM		+S.MAT		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
2 - 9	65	13.2	4	6.2	0	0	1	1.5	4	6.15
10 - 19	32	6.5	14	43.7	7 (3)	22	2	6.3	17	53.1
20 - 29	72	14.6	28	39.0	4	0.6	0	0	28	39.0
30 - 39	101	20.4	38	37.6	12 (6)	12.0	5	5	44	44.0
40 - 50	163	33.0	57	35.0	11 (7)	6.7	5	3.1	64	39.0
50+	60	12.3	8	13.3	4 (2)	6.6	0	0	10	16.3
Overall Total :	493	-	149	30.1	38 (18)	7.7 (3.6)	13	2.6	167	33.8

* Figures in parenthesis refer to pure S. mansoni infections.

From these tables it is apparent that in the African the highest incidence of bilharziasis is in the 2nd decade. Thereafter the infection maintains a constant rate in the 3rd - 6th decades and then rapidly diminishes.

The/...

TABLE VIII

AGE INCIDENCE OF BILHARZIASIS IN 330 AFRICAN FEMALE AUTOPSIES

AGES	TOTAL IN AGE GROUP		+ SH		+ SM		+ S.MAT		TOTAL + VE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
2 - 9	70	21.2	7	10	1	1.4	0	0	7	10
10 - 19	31	9.4	10	32.2	1 (1)	3.2	0	0	11	35.4
20 - 29	42	12.7	12	28.6	2 (1)	4.8	1	2.4	13	30.1
30 - 39	68	20.6	24	35.6	3 (1)	4.4	0	0	25	36.8
40 - 50	79	24.0	21	26.6	2 (1)	2.5	3	3.8	22	27.8
50+	40	12.1	7	17.5	1 (1)	2.5	1	2.5	8	20.0
Overall Total :	330	-	81	24.5	10 (5)	3 (1.5)	5	1.5	86	26

* Figures in parenthesis refer to pure S. mansoni infections

The tables reveal that 30% of African males, 33% of Indian males and 24.5% of African females harboured S. haematobium.

7.7% of African males were infected with S. mansoni (3.6% pure S. mansoni infection) compared with 15.4% (9.6% pure S. mansoni) in the Indian group ($p = 0.19$). Only 3% (1.5% pure infections) of the African females harboured S. mansoni infections.

Thus/...

TABLE IX

AGE INCIDENCE OF BILHARZIASIS IN 52 INDIAN MALE AUTOPSIES

AGES	TOTAL IN AGE GROUP		+ SH		+ SM		+ S.MAT		TOTAL +	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
2 - 9	6	12	0	0	0	0	0	-	0	0
10 - 19	10	19	4	40	1 (1)	10	0	-	5	50
20 - 29	9	17	5	56	3 (1)	33	0	-	6	67
30 - 39	10	19	2	20	0	0	1 (1)	-	3	30
40 - 50	10	19	5	50	1	10	0	-	5	50
50+	7	14	1	14	3 (3)	43	0	-	4	57
Overall Total :	52	-	17	32.7	8 (5)	15.4	1	-	23	44.2

Figures in parenthesis refer to pure S. mansoni infections.

TABLE X

INCIDENCE OF BILHARZIASIS IN 25 INDIAN FEMALE AUTOPSIES:

(Insufficient for break-down.)

TYPE	NO.	%
SH	4	16
SM	2	8
S. MAT.	1	4
Total +ve	4	16

From/...

Thus it would appear in the local Indian and African male populations that S. haematobium infection is almost four times as common as S. mansoni infection. It is eight times as common in the African female.

These studies also demonstrate the relative rarity of S. mattheei infections in the local population. In no instance was there a pure S. mattheei infection - it was always associated with S. haematobium.

2. INCIDENCE OF S. HAEMATOBIUM IN SCHOOL CHILDREN

The World Health Organisation Expert Committee on Bilharziasis (Anon: 1953) decided for numerous reasons that children of school-going age constituted the best material for comparative infection rates.

Materials & Methods

In each of two widely separated areas in Durban a

pair/...

pair of schools, one Indian and one African, in proximity to one another, were selected so as to compare the two social groups under similar exposure. The fifth school comprised coloured school children. Urine specimens from a total of 1014 children were examined. Ages ranged from 6 - 16 years.

Results

These results are summarised in Tables XI, XII & XIII.

TABLE XI

INCIDENCE OF BILHARZIASIS IN COLOURED SCHOOL-CHILDREN

SCHOOL	MALE			FEMALE			TOTAL		
	NO.	SH+	%	NO.	SH+	%	NO.	SH+	%
BRIARDENE	106	5	4.7	89	1	1.1	195	6	3.07

TABLE XII

INCIDENCE OF BILHARZIASIS IN AFRICAN SCHOOL-CHILDREN

SCHOOL	MALE			FEMALE			TOTAL		
	NO.	SH +	%	NO.	SH +	%	NO.	SH +	%
Stormville Redhill	87	11	12.6	87	8	9.2	174	19	11
Marantha-Umhlatuzana	113	80	70.8	86	54	62.7	199	134	67
TOTAL	200	91	45.5	173	62	35.8	373	153	41

TABLE XIII/...

TABLE XIII

INCIDENCE OF BILHARZIASIS IN INDIAN SCHOOL-CHILDREN

SCHOOL	MALE			FEMALE			TOTAL		
	NO.	SH +	%	NO.	SH +	%	NO.	SH +	%
Redhill	138	2	1.4	108	3	2.8	246	5	2
Umhlatuzana	100	30	30.0	100	5	5.0	200	35	17.5
TOTAL	238	32	13.4	208	8	3.8	446	40	9

The overall incidence of S. haematobium infection in the 1014 school children thus examined was 19.6%. However, the varying rates in different areas demonstrate the focal endemicity of the disease. In an area of high endemicity like Umhlatuzana, the incidence in the African group (male and female) was 67%, whilst in the Stormville group, the incidence, in a similar age group, was only 11%. This trend is also shown by the Indian group; the Umhlatuzana group (male and female) having an incidence of 17.5% but only 2% in the Redhill area.

It is also apparent from the tables that there is little difference between the African male and female rates in children. By contrast, there is a marked difference in the sex incidence in Indian children. Whereas 30% of the boys were infected in Umhlatuzana, only 5% of the girls from the same school showed infection with S. haematobium.

African school children have the highest incidence (41%) - being almost five times that of the Indian group (9%) whilst Coloured school children have the lowest rate (3%).

3./...

3. INCIDENCE OF S. HAEMATOBIUM IN MEDICAL OUT-PATIENTS

Materials & Methods

The results of 2200 urine specimens examined in the laboratory attached to the King Edward VIII Hospital out-patients department were analysed. Specimens examined from children under two years of age were excluded from this study. Of these, 688 were from Indian and 1512 from African patients. The ages ranged from 2 - 75 years of both sexes.

Choice of Specimens:

These were "routine" specimens passing through the laboratory. As the majority of patients presented with "medical complaints", a mid-stream specimen of urine was usually requested by the physician-in-charge for examination. A certain unknown number of patients, however, presented with terminal haematuria as their main complaint, and in these cases, presumably a terminal specimen of urine was examined. As discussed in an earlier chapter, Bennie (1949), Gerritsen et al. (1953) and Stimmel & Scott (1956) have demonstrated that the early afternoon specimen was most likely to reveal ova of S. haematobium. More recently, Jordaan (1960) and Onori (1962) have confirmed these observations. As the "best" specimen was not examined in a high proportion of these cases, it is probable that the incidence of bilharzia is higher than that revealed. This should be borne in mind in the interpretation of the results.

Results

The results are tabulated in Table XIV.

TABLE XIV/...

TABLE XIV

INCIDENCE OF S. HAEMATOBIUM IN ROUTINE

OUT-PATIENT URINE SPECIMENS.

RACE	TOTAL NO. EXAMINED	S. HAEMATOBIUM	
		NO.	%
AFRICAN	1512	387	25.6
INDIAN	688	169	24.6
TOTAL	2200	556	25.3

The incidence of S.haematobium is almost equal in the two race groups and does not differ greatly from the figures revealed by digestion of autopsy material, or from those shown by the single urine examination of school children of the same race groups.

OVERALL INCIDENCE OF S. HAEMATOBIUM

The results obtained from all the methods applied are tabulated in Table XV.

TABLE XV/...

TABLE XV

INCIDENCE OF S. HAEMATOBIUM INFECTIONS IN THE DURBAN AREA AFRICANS & INDIANS BY VARIOUS METHODS:

METHOD OF EXAMINATION:	AFRICAN			INDIAN			TOTAL		
	No.Examined	SH+	%	No.Examined	SH+	%	No.Examined	SH+	%
P.M. BLADDER AND RECTAL SNIP	-	-	-	-	-	-	900	231	26
P.M. HISTOLOGY	-	-	-	-	-	-	900	211	23
P.M. DIGESTION	823	230	28	77	21	27.3	900	249	28
URINE EXAMINATION (SCHOOLS)	373	153	41	446	40	9.0	819	193	23.5*
URINE EXAMINATION (O.P. - K.E.H.)	1512	387	25.6	688	169	24.6	2200	556	25.3

* Excluding coloured children.

From the Table it is apparent that the overall incidence of Bilharziasis in the local African and Indian populations, as ascertained by any method, is of the order of 28%. Surprisingly, all three methods gave very similar results.

4. INCIDENCE OF S. MANSONI IN AUTOPSY MATERIAL

Mass survey to determine the prevalence of S. mansoni infections is not easy. A general population survey either by stool examination or by rectal snip method, could not be done.

However, it is believed that a sufficiently large

group/...

group has been sampled by the autopsy digestion technique and that the results therefrom are fairly representative of the population. The materials and methods were the same as described earlier.

Results

These results have been tabulated in detail for race, sex and age in Tables VII, VIII, IX & X.

Table XVI compares the rectal snip findings at autopsy and the results of tissue digestion.

TABLE XVI

INCIDENCE OF S. MANSONI INFECTION IN AFRICANS & INDIANS AT AUTOPSY:

RACE	RECTAL SNIP:				DIGESTION:			
	PURE SM	%	TOTAL SM.	%	PURE SM	%	TOTAL SM.	%
INDIAN [1]	6	7.8	10	13	5	6.5	10	13
AFRICAN [2]	31	3.7	48	11.3	23	2.8	48	11.3
TOTAL	37	4.1	58	6.4	28	3.1	58	6.4

[1] Total Number Examined : 77.
[2] " " " : 823.

Table XVI reveals that there was no difference in the overall results by the two methods, the rectal snip technique being as efficient as the digestion technique. Moreover, the technique is simple and rapid and such a procedure could be adopted routinely in autopsy work for diagnosis of S. mansoni.

A/...

A slightly higher incidence of pure S. mansoni infection was found by snip results than by digestion. This is explained by the fact that in some instances of mixed infection, the S. haematobium infection was not detected by the snip technique.

5. INCIDENCE OF S. MANSONI IN CLINICAL STUDY

Materials & Methods

The author was in charge of the bilharzial out-patient clinic at the King Edward VIII Hospital during the years 1963-1964 (part-time capacity). Rectal snips were done on patients who presented initially with terminal haematuria and in whom S. haematobium were found in the urine.

A child's proctoscope was inserted into the rectum (in adults and children) and a snip of mucosa, no larger than a rice grain, was obtained by means of a punch biopsy under direct vision. This was squashed between two microscope slides, bound with adhesive strapping and examined immediately.

A total of 225 patients, of which 75 were Indians and 150 Africans, were examined. The large majority were males.

Results

The results are tabulated in Table XVII.

TABLE XVII/...

TABLE XVII

RECTAL BIOPSY RESULTS OF 225 PATIENTS WITH S. HAEMATOBIUM INFECTIONS.

RACE:	TOTAL EXAMINED	SM+	%	SH+	%
INDIAN	75	20	23	48	64
AFRICAN	150	25	17	117	78
TOTAL	225	45	20	165	73.3

S. mansoni was detected in 20% of the 225 patients harbouring S. haematobium. The probability of chance double infections is less than 2% (calculated from Table VI) and the rate of 20% probably reflects the similar transmission of the two parasites, both Physopsis sp. and Biomphalaria sp. inhabiting the waters around Durban. Surprisingly, the digestion technique revealed an overall mixed infection rate of only 3% (Table VI). However, of the 249 autopsy cases with S. haematobium, 12% had a mixed infection.

An interesting finding was that in proven S. haematobium infections (ova recovered in urine) approximately 75% have rectal involvement as well. It also reveals that rectal biopsy as a means of diagnosing S. haematobium infections is only 75% accurate. From post mortem rectal biopsy studies, only 51.5% (128/249) of S. haematobium infections were detected by this method.

DISCUSSION

From the results obtained, it is apparent that the overall incidence of S. haematobium infections in the Durban

African/...

African and Indian population is of the order of 30%, whilst that of S. mansoni is under 10%.

The focal encemic nature of the disease is demonstrated by the high incidence of S. haematobium in school children in one area (67%) whilst in another area in a similar group the incidence was only 2%.

The overall incidence quoted contrasts with the opinion of Elsdon-Dew (1962) that approximately 100% of the population are probably infected with S. haematobium and that at least a quarter of a million are infected with S. mansoni (1964).

According to the results demonstrated in this study, the Durban area falls in the "endemic" area as defined by Manson-Bahr (1958) unlike the hyperendemic areas of Egypt (Mousa, 1962), Mozambique (Prates & Gillman, 1959) and Rhodesia (Gelfand, 1950).

The incidence of S. mansoni in Durban (10%) is also considerably lower than that cited by Pitchford (1954 - 77.6% - 41.9%), Azar, et al. (1958 - 61%) and Schneider (1958 - 32.7%) for the Transvaal lowveld.

From the findings in this study, S. haematobium is almost three times as common as S. mansoni infections. This is contrary to the finding of Cosnett (1957) that ova of S. mansoni were found in stool as commonly as ova of S. haematobium in urine of patients in King Edward VIII Hospital. The results reveal the simplicity and efficiency of the rectal-snip for the diagnosis of S. mansoni infections in autopsy material.

The incidence of S. haematobium in the two race groups in Durban is approximately equal. The overall incidence in the autopsy material and that in the out-patient group is similar. There is, however, a marked racial difference in the school-going

age/...

age group (compare 41% for Africans with 9% for Indians).

Whereas there is a higher incidence of bilharziasis in the African male compared with the African female in autopsy material, no such difference exists in African school children. However, there is a marked sex difference in Indian school children, bilharzia being six times as common in boys as in girls in the same school. Prates & Gillman (1959) found only a slight preponderance of males in Mozambique whilst Mousa (1962) stated that in Egyptian peasants the rate of infection was definitely higher in males.

Tables VII, VIII & IX show the age incidence of S. haematobium infections in autopsy material, and that the incidence is highest in the second decade, which is in agreement with the reports of Mousa (1962) and Prates & Gillman (1959). However, in contrast to the reports of these authors that thereafter the infection rates decrease considerably, the present author found that the rate of infection is maintained at a high level up to the fifth decade and only in the sixth decade does the incidence decline considerably.

Both autopsy results and the rectal biopsy findings in clinical patients confirm the experience of previous observers that rectal biopsy is a simple and efficient procedure for the diagnosis of S. mansoni infections and that approximately 75% of S. haematobium infection can be similarly detected (Figs. 2 - 7).

The autopsy results revealed the minor problem of zoonosis - S. mattheei being present in 2% of cases. However, in no instance was there a pure S. mattheei infection, this parasite always being associated with S. haematobium infections. Rectal biopsy from 225 patients revealed S. mattheei in only 2 cases (Figs. 4, 5, 7).

SUMMARY/...

SUMMARY

(1) The incidence of S. haematobium infection in the local African and Indian population was assessed using three methods:

(a) Autopsy digestion technique in 900 consecutive post mortems (also comparing snip and histology results).

(b) Single urine examination of 1014 school children in the age group 6 - 16 years;

(c) Analysis of urine examination results of 2200 medical out-patients.

The efficacy of the various methods is demonstrated. The overall incidence of S. haematobium infection is not more than 30%.

(2) The incidence of S. mansoni was established by:

(a) Autopsy digestion technique and rectal snips in 900 consecutive post mortems, with an incidence of 6.4%.

(b) Rectal biopsies performed on 275 clinical patients with S. haematobium infection, with an incidence of 20%.

It is believed that the probable incidence is of the order of 10%.

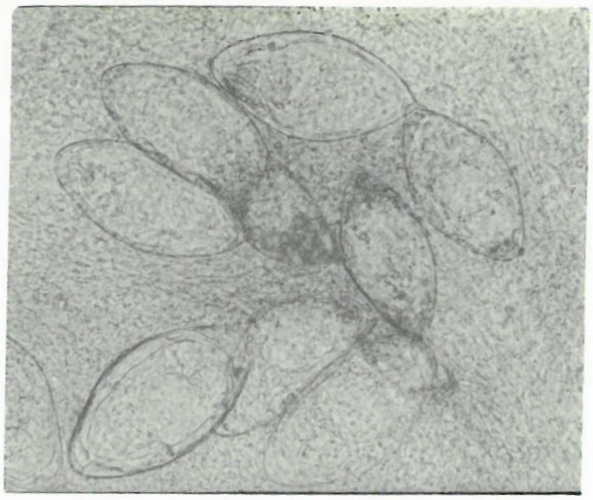
(3) The incidence of S. mattheei infection was shown to be 2% in the total autopsy material.

(4) Whereas only 12% of S. haematobium infections had concomitant S. mansoni infections in autopsies, the incidence of double infections in 225 S. haematobium infections was 20%.

(5) The race and sex incidence of schistosomiasis in the local population was demonstrated.

(6) These results were compared with those quoted by other local workers and also with the results of workers in other endemic areas.

CHAPTER IV/...



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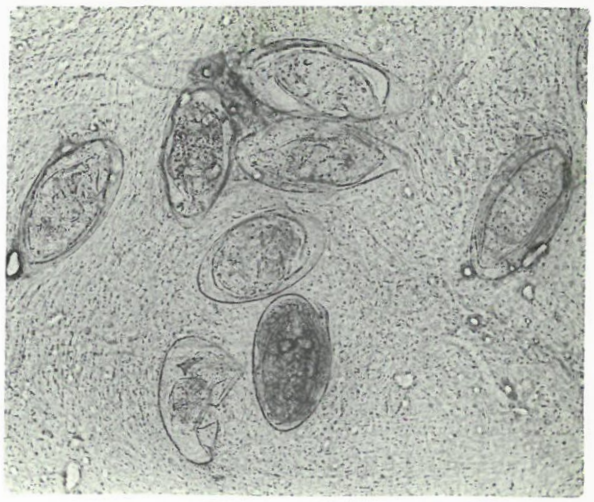

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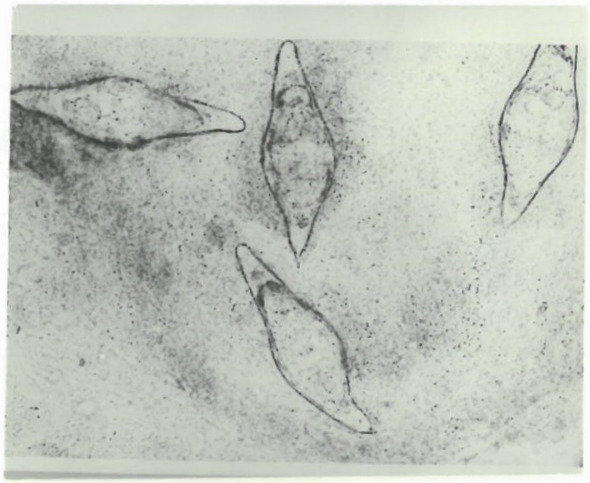

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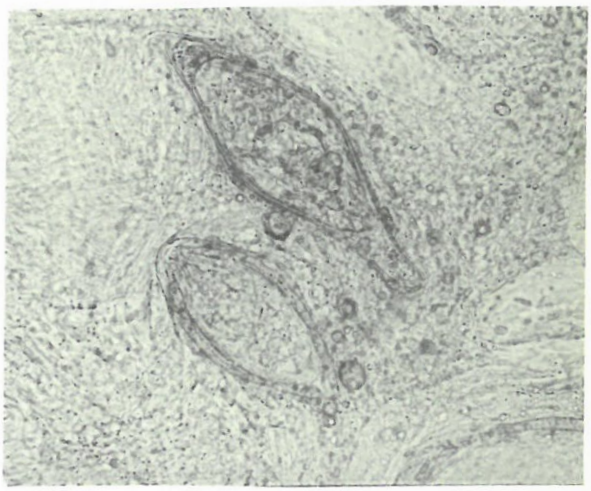

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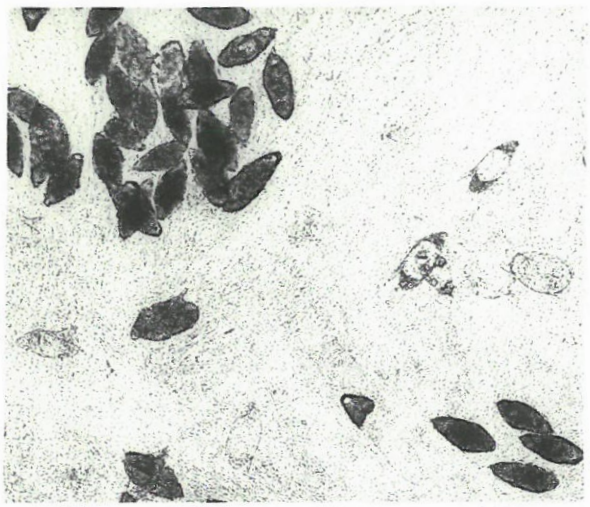

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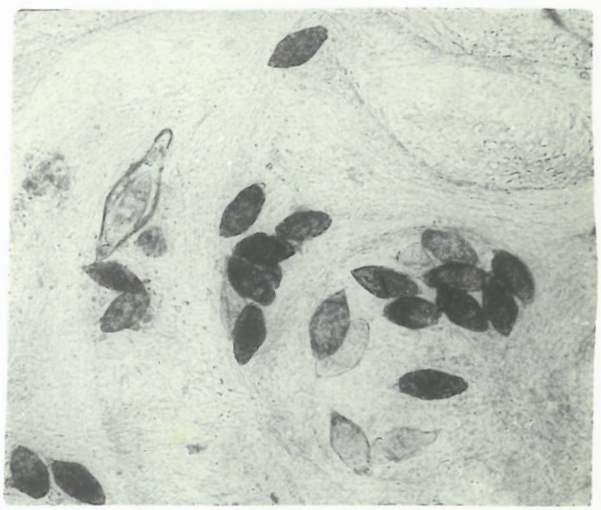

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CHAPTER IV

U R I N A R Y S C H I S T O S O M I A S I S

A. CLINICAL PRESENTATION

INTRODUCTION

The clinical presentation of Urinary Bilharziasis (aetiological agent S. haematobium) was comprehensively described by Fairley (1919b) as early as 1919. He recorded and described the progression of the symptoms and the disease in Australian troops stationed in Egypt and recognised two stages : (a) the "toxaemic" stage; which he likened to Katayama Disease (Miyagawa, op.cit. Fairley, 1919) and (b) the later stage when the disease had localised to the bladder. The first stage became manifest 4-10 weeks after the initial infection and the second stage "from three months up to two and a half years after infection" (Fairley, 1919b).

Since then the subject has received the attention of workers in all the major endemic areas of S. haematobium in Africa. Cawston (1920), Vermooten (1937) and Campbell-Begg (1944) amongst earlier workers, described the clinical presentation of the disease in South Africa.

Barlow & Meleney (1949) recorded the chronological progress of all aspects in a voluntary infection of one of the authors. It is interesting that in this case ova were recovered first from the seminal fluid and later from the stool, even before they appeared in the urine.

The observations of the various authors have been crystallised in the presentation of Faust & Russell (1964) who

divide/...

divide the clinical manifestations into three stages:

(i) Incubation stage - lasting 10-12 weeks, from the time of exposure until eggs are first deposited.
(ii) Stage of egg deposition and extrusion.
(iii) Period of tissue proliferation and repair.

The symptomatology differs in the three stages. In the first stage though Faust & Russell (1964) describe features akin to the Katayama Syndrome, many observers, including Vermooten (1937), Campbell-Begg (1944), Gelfand (1950) and Manson-Bahr (1958), have emphasised the lack of symptoms in this period.

In the second stage or stage of egg deposition and excretion, these authors emphasised that the only symptom may be a painless terminal haematuria. Associated symptoms may be pain or "scalding" in the urethra, supra-pubic pain and frequency of micturition.

Symptoms in the late stage of the disease are related to involvement of the upper renal tract (Makar, 1948; Kisner, 1952; Marcks, 1956; Honey & Gelfand, 1960) or to such vesical complications as fibrosis and ulceration (Sayegh, 1950; Dimmette et al., 1956; Marcks, 1956 and Honey & Gelfand, 1960).

PRESENT STUDY

The present study was undertaken to determined the clinical presentation of urinary bilharziasis (S. haematobium) in the Durban Indian and African population.

Materials & Methods

225 patients with active urinary bilharziasis were investigated. Viable ova of S. haematobium were recovered from the urine of all patients. Detailed history and clinical examination findings were recorded. Special laboratory investigations

included/...

included:

(i) Rectal biopsy.
(ii) Urine examination.
(iii) Haematological examination.
(iv) Serum electrophoretic protein studies.

The age and race distribution of the patients is set out in Table I. Only 19 females were included in this study.

TABLE I

AGE AND RACE DISTRIBUTION OF 225 PATIENTS WITH S. HAEMATOBIUM

AGE RANGE IN YEARS:	AFRICAN		INDIAN	
	NO.	%	NO.	%
5 - 10	18	12	3	4
10 - 15	58	39	28	37
15 - 20	56	37	27	36
20 - 25	15	10	10	13
25 - 30	3	2	2	3
30+	0	0	5	7
TOTAL	150		75	

The majority of patients were in the 2nd and 3rd decade.

Results.

Symptomatology:

The presenting symptomatology is summarised in Table II.

TABLE II/...

TABLE II

SYMPTOMS OF PATIENTS WITH ACTIVE URINARY BILHARZIASIS

SYMPTOMS	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
Terminal haematuria	149	99	72	96	221	98
Frequency of micturition	99	66	51	68	150	67
Terminal dysuria*	106	71	39	52	145	64
Suprapubic pain	33	22	12	16	45	20
Iliac fossa pain	10	7	12	16	22	10

* Terminal Dysuria includes: a "burning" sensation, discomfort or "prickly" sensation, at the end of micturition.

It is evident from Table II that in the active phase of the disease terminal haematuria is the commonest presenting symptom (98%). In the majority of the patients this amounted to a few drops of fresh blood at the very end of micturition whilst only in a small number was the entire stream bloody. It is also evident that terminal dysuria and frequency of micturition were prominent symptoms. All patients presented with more than one symptom.

Although a history of exposure to infection was obtained from all patients, none recalled symptoms suggestive of "swimmer's itch" (cercarial penetration) or of the Katayama syndrome (toxic invasive phase). Both Walt (1954) and Lurie (1953) recorded symptoms of the toxic phase (Katayama Syndrome) in European patients and Fairley (1919b) first described it in

association/...

association with S. haematobium in Australian troops in Egypt, but in the present series, it apparently passed unnoticed. It was impossible to relate the appearance of symptoms to the probable date of exposure.

The duration of symptoms before patients sought medical attention is summarised in Table III.

TABLE III

DURATION OF SYMPTOMS IN PATIENTS WITH ACTIVE URINARY BILHARZIASIS

DURATION (IN MONTHS)	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
< 1	20	13	12	16	32	14
1 - 3	23	15	18	24	41	18
3 - 12	29	19	18	24	47	21
12 - 24	35	23	10	13	45	20
24 - 36	15	10	7	9	22	10
36+	25	17	8	11	33	15
Unknown	3	2	2	3	5	2

The long delay in seeking medical attention suggests that symptoms were not severe.

The relative asymptomatic nature of the disease also became apparent during a separate survey of school children to ascertain the incidence of bilharziasis. In one African school, 70% of the children examined had S. haematobium infection with macroscopic evidence of haematuria, yet none complained of any symptoms. Campbell-Begg (1944) and Elsdon-Dew (1962) emphasised the asymptomatic nature of S. haematobium infections generally.

Physical/...

Physical Examination:

All the patients appeared in good health. No significant abnormalities were found.

Urine Examination:

A terminal specimen of urine was examined microscopically in every case. All had red blood cells, pus cells, albumin (from + to +++) and viable ova of S. haematobium.

A midstream specimen of urine from 40 patients was submitted for bacteriological studies. In every case the urine was sterile and it soon became evident that the "pus cells" in the urine of cases with active bilharziasis did not signify secondary bacterial sepsis. Cognisance of the eosinophilic nature of bilharzial granlomata (vide infra) led to the concept that the so-called pus cells were in fact eosinophils.

To confirm this, a smear of the urinary sediment stained by the H & E method was examined. To determine the relationship, if any, between blood eosinophilia and probable urinary eosinophils, a differential cell count was done on both urine and blood in 20 cases. In these cases culture of a mid-stream specimen of urine also proved sterile. The differential cell counts are set out in Table IV.

Eosinophils are a prominent feature of the cellular exudate in the urine, but there was no correlation between the blood and urine pictures. Fairley (1919b) as early as 1919 had emphasised " - the fact that the majority of the pus cells in the bilharzial exudate are eosinophils -" and Hutchison (1928) made a similar observation. It is surprising that this fact is not more generally recognised.

TABLE IV/...

TABLE IV

URINE EOSINOPHIL COUNT COMPARED WITH BLOOD EOSINOPHIL COUNT IN 20 RANDOM CASES OF ACUTE S. HAEMATOBIUM INFECTION

URINE	BLOOD	
% EOSINOPHILS	% EOSINOPHILS	TOTAL EOSINOPHILS
78	43	4500
76	15	1670
75	5	420
66	28	3050
64	20	940
52	50	3500
52	12	470
51	21	1430
48	19	2310
41	32	2530
35	3	352
34	28	1710
33	14	1880
32	12	880
30	17	1700
23	17	1580
22	9	900
22	1	100
20	16	950
3	2	260

Although in the present study no evidence of secondary bacterial cystitis was evident, Gelfand (1950) reported that of

his/...

his patients with active bilharziasis 28% had secondary bacterial sepsis.

Rectal Biopsy Results:

The rectal biopsy results are summarized in Table V.

TABLE V

RECTAL BIOPSY RESULTS IN 225 CASES WITH S. HAEMATOBIUM INFECTIONS

TYPE	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
S. haematobium	117	78	48	64	165	67
S. mansoni	25	17	20	23	45	20

A remarkable feature was that rectal biopsy revealed a hitherto unsuspected S. mansoni infection in 20% of cases. In addition, though generally considered a bladder parasite, rectal biopsy showed eggs of S. haematobium in 67% of cases.

Special Investigations

The following investigations were carried out:

(a) Haematological
  (i) Haemoglobin
  (ii) White cell count
  (iii) Eosinophil count
  (iv) E.S.R.

(b) Biochemical
  (i) Serum Electrophoresis

(ii)/...

(ii) P.I.
(iii) Serum Bilirubin
(iv) Alkaline Phosphatase
(v) Thymol & Zinc turbidity tests.

(a) Haematological

(i) Haemoglobin: (Hb)

The results are summarised in Table VI.

TABLE VI

HAEMOGLOBIN VALUES IN 225 PATIENTS WITH S. HAEMATOBIUM INFECTION

Hb/in gm/%.	AFRICAN	INDIAN	TOTAL	%
10.5 - 11.0	4	0	4	2
11.0 - 11.5	7	1	8	4
11.5 - 12.0	8	5	13	6
12.0 - 12.5	21	11	32	14
12.5 - 13.5	46	20	66	29
13.5 - 14.5	32	16	48	21
>14.5	32	22	54	24

Only 12% of patients had a haemoglobin value of under 12 gm.%. It is apparent that in this series there is no significant anaemia. Fairley (1919b) reported that in his studies, "the average grade of anaemia was extremely slight".

(ii) White Cell Series:

The total leucocyte counts are summarised in Table VII.

TABLE VII/...

TABLE VII

LEUCOCYTE COUNTS IN 225 PATIENTS WITH S. HAEMATOBIUM INFECTIONS

RANGE	AFRICAN	INDIAN	TOTAL	%
5 - 10,000	93	47	140	62
10 - 12,000	34	19	53	24
12 - 15,000	16	3	19	9
15 - 20,000	4	6	10	4
20,000+	3	0	3	1

Wintrobe (1961) quotes the normal range for adults as being between 5,000 - 10,000 per cmm. but concedes that wider ranges have been recorded. The upper limit for a normal count in children up to 18 years old, according to him, is around 13,500. In this study only 14% of patients had a leucocyte count of more than 12,000.

(iii) Eosinophilia:

The absolute eosinophil counts in all patients is summarised in Table VIII.

Wintrobe, (1961) states that the normal count is up to 250 per cmm. In the present study 95% had an eosinophil count in excess of 250. The wide variation in counts is evident from Table VIII. In five patients the eosinophil count was over 7,000. These were as follows:

Eosinophil/...

Eosinophil count	Total white cell count
7,183	13,000
7,645	14,000
7,892	13,000
11,550	22,000
17,600	22,000

TABLE VIII

EOSINOPHILS (TOTAL COUNT) IN 225 PATIENTS WITH S. HAEMATOBIUM INFECTION

RANGE	AFRICAN	INDIAN	TOTAL	%
0 - 250	9	3	12	5
250 - 500	22	12	34	15
500 - 1,000	38	12	50	22
1,000 - 2,000	40	28	68	30
2,000 - 3,000	18	13	31	14
3,000 - 4,000	9	5	14	6
4,000 - 5,000	6	0	7	3
5,000 - 6,000	3	2	5	2
\6,000	5	0	5	2

Fairley (1919b) first demonstrated that eosinophilia was most prominent in the toxic phase (Katayama Syndrome) and gradually diminished from the sixth to the eighteen month after infection. Walt (1954) and Lurie (1953) emphasised the eosinophilia in the toxaemic phase of their patients. The eosinophilia, shown in the present study, was apparently still present in the second, or egg-laying stage.

(iv)/...

(iv) Erythrocyte Sedimentation Rate (E.S.R.)

The E.S.R. (Wintrobe method, result read after one hour) results are summarized in Table IX.

Girls were excluded.

Accepting 10 as being the upper limit of normal, then 82% had a raised E.S.R. The range is evident from Table IX. Other possible causes for a raised E.S.R. were not excluded and the significance of the results are doubtful.

TABLE IX

E.S.R. VALUES IN PATIENTS WITH S. HAEMATOBIUM INFECTION (WINTROBE : 1 HR.)

RANGE	AFRICAN	INDIAN	TOTAL	%
5	7	10	17	8
5 - 10	13	7	20	10
10 - 20	32	20	52	25
20 - 30	36	15	51	24
30 - 40	32	13	45	21
40+	20	5	25	12

(b) Biochemical

(i) Serum Electrophoresis

Serum Proteins

The serum proteins were studied by electrophoresis in both Indian and African patients. As the estimations

were/...

were done in the same laboratory, the results can be compared with the series of Joubert et al. (1959) who studied the racial differences of serum proteins of apparently healthy Durban European, Indian and African subjects, hereafter referred to as the control group.

The results of the present study are summarised in Table X.

TABLE X

SERUM ELECTROPHORETIC PATTERN OF AFRICAN AND INDIAN BILHARZIAL PATIENTS

(in g/%)

	AFRICAN		INDIAN	
	MEAN	S.D.	MEAN	S.D.
TOTAL PROTEIN	7.10	0.65	7.07	0.62
ALBUMIN	2.38	0.53	2.72	1.11
GLOBULIN	4.60	0.75	4.42	1.05
GAMMA GLOBULIN	2.10	0.42	2.20	0.47

S.D. = Standard Deviation.

Total proteins

Comparison of the total protein findings in the bilharzial group with the corresponding control groups, showed no significant difference in either the African ($P = 0.024$) or the Indian ($P = 0.38$). Similarly, within the bilharzial group there was no difference ($P = 0.16$) between the 2 races (Table X). The results are shown graphically in Fig. 8.

Albumin/...

Albumin Levels

The Albumin levels of the 2 racial groups with bilharziasis (Table X) not only differed one from the other ($P = 0.006$) but were significantly lower than the corresponding control groups. (African : $P < 0.01$; Indian : $P = < 0.01$). The results are shown graphically in Fig. 9.

Globulin Levels

No significant difference was apparent between the African (S.D. = 0.75) and Indian (S.D. = 1.05) bilharzial patients (Table X). Neither did the results differ from those of the controls.

Gamma Globulin

Though there was no racial difference ($P = 0.08$) within the Bilharzial group (Table X), comparison with the controls shows much higher levels of gamma globulins (African : $P < 0.01$; and Indian $P : < 0.01$). This is even more apparent on the graph (Fig. 10).

From these findings, it is apparent that in the Bilharzial group none of the protein fractions showed any racial difference except that Indian patients had a significantly higher albumin level.

No significant difference was apparent in the total proteins or globulins of controls and Bilharzial patients, but the latter showed a significantly lower albumin and raised gamma globulin fractions.

Bersohn & Lurie (1953) in experimental infections of monkeys demonstrated that gamma globulin showed a significant increase around 25 weeks after the initial infection and noted that the albumin fraction showed a corresponding decrease .

They/...

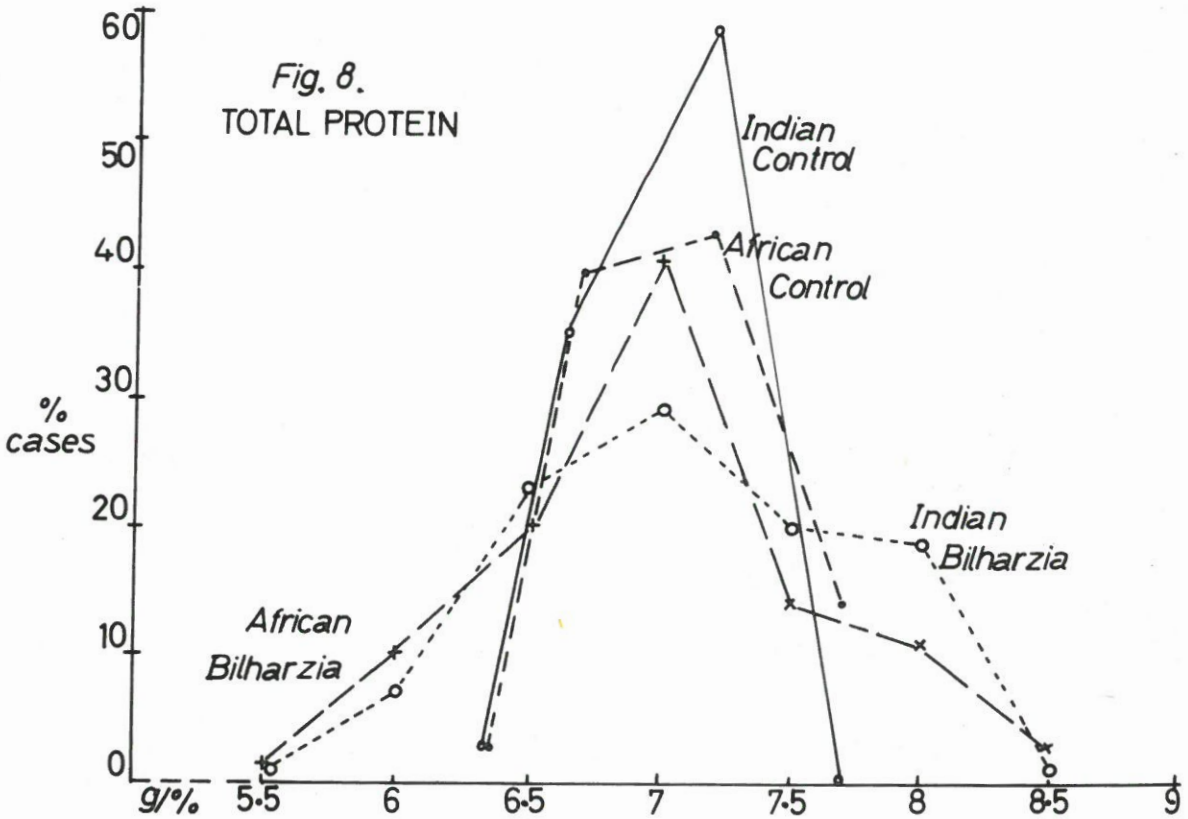


Fig. 8.
TOTAL PROTEIN
Indian Control
African Control
Indian Bilharzia
African Bilharzia
% cases
60
50
40
30
20
10
0
g/%
5·5
6
6·5
7
7·5
8
8·5
9

Fig. 9.

SERUM ALBUMIN

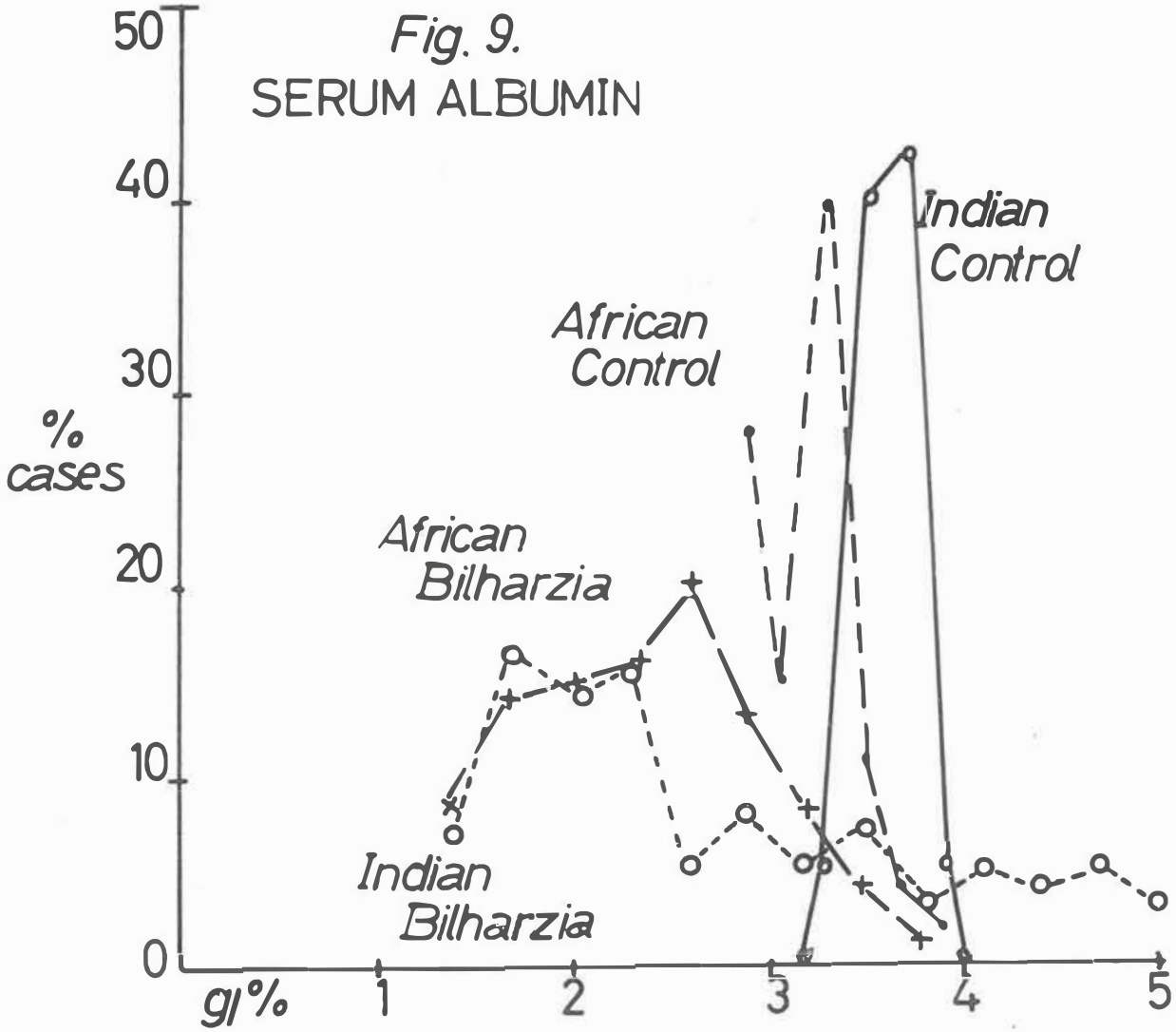
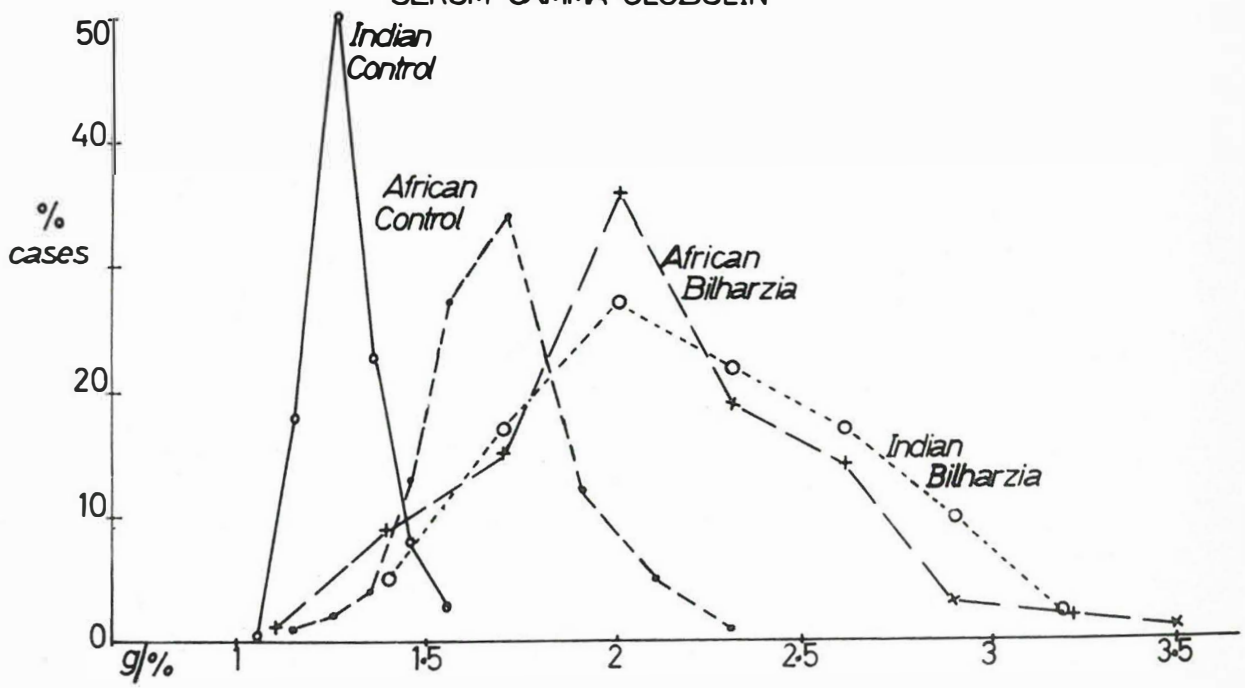


Fig. 10.

SERUM GAMMA GLOBULIN



They suggested that the gamma globulin increase resulted from a generalised stimulation of the reticulo-endothelial system and the decrease in the albumin was a manifestation of parenchymal liver damage. Bruce et al. (1963), also from experimental evidence, confirmed these observations.

El Mofty (1962) discussing electrophoretic studies in Hepatic Bilharziasis reported a moderate decrease in the albumin levels but a pronounced increase in the gamma globulin and alpha globulin fractions.

The present study revealed that bilharzial patients have a raised gamma globulin and a corresponding decrease in the albumin levels.

Other Liver Function Tests

Other liver function tests examined in the present study were prothrombin index, serum bilirubin, alkaline phosphatase, thymol turbidity and zinc turbidity. All the results were within normal ranges except the turbidity tests which gave anomalous results. The significance of these have been discussed by Joubert et al. (1959).

SUMMARY

The symptomatology of urinary bilharziasis in the Durban African and Indian has been presented and no racial difference was apparent. It has been shown that the commonest presenting symptom was terminal haematuria and that a surprisingly large number of active infections are asymptomatic.

The acute toxaemic stage of the disease (Katayama

disease/...

disease) was not encountered in this study. Walt (1954) and Lurie (1953) however reported typical Katayama disease in Europeans of South Africa. Manson-Bahr (1958) reported that Katayama disease, when encountered in East Africa, was frequently found to affect the Asians and Europeans. He postulated that the lack of immunity in the immigrant compared with the high immunity of a native population in an endemic area probably accounted for this difference in clinical presentation. It will be remembered that Fairley (1919b), like Walt (1954) and Lurie (1953) described the toxaemic Katayama disease in Europeans.

It is apparent that the clinical presentation of the disease may be altered by the level of immunity (Manson-Bahr, 1958).

The clinical presentation of the disease in the active stage of egg deposition and excretion in the Durban Indian and African has been demonstrated and compared with the reports of other workers. Urinary eosinophilia, first reported by Fairley (1919b) is emphasised. The haematological findings have been compared with the results of other workers. Eosinophilia, of varying levels, was a prominent feature.

Electrophoretic studies of the serum proteins revealed a raised gamma globulin and a decreased albumin fraction. The results have been compared with those of Joubert et al. (1959) who conducted tests on apparently healthy Durban Indian and African subjects, and with results of other workers.

VESICAL/...

VESICAL & URETERIC BILHARZIASIS

This study was directed at the manifestations of bilharzia shown by the bladder and by the ureters in both clinical cases and at autopsy. The same material was used for both vesical and ureteric studies but the effects on these organs will be discussed separately.

Materials & Methods.

CLINICAL STUDY

108 random patients with known active urinary bilharziasis (S. haematobium positive) were investigated. None of the patients had symptoms suggestive of upper renal tract involvement.

Intravenous pyelogram (IVP) studies were conducted on all and cystoscopic examination on 65 patients. Most of the patients failed to report for follow-up studies but on 13 cases, IVP, and on 25 cases, cystoscopic examination, were repeated at monthly intervals, (Table I).

AUTOPSY STUDY

For this aspect of the study 30 consecutive cases with macroscopic evidence of vesical bilharziasis were selected. The urinary tract, with bladder, ureters and kidneys was removed intact from each case and examined macroscopically. After the specimen had been fixed in 10% formol-saline, specimens for

histological/...

TABLE I

AGE, RACE & NATURE OF SPECIAL EXAMINATION ON 108 CASES WITH URINARY BILHARZIASIS:

AGE RANGE YEARS	INDIAN		AFRICAN		TOTAL	
	IVP.	Cysto-scopy.	IVP.	Cysto-scopy.	IVP.	Cysto-scopy.
10 - 15	14	7	25	13	39	20
15 - 20	14	10	24	15	38	25
20 - 25	11	9	6	1	17	10
25 - 35	6	4	5	3	11	7
35+	1	1	2	2	3	3
TOTAL	46	31	62	34	108	65
REPEAT EXAMINATIONS	6	15	7	10	13	25

histological examination were selected from the following sites:

Bladder : Sections from the trigone, base and some (including any apparent lesions).

Ureters : Sections from both ureteric orifices, and from the lower, middle and upper thirds.

Kidney : A section through and including the renal pelvis.

All sections were stained by H & E, and in appropriate cases Masson's Trichrome, Von Kossa's silver technique for calcium and Weigert's Iron haematoxylin with a Van Gieson counterstain to demonstrate mature collagen were also employed in select cases.

Of the 30 cases, 24 were African males, 2 African

females/...

females and 3 Indian males. The age distribution was as follows:

Age Range	No. of Cases
8 - 15 years	6
15 - 20 years	7
20 - 30 years	8
30 - 40 years	6
40 - 50 years	3

The results of this study will be presented in 2 parts :

VESICAL BILHARZIASIS

and

URETERIC BILHARZIASIS.

B. VESICAL BILHARZIASIS.

INTRODUCTION.

There is an abundance of literature on various aspects of urinary bilharziasis and the vesical lesions produced by S. haematobium. Fairley (1920) noted papillomatous vesical lesions produced experimentally in monkeys. Gordon Shaw (1921) described the cystoscopic appearances in Australian troops serving in Egypt and listed four types of lesion:

(i) Granules of two types, the recent ones being golden-yellow in colour and surrounded by a hyperaemic zone and older, white small papules;
(ii) Areas of fibrosis which he considered to be healed granules. These had a pearly-white, avascular appearance;
(iii) Granulation tissue;
(iv) Polypi and infiltrations.

He made no reference to sandy-patch lesions.

The earliest lesions seen cystoscopically, according to Dew (1923) were tubercles. In autopsy material he noted, what he considered to be lesions "much further advanced and represent the tissue changes resulting from a long standing infection. The same bladder frequently exhibits the two characteristic lesions, papillomata and the so-called 'sandy-patch'". He also noted from histology that the papillomata were proliferative, active lesions, whereas the sandy-patches were atrophic, late lesions.

Hutchison (1928) contrary to the opinion of Dew (1923) regarded the sandy-patch as being an early manifestation and

believed/...

believed that the proliferative lesions developed subsequently in areas of mucosal ulceration. He noted the predominant eosinophil cellular infiltrate in the proliferative lesions.

Girges (1934) cystoscopically recognised 4 stages of bladder involvement:

(i) Congestion of the mucosa, which he considered as being the earliest visible changes and occurring in the toxaemic phase.
(ii) Swollen mucosa, corresponding to the stage of infiltration.
(iii) Tubercles, sandy-patches, vesicles or retention cysts, ulcers and papillomata. He reported that papillomata were either true papillomata or bilharzial granulation tissue and noted that the sandy-patch was due to congregation of dead ova.
(iv) The "cirrhotic" stage of progressive fibrosis.

Makar (1955) identified 8 different macroscopic lesions : (i) bilharzial hyperaemia; (ii) tubercles; (iii) bilharzial nodules; (iv) sandy patches; (v) bilharzial ulcers; (vi) bilharzial granlomata; (vii) ground-glass membrane, and (viii) bilharzial papillomata.

Hashem (1961) from autopsy studies recognised 11 types of lesions. These were (i) the earliest stage with patchy granularity and hyperaemia of the mucosa; (ii) aggregates of bilharzial tubercles giving rise to nodules; (iii) bilharzial polypi or granulomatous lesions; (iv) patchy or diffuse thickening of the mucous membrane; (v) bilharzial sandy patches; (vi) patchy or diffuse villous cystitis; (vii) cystitis pseudoglandularis; (viii) single or multiple benign villous papillomata; (ix) squamous metaplasia with or without leukoplakia; (x) benign squamous cell papilloma, and (xi) bilharzial ulceration.

All/...

All the above reports emanated from Egypt and it is apparent that although there is general agreement on some aspects there is considerable difference of opinion especially in the staging of the disease.

Observers in other endemic areas have similarly described various types of vesical pathology. Thus, Kirkaldy-Willis (1948) describing the cystoscopic lesions in East Africa noted hyperaemia, tubercles, closely set tubercles, granulomatous polypoidal lesions, bullous cysts, ulcers and chronic bilharizl cystitis with a hazy mucosa.

From autopsy studies, Gelfand (1950) in Rhodesia found that sandy-patches were the most common lesion. He also described tubercles, larger plaques of coalesced tubercles and papillomata, which he preferred to call "vesical bilharzioma". Marcks (1956) described the cystoscopic appearances in Rhodesia. He noted tubercles and bilharzial papillomata and like Gelfand, called the latter lesions "papillary bilharzioma". He believed that "massive vesical ovideposition may result in a chronic interstitial cystitis resulting in a small contracted bladder - bilharzial ulcers, in his experience were rare. Honey & Gelfand (1960) from an extensive clinical study of African and European patients, described the cystoscopic lesions as : (i) acute and chronic tubercles; (ii) ground glass appearance of the mucosa; (iii) sandy patches and (iv) areas of granulation tissue appearing sometimes as ulcers or as papillomata.

Prates & Gillman (1959) reviewed the macroscopic lesions in autopsy material in Mozambique and correlated these with the histopathology. They described bilharzial hyperaemia as being the earliest stage followed shortly by bilharzial tubercles, aggregations of tubercles, and polypoidal lesions. Sandy patches were late lesions and if fibrosis was extensive, the mucosa assumed a ground-glass appearance.

There/...

There is some difference of opinion amongst South African workers. Campbell-Begg (1944) noted that sandy patches, granulomata and ulcers were uncommon in the Transvaal. The commonest lesion he found was the tubercle. On the other hand, Kisner (1952) described (i) granulomata, the polypoidal lesions which he considered the earliest lesions; (ii) tubercles, or subacute lesions, and (iii) the late sandy patches, which were fine, coarse or plaque-like. He also described a bilharzial papilloma similar to the "vesical bilharzioma" of Gelfand (1950) but noted that this was a rare finding.

PRESENT STUDY:

The aim of the present study was to correlate the cystoscopic and radiographic observations in clinical cases with the morbid anatomical and histopathological studies of autopsy material. It was intended thereby not only to demonstrate the pathological nature of the various bladder lesions seen clinically, but also to determine the natural history and sequelae of vesical bilharziasis.

Results.

Correlation of the I.V.P. and cystoscopic appearances with the morbid anatomical and histopathological findings indicated that the natural history of vesical bilharziasis may be classified into 3 stages:

1. Acute Stage
2. Subacute or intermediate stage
3. Chronic or late stage.

In each stage, bilharzial involvement may be (i) mild, (ii)

moderately/...

moderately severe, or (iii) severe. The lesions at each stage will be described in greater detail.

STAGES OF VESICAL BILHARZIASIS

1. ACUTE STAGE

(i) Mild Lesions:

The cystoscopic appearance of the mild acute stage is quite typical and is characterised by lesions termed pseudo-tubercles. These are tiny, discrete nodules no larger than a millimetre in diameter. They are golden-yellow in colour with a surrounding halo of hyperaemia. The pseudotubercles may occur in crops or may be discretely scattered but the intervening bladder mucosa is normal in appearance. They are commonly found on the base and trigone but may occur anywhere.

Histopathology of a pseudo-tubercle is characteristic (Figs. 12 & 13). In the centre lies a cluster of viable eggs. Viability has been demonstrated by squash-preparation examination from fresh autopsy specimens. In sections this is suggested by the presence of a mature miracidium and the lack of calcification. The ova are surrounded by a zone of eosinophilic necrosis and around this is a zone of predominantly eosinophil cellular infiltrate. Some lymphocytes and monocytes are also evident. The pseudotubercle is situated in the submucosa with an intact but slightly hyperplastic overlying epithelium (Fig. 13). The surrounding mucosa is normal.

Histology reveals that the pseudotubercle is really

an/...

an eosinophilic microabscess and explains the golden-yellow colour evident on cystoscopy.

(ii) Moderately Severe Lesions:

Cystoscopy reveals 2 types of lesions, tubercles and bilharzial granlomata. The pseudotubercles occur in crops and have the same appearance recounted above.

Bilharzial granulomata, on the other hand, are elevated, flat-topped, haemorrhagic papules approximately 1 cm. in their longest diameter. They are usually surrounded by satellite tubercles and a focal patchy zone of hyperaemia. The lesions are commonest on the base of the bladder and around the ureteric orifices, but, like tubercles, may arise in any site.

Histopathology of such a lesion (Fig. 14) reveals the basic pattern of a pseudotubercle except that the lesions are more extensive. The lesion is usually confined to the submucosa but not infrequently extends into the muscle layer. The overlying epithelium is hyperplastic and pegs of epithelium may extend deep into the submucosa. When their surface connections are lost, the epithelial elements resemble Brunn's nests. At the base of the granuloma, deep to the muscle, adult worms are frequently found in venous channels.

(iii) Acute Severe Lesions:

Cystoscopic examination of these cases reveals a remarkable picture. In addition to pseudotubercles and flat-topped granulomata are numbers of proliferative polypoid lesions with gross features not unlike

raspberries/...

raspberries and mulberries. They are elevated, lobulated and velvety in appearance with a deep purple or reddish hue. Their size varies from 1 - 2 cm. in diameter, and are extremely friable and bleed readily when disturbed with the cystoscope or ureteric catheter. An exudate of altered blood often coats part of the granuloma. Although found in any site, they are commonest around the base and ureteric orifices. They are relatively uncommon in the trigone area. The surrounding mucosa often shows extensive bullous cystitis and a filmy, muco-granular exudate overhangs these lesions.

Histopathology of a proliferative granloma (Fig. 15) is similar to that of the flat-topped granloma. Large numbers of eggs are present in all areas of the lesion, which, although arising in the submucosa, extends to involve all layers. The predominant eosinophil cellular infiltrate is again prominent and areas of eosinophilic necrosis frequently involve the muscle deep to the granuloma (Fig. 19). The epithelium shows a pronounced pseudo-papillary hyperplasia and chords of epithelium extend deep into the submucosa (Fig. 16). The more superficial epithelium may be shed leaving flask-like projections into the submucosa. These epithelial changes are restricted to the area immediately overlying the granuloma. Numerous adult worms are frequently encountered in the veins of the mucosa, submucosa and muscular levels (Fig. 18).

The best descriptive term for these lesions is Proliferative Bilharzial Granlomata.

An interesting observation from I.V.P. and cystogram

studies/...

studies on acute bilharzial patients was the not infrequent finding of filling defects and prominent irregularity of the bladder outline. Subsequent cystoscopy revealed proliferative bilharzial granulomata (Fig. 17).

2. SUBACUTE STAGE

In the subacute stage, all the lesions described above are in the stage of organisation. The cystoscopic appearance is therefore different. The severity of the initial infection determines the type of lesion encountered. Three types of lesions can be recognised (i) the healing pseudotubercle; (ii) Coarse sandy patches, and (iii) Healing granulomata.

(i) Healing pseudotubercles:

The cystoscopic appearance of the subacute healing tubercle differs from that of the acute stage in that they resemble pearly-white sago grains with no surrounding areola of hyperaemia.

Histology (Fig. 21) reveals a centre of calcifying or degenerate ova surrounded by a foreign-body giant-cell reaction. This is encircled by a concentric zone of epitheloid cells and monocytes with a peripheral zone of fibrocellular reaction and variable numbers of lymphocytes and plasma cells. Occasional eosinophils are present.

(ii) Coarse Sandy-patches:

Cystoscopically they resemble areas of wet chamois leather. By follow-up cystoscopic study of acute

cases/...

cases, it was evident that this lesion represented the healing phase of the flat-topped acute granuloma.

Histology reveals a pattern resembling aggregates of subacute pseudotubercles (Figs. 21, 22 & 23). Adult worms are seldom found around these lesions and the epithelium, though ragged, is no longer hyperplastic. Columns of trapped epithelium in the submucosa resemble cystitis cystica and cystitis-glandularis.

(iii) Healing Granuloma:

The cystoscopic appearance of this lesion differs from the acute counterpart in being less vascular, and less polypoid. It has a grey avascular appearance with an organising crust of altered blood and calcium deposition.

Histology demonstrates large numbers of calcifying and degenerate eggs with pronounced fibrocellular and chronic inflammatory cellular reaction (Fig. 20). Eosinophils are not prominent. The surface epithelium is ragged with columns of cells trapped in the submucosa.

3. CHRONIC OR LATE STAGE

In the chronic or late stage; three types of lesions are recognisable : (i) fine sandy-patches; (ii) fibrotic plaques and (iii) bilharzial papillomata.

(i) Fine Sandy Patches:

The sandy patches seen cystoscopically have generally come to be recognised as synonymous with bilharziasis.

The/...

The bladder mucosa is lustreless, golden-brown and finely granular like sand paper. Sandy-patches are commonly seen around the trigone, base and lateral walls. It may be extensive enough to cover the entire bladder.

Histologically the mucosa is atrophic (Figs. 24 & 25) though the trapped epithelial cells described in subacute lesions give rise to lesions identical to those of cystitis cystica (Fig. 30) and cystitis glandularis (Fig. 31). The most prominent feature is the clusters or sheets of calcified eggs with little or no surrounding cellular reaction. The eggs are confined largely to the submucosa but often extend to involve the muscle layers (Fig. 25). Focal degeneration of muscle fibres with fibrous tissue replacement is common.

When the sandy patches are extensive, a scout x-ray of the pelvis often reveals a calcified shell outlining the bladder (Fig. 26).

(ii) Fibrotic Plaques:

Occasionally, healing of a proliferative granuloma is accompanied by a more exuberant fibrocellular response around calcified eggs. On cystoscopy such a lesion appears as a slightly elevated, pearly-white plaque.

Histology reveals clusters of fibrotic pseudotubercles with dense whorls of mature collagen in which are imbedded calcifying and degenerate ova (Figs. 27 & 28). The epithelium is atrophic and inflammatory cellular response inconspicuous.

(iii)/...

(iii) Bilharzial Papillomata:

These rare lesions were encountered on two occasions only. On cystoscopy the lesion has a pedunculated polyp-like appearance. It has a narrow stalk and is grey and avascular with calcium deposition on the surface.

Histology shows that the lesion is made up of a cluster of calcified ova with minimal stromal tissue and a stalk of fibrous connective tissue (Fig. 29). It is avascular and resembles a heaping up of the mucosa which has previously been the site of egg deposition.

Acute, subacute and chronic lesions may co-exist in the same bladder (Fig. 11). Although, in the present study, all cases had evidence of acute bilharzia, the earliest stage of acute generalised hyperaemia described by other authors was not encountered exclusively with bilharziasis. The one case with such an appearance had a co-existent bacterial cystitis. It is the author's opinion that such a picture when seen denotes a secondary bacterial cystitis and is not diagnostic of bilharzial cystitis.

It will be appreciated that subacute lesions vary in appearance, ranging from those bordering on the acute lesions to those resembling late lesions. For the purpose of the clinical presentation, all granulomatous lesions were classified as active acute lesions and healing pseudotubercles and coarse sandy-patches were considered chronic lesions.

On this basis, the cystoscopic appearances in clinical cases and macroscopic lesions in necropsy cases were found to be as shown in Table II.

TABLE II/...

TABLE II

CLASSIFICATION OF BLADDER LESIONS FROM CYSTOSCOPIC AND NECROPSY STUDIES

	CYSTOSCOPY		AUTOPSY	
TYPE OF LESION:	ACUTE	CHRONIC	ACUTE	CHRONIC
MILD	7	3	2	3
MODERATE	32	6	6	8
SEVERE	14	3	5	6
NO. OF CASES EXAMINED	65		30	

It was evident from cystoscopic evidence that there were no qualitative differences in the bladder lesions of Africans and Indians. The results have consequently been considered together.

It is evident from Table II that of the clinical cases 80% had predominantly acute lesions whilst in the remainder chronic lesions predominated. In the autopsy series 13/30 (43%) had acute lesions.

Lesions were deemed severe in 26% of the clinical cases and in 37% (11/30) of the autopsy cases.

The cystoscopic observations reveal that vesical bilharziasis in the Durban African and Indian populations is usually of a moderately severe degree.

This view is supported by evidence gained from the

digestion/...

digestion procedures on 900 autopsies reported in Chapter III. The results of the egg-load determination are shown in Tables III & IV.

TABLE III (see over)

TABLE IV

RELATIONSHIP OF EGG-LOAD OF TISSUES TO SEVERITY OF INFECTION

Load/grm. of Tissue	Severity of Infection
$>10^5$	Severe
$10^3 - 10^5$	Moderately Severe
$1 - 10^3$	Mild

From Table III it is evident, then, that the majority of cases with bilharzial infection have a mild to moderately severe infection supporting the cystoscopic observations.

BLADDER LESIONS REVEALED BY RADIOGRAPHY

Both scout x-ray of the pelvis prior to I.V.P examination and subsequent cystogram revealed a significant number of cases with bladder abnormalities in the form of calcification or filling defects due to granulomata. The results are summarized in Table V.

It is evident from Table V that:

1. Radiographic evidence of bladder lesions were present in 61% of cases.

2./...

TABLE III

EGG LOAD OF TISSUES (BLADDER OR RECTUM WHICHEVER SHOWED A HEAVIER INFESTATION) IN BILHARZIASIS

AGES	2 - 9		10 - 19		20 - 29		30 - 39		40 - 50		50+		TOTAL		TOTAL +ve	% + ve
OVA/gm. tissue	A	I	A	I	A	I	A	I	A	I	A	I	A	I		
$>10^6$	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1	0.4
$10^5 - 10^6$	0	0	2	0	1	0	1	0	4	0	0	0	8	0	8	2.9
$10^4 - 10^5$	3	0	13	3	14	1	22	0	26	2	9	2	87	8	95	33.9
$10^3 - 10^4$	2	0	4	1	9	2	17	2	16	3	4	0	52	8	60	21.4
$10^2 - 10^3$	4	0	7	1	10	3	14	0	20	2	5	2	60	8	68	24.3
$10 - 10^2$	1	0	0	0	5	1	11	0	10	0	0	1	27	2	29	10.4
<10	1	0	2	0	2	0	3	1	10	0	0	0	18	1	19	6.8
0	124	11	35	8	73	5	99	12	156	9	83	5	570	50	-	-
TOTAL	135	11	63	13	114	12	168	15	242	16	101	10	823	77	280	-

A = African

I = Indian.

TABLE V

BILHARZIAL BLADDER LESIONS REVEALED BY RADIOGRAPHIC EXAMINATION

TYPE OF LESIONS	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
Granulomata only	16	26	21	46	37	34
Calcification only	9	14.5	4	9	13	12
Calcification and Granulomata	14	23	1	4	16	15
NO. OF CASES EXAMINED	62		46		108	

2. Although all patients complained of acute symptoms, 27% had evidence of chronic bladder lesions in the form of calcification. African patients (37.5%) had a higher incidence of bladder calcification than the Indian (13% and $P = <0.01$) indicating that the African had infections of longer duration.

3. African patients (23%) had a higher incidence of acute on chronic bilharziasis (granulomata with calcification) than Indian (4%) suggesting that either African cases were exposed to repeated infections, or that they sought medical attention long after the initial infection.

From the study it was also evident that bladder calcification was common even in a young age group. In the age range 10 - 12 years calcification was seen in 13/49 (26%).

COMPLICATIONS/...

COMPLICATIONS OF VESICAL BILHARZIASIS

Most reports of grave bladder complications have emanated from Egypt.

1. CYSTITIS CYSTICA & CYSTITIS GLANDULARIS

Makar (1952), Dimmette *et al.* (1956), Hashem (1961) and Aboul-Nasr *et al.* (1962) have demonstrated the genesis of these lesions in bilharzial bladders. These authors regard cystitis cystica and cystitis glandularis as potentially malignant whilst Prates & Gillman (1959) believe that this epithelial hyperplasia with subsequent down growth of epithelial pegs is a reparative process. Honey & Gelfand (1960) reported on the rarity of cystic lesions in their cases.

In the present autopsy study, cystitis cystica (Fig. 30) and the earlier stages resembling Brunn's nests (Figs. 15 & 16) were a not uncommon finding (10/30 cases). Their genesis has been suggested earlier in this study. Cystitis glandularis (Fig. 31) on the other hand, was identified in only 3/30 bladders.

The possible relationship to malignancy will be considered in the chapter on Carcinoma of the Bladder.

2. LEUKOPLAKIA

Various authors have commented on the frequency of squamous metaplasia and leukoplakia supervening on bilharzial bladders (Makar, 1952; Dimmette *et al.*, 1956; Hashem, 1961 and Prates & Gillman, 1959).

In the present study, no example of leukoplakia or of

definite/...

definite squamous metaplasia was discovered. As will be shown later, however, this was not uncommonly associated with vesical malignancy.

3. SECONDARY VESICAL SEPSIS

Authors from endemic areas of bilharziasis have emphasised the frequency of secondary bacterial bladder sepsis (Makar, 1952; Sayegh, 1950; Hashem, 1961; Prates & Gillman, 1959 and Honey & Gelfand, 1960).

In the clinical study reported earlier in this chapter, no cases presented with secondary sepsis and it would appear that in contrast to reports from other areas, such sepsis is rare in Durban.

4. CHRONIC BILHARZIAL ULCERS

Chronic ulceration superimposed on a bilharzial bladder is a common complication in Egypt (Makar, 1948; Sayegh, 1950; Dimmette & Sayegh, 1955; Sayegh & Dimmette, 1956; Hashem, 1961 and Aboul-Nasr et al., 1962). Sayegh (1950) reported that these were true trophic ulcers and noted that they penetrated sufficiently deeply to involve the muscle layers and extravesical tissue. The healing of the abscess results in fixation of the fibrotic contracted bladder to the pelvic floor. He observed that malignancy is not an uncommon complication in such bladders.

Kirkaldy-Willis (1948) from East Africa, noted occasional shallow mucosal ulcers and Prates & Gillman (1959) did not comment on bladder ulceration in autopsy studies, presumably therefore, it was not encountered. Gelfand (1950) could not find any cases in his series and Honey & Gelfand (1960) in their study did not encounter a single case.

Marcks/...

Marcks (1956) reported that penetrating bladder ulcers are rare in Southern Rhodesia. Kisner (1962) in South Africa, raises the possibility that a sandy patch might slough and result in severe haemorrhage but he does not specifically describe acute or chronic ulcers.

In the present study, bladder ulcers were not encountered in either clinical or autopsy studies.

From the literature it is apparent that chronic penetrating ulceration of a bilharzial bladder is a complication restricted to Egypt where Sayegh & Dimmette (1956) concluded that: "latent ulcers of the bladder following treatment for vesical schistosomiasis constitute a clinical entity for which surgical resection is the only effective treatment".

5. FIBROSED CONTRACTED BLADDER & BLADDER NECK OBSTRUCTION

The healing stage of bilharziasis is accompanied by a variable amount of fibrosis and atrophy of the bladder musculature (Figs. 24, 25 & 27). The extent is dependent on the severity of infection. If the infection is light the resultant focal areas of fibrosis and of plaques of calcified ova produce little or no impairment of bladder function. Such contracted, fibrosed bladders are apparently a common sequel of late bilharziasis in Egypt (Sayegh, 1950; Sayegh & Dimmette, 1956; Hashem, 1961). Honey & Gelfand (1960) also reported that it was not an uncommon complication in African bilharzial patients of Southern Rhodesia.

Whereas histological evidence of focal bladder fibrosis was not unusual and bladder calcification was frequently encountered in x-ray studies, the classical contracted, fibrosed bladder with diminished capacity was not encountered in the present study.

Badr *et al.* (1958) and Aboul-Nasr *et al.* (1962) described the syndrome of bladder-neck obstruction, a clinico-pathological entity peculiar to late vesical bilharziasis. Honey & Gelfand (1960), in spite of meticulous investigation, failed to detect a single case in Rhodesia.

In the present study, bladder-neck obstruction due to bilharzial fibrosis was not detected in either the clinical or autopsy study.

6. VESICAL CALCULI

Afifi (1934) and Bitschai (1950) showed the high incidence of vesical calculi associated with bilharziasis in Egypt. Kirkaldy-Willis (1948) in East Africa encountered calculi in 7 out of 84 cases with bilharzial cystitis. Gelfand (1950) in Rhodesia and Vermooten (1937) in South Africa, reported on the rarity of urinary calculi in Africans. Honey & Gelfand (1960) found no increase in the incidence of vesical calculi in European Bilharzial patients of Rhodesia. Marcks (1956) commenting on the rarity of urinary calculi in bilharziasis with chronic sepsis in the Rhodesian African stated - "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".

In the present study in 108 clinical and 30 autopsy cases no urinary calculi were found. Similarly in the 249 cases of *S. haematobium* infection encountered in the series of 900 autopsies, not a single case of urinary calculosis was encountered.

7./...

7. CARCINOMA OF THE BLADDER & BILHARZIASIS

This forms the subject of the next chapter.

SUMMARY

The natural history of the various bilharzial lesions has been demonstrated by correlation of cystoscopic and histopathological features. A simplified classification of the vesical pathology has been presented. It has been shown that pseudotubercles and granulomata are the earliest lesions of active bilharziasis. This finding is contrary to the observations of Marcks (1956), Kirkaldy-Willis (1948) and Honey & Gelfand (1960) who regarded the granulomatous lesions as representing a late stage of bilharzial involvement. Whereas Campbell-Begg (1944) from South Africa reported that such granulomata of the bladder were rare, the present study has revealed that they are in fact common. Fibrotic plaques, fine and coarse sandy patches are associated with calcified ova, and thus appear late in the disease.

The value of radiography in the diagnosis of bladder lesions has been demonstrated. The high incidence of bladder calcification in young African patients indicates the long duration of infections.

The severity of bladder involvement has been demonstrated both in clinical and in autopsy material and evidence provided to show that even the young age group is affected.

In contrast to reports from Egypt, the complications of chronic penetrating ulcers, fibrosed contracted bladders, bladder neck obstruction and vesical calculosis have been shown

to/...

to be rare. The difference in pathology may be related to the difference in severity of infection in the two areas.

Finally, the clinical study confirmed the report of Kirkaldy-Willis (1948) of the value of cystoscopy in the assessment of the result of therapy. In mild cases, a single course of antimony abolished the vesical lesions, but in more severe cases further treatment was necessary. Though eggs had disappeared from the urine, cystoscopy left no doubt as to the activity of the lesions.

PLATE II

Fig. 11 The mucosal surface in this autopsy specimen of the bladder has the appearance of wet chamois-leather (coarse sandy patches). Granulomata are apparent on the dome and in the vicinity of the left ureteric orifice (arrow points to internal urethral meatus).

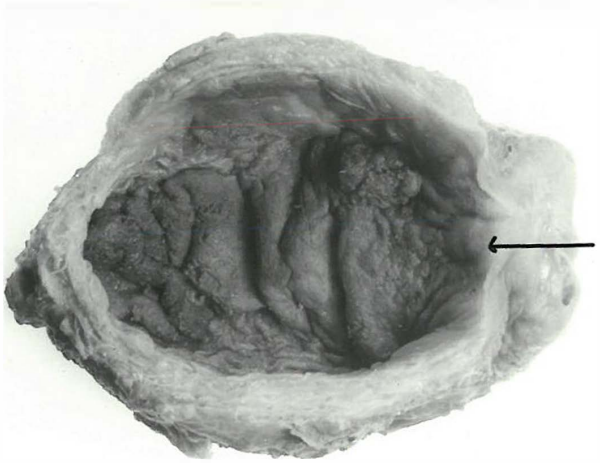
Fig. 12 Reveals active pseudotubercles with clusters of ova in the centre. The lesion is confined to the submucosa. HE x 20

Fig. 13 High power view of an acute pseudotubercle reveals an eosinophilic microabscess with ova occupying the centre of the lesion. Mild epithelial hyperplasia (lower right) suggests a pattern of Brunn's nests. HE x 50

Fig. 14 Histology of a flattened granuloma demonstrates a pronounced pseudoepitheliomatous hyperplasia and numerous ova. A pair of adult worms is seen in a dilated vein. The lesion is confined to the mucosa and submucosa. HE x 20

Fig. 15 An acute bilharzial granuloma. The elevated, pseudopolypoid nature of this lesion is apparent. Numerous microabscesses may be discerned and the striking epithelial hyperplasia, with columns of epithelial cells trapped in the submucosa, provides a pattern simulating cystitis cystica and Brunn's nests. HE x 20

Fig. 16 The pronounced epithelial hyperplasia is evident in this high power view of an acute granuloma. Both calcified and apparently viable ova are seen in the submucosa. HE x 50



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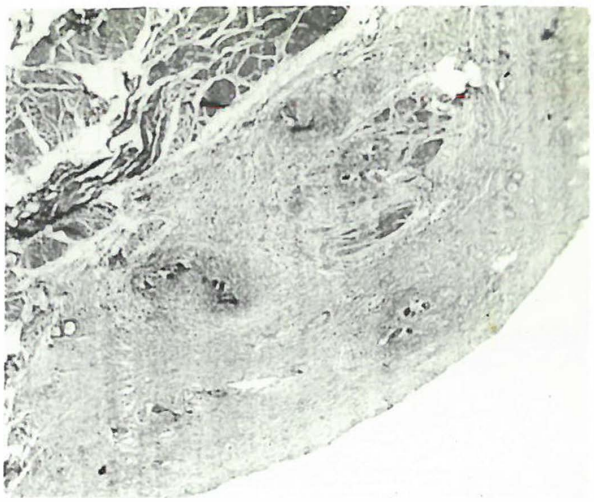

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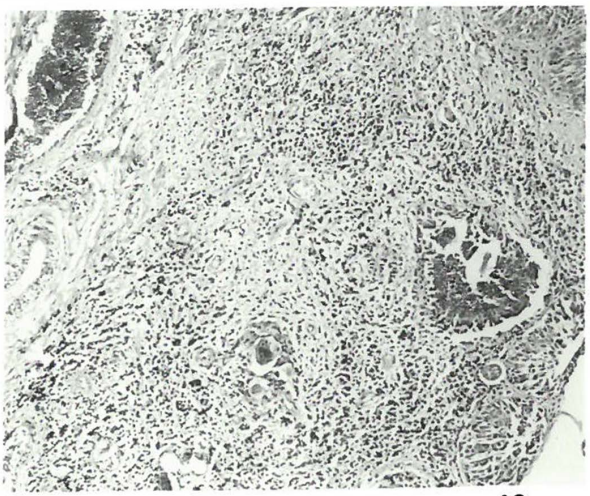

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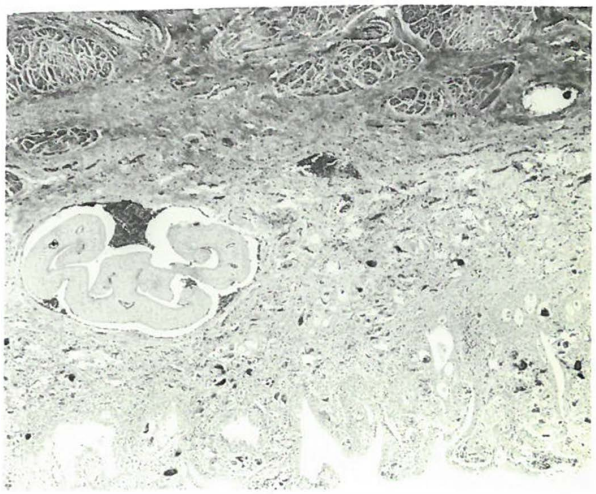

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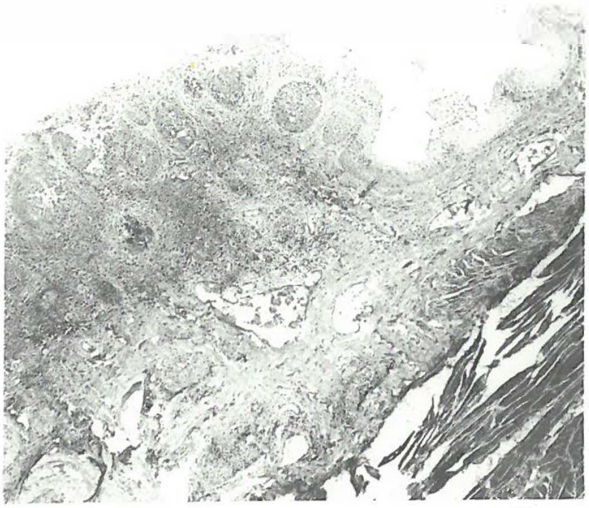

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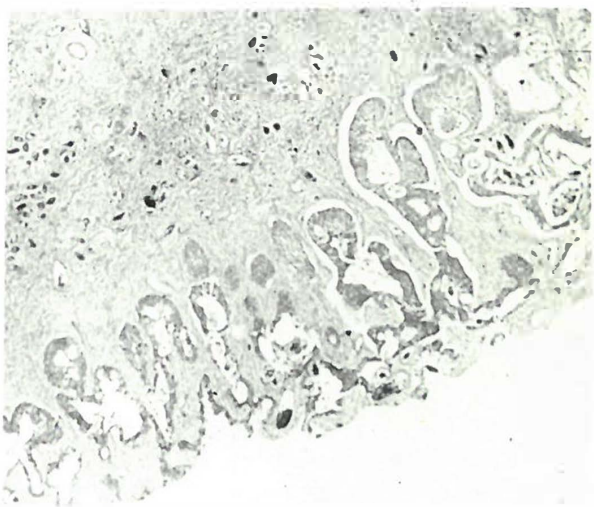

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PLATE III

Fig. 17 The markedly irregular left upper and lateral walls of the bladder seen on this cystosgram were found, at cystoscopy, to be related to acute proliferative bilharzial granlomata.

Fig. 18 A view of the base of an acute granuloma reveals numerous paired adult worms, large numbers of ova and the intense inflammatory infiltrate (predominently eosinophils). HE x 20

Fig. 19 The extensive eosinophilic necrosis spreading tp involve the bladder musculature, is evident in this view of the base of an acute granuloma. The ova, situated in the centre of the abscesses, are surprisingly few in umber. The cellular infiltrate was predominantly eosinophils. HE x 20

Fig. 20 The pseudotuberculoid pattern of a subacute granuloma with fibrosis commencing around clusters of ova. In this stage the inflammatory infiltrate consists largely of lymphocytes with plasma cells and eosinophils less prominent. HE x 20

Fig. 21 A later stage of the subacute granuloma showing more advanced fibrosis around clusters of ova. HE x 20

Fig. 22 An even later stage of the subacute granuloma with prominent fibrosis around calcified and degenerate ova. The epithelium is atrophic and there is a minimal inflammatory reaction. HE x 20

PLATE IV

Fig. 23 Histology of a healing granuloma reveals large numbers of calcified ova and although the epithelium is ragged, it is no longer hyperplastic. HE x 20

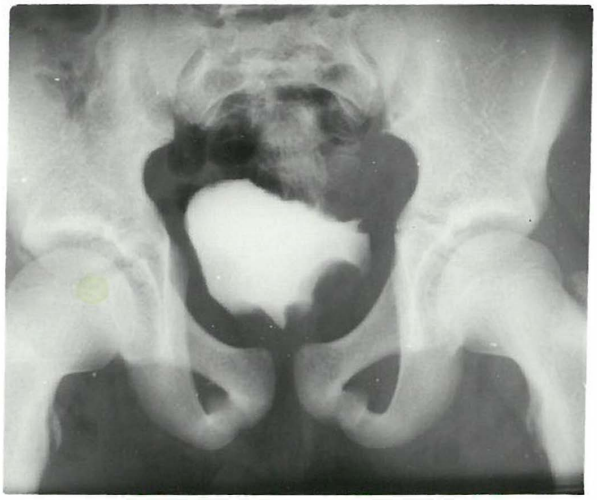
Fig. 24 The histological appearance of the sandy-patch reveals myriads of calcified ova. The ova are confined to the submucosa, the epithelium is atrophic and there is a complete absence of inflammatory reaction. HE x 20

Fig. 25 Another example of a sandy patch lesion with calcified and "ghost forms" of ova in the mucosa (right) and a dense plaque of calcified ova in the muscle layers. There is no evidence of an inflammatory reaction. HE x 20

Fig. 26 The bladder in this scout x-ray of the pelvis is outlined by the fine egg-shell pattern of calcification. The histological appearance of such a bladder is shown in Figs. 24 & 25.

Fig. 27 A late fibrotic plaque reveals whorls of dense collagen surrounding clusters of calcified and degenerate ova. There is no active inflammatory response and the mucosa is atrophic. HE x 20

Fig. 28 A higher power view of the late fibrotic plaque demonstrates the whorls of dense collagen and centres of degenerate and calcified ova. HE x 50



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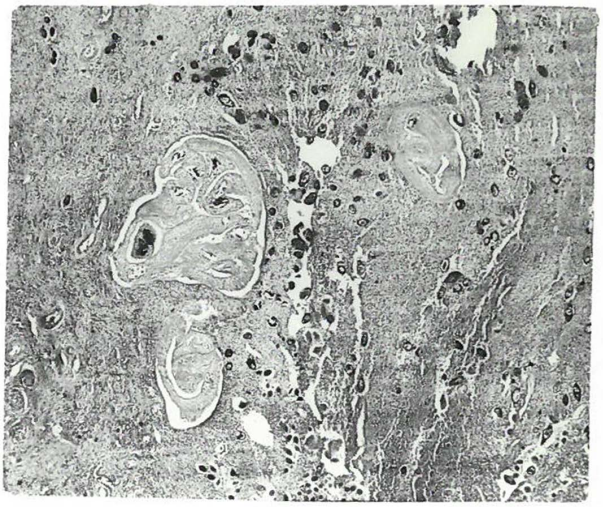

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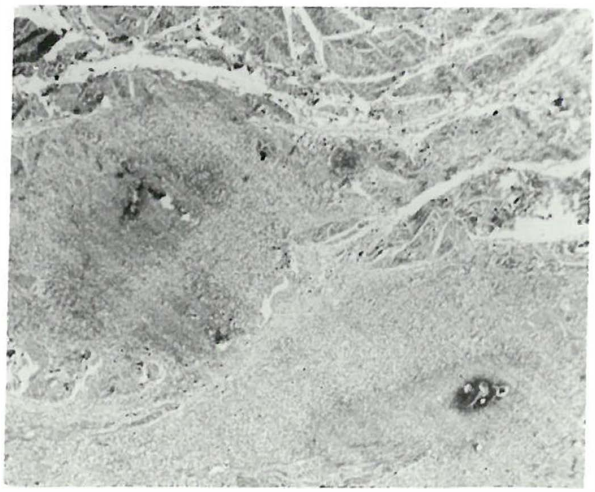

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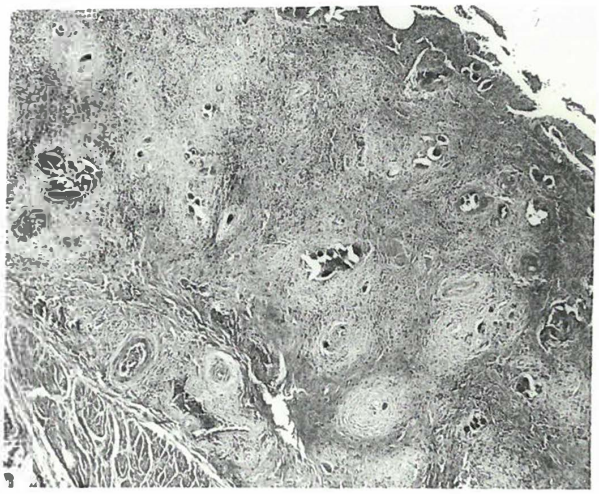

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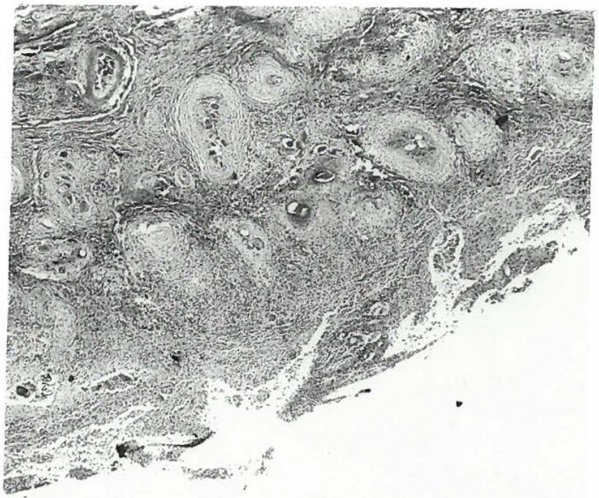

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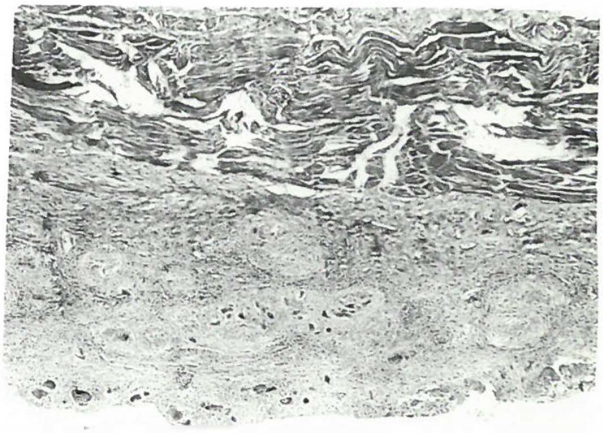

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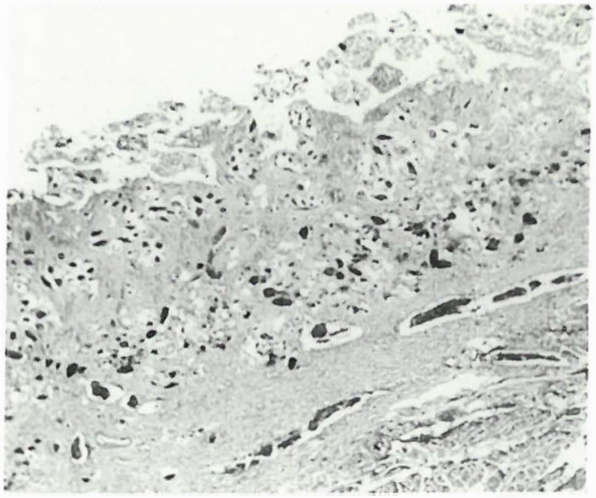

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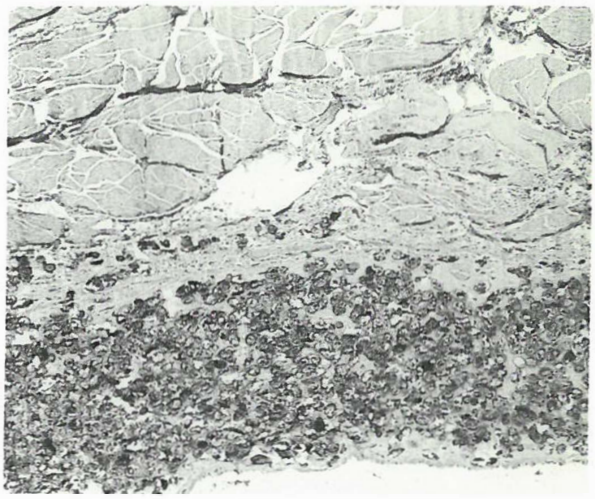

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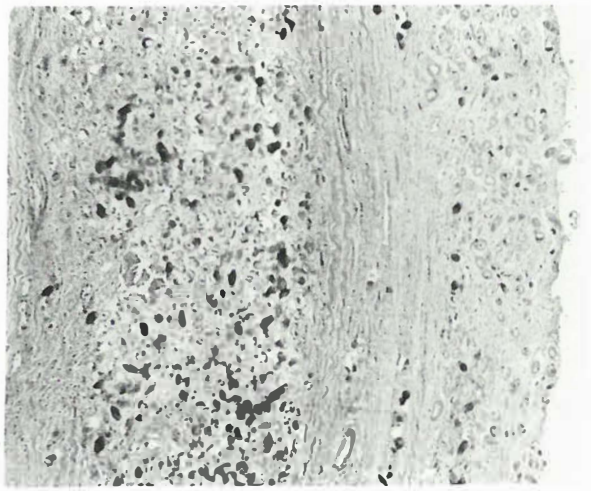

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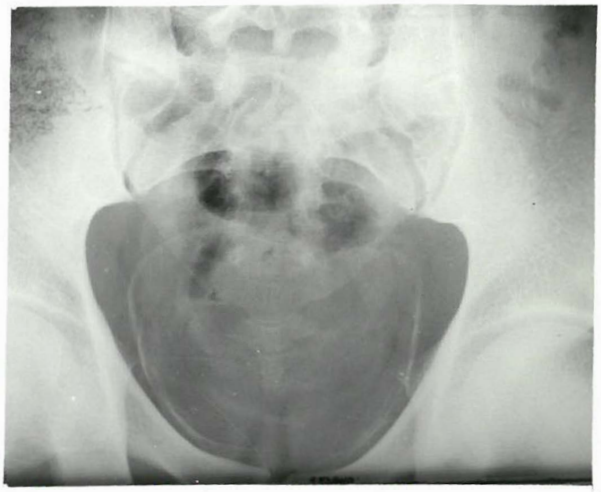

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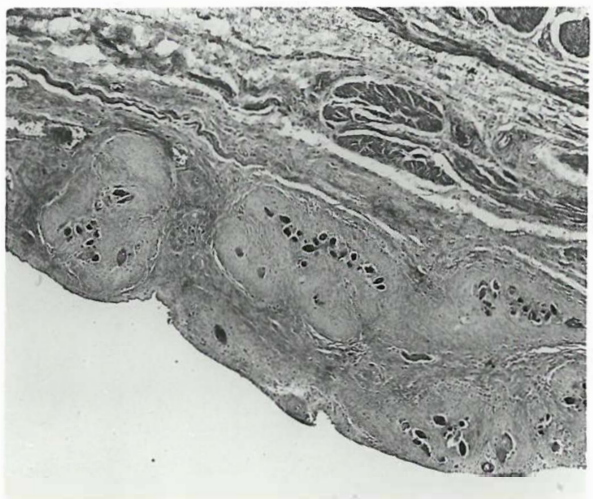

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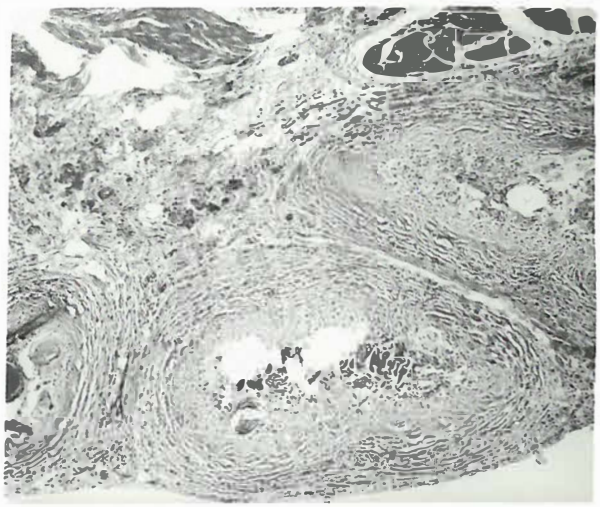

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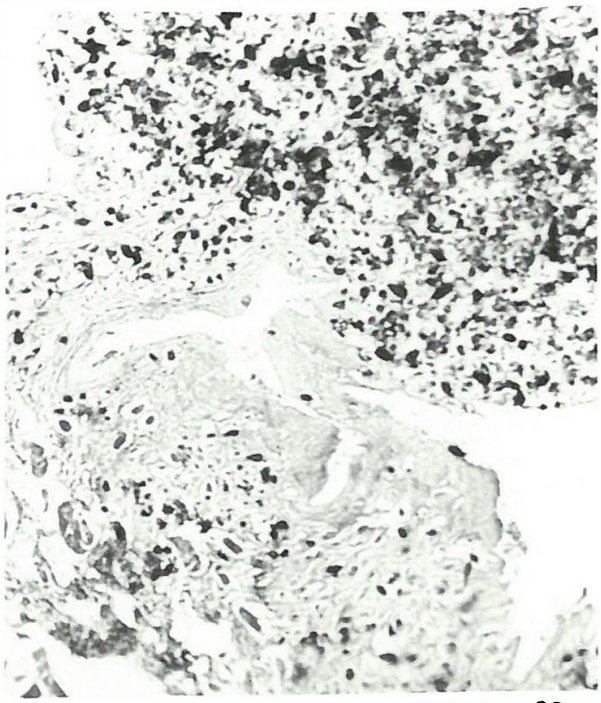

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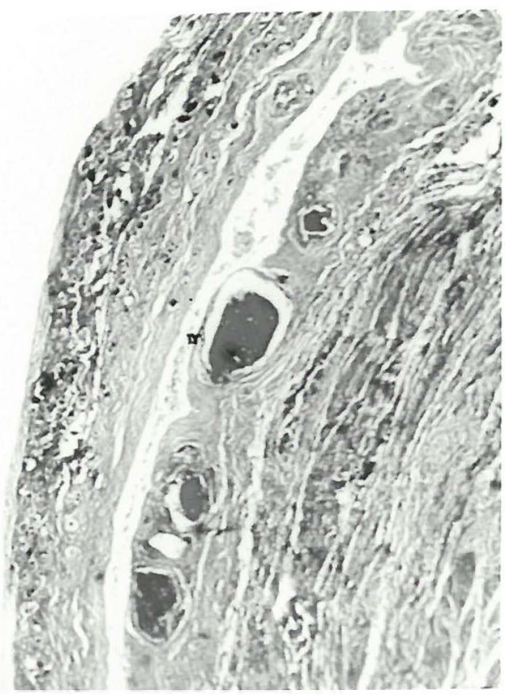

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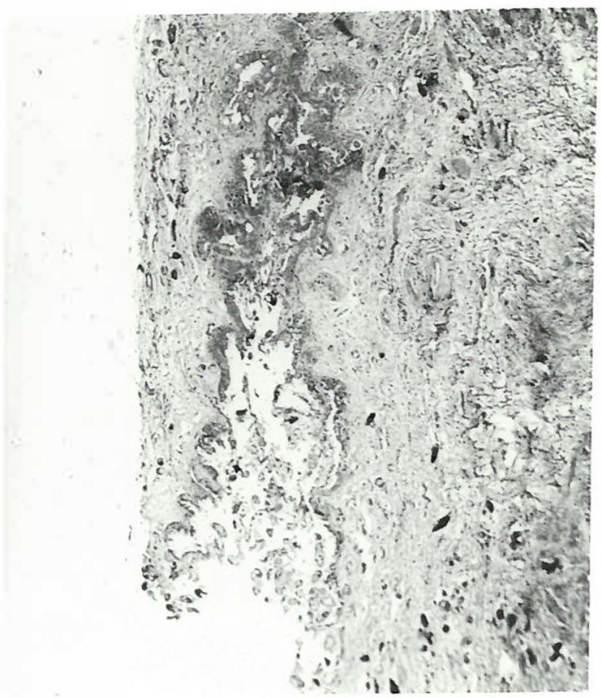

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PLATE V

Fig. 29 A "bilharzial papilloma" reveals clusters of calcified ova trapped in a fold of submucosa. There is a complete lack of an inflammatory reaction. HE x 20

Fig. 30 Cystitis cystica with a fold of overhanging mucosa with calcified ova. There is no evidence of an inflammatory reaction. HE x 20

Fig. 31 Bladder epithelium actively proliferating down into the submucosa and producing a pattern of cystitis glandularis. Numerous calcified ova are apparent but there is no evidence of an inflammatory reaction. HE x 20

C. URETERIC BILHARZIASIS

INTRODUCTION

Workers from Egypt have frequently reported on the involvement of the ureter in vesical bilharziasis.

Fairley (1919b) recognised the frequency with which this occurred in early cases. Subsequently (1920) he demonstrated severe bilharzial disease of the lower ends of the ureters. Shaw (1921) described the cystoscopic appearances of the ureteric orifices in bilharzial disease and noted that these may be either widely patent or contracted and fibrosed.

Dew (1923) from autopsy examinations, reported that the lower third of the ureter was frequently involved by bilharziasis and like Fairley (1919b), noted that this was not surprising in view of the common blood supply of the bladder and lower ends of the ureters. Dew noted that stricture formation occurred early in the disease and described the "golf-hole" orifice in late bilharzial involvement.

Ibrahim (1923) described the pathological changes in the ureters. Egg deposition resulted in sandy patches and granulomatous lesions. The subsequent ulceration and fibrosis resulted in stricture formation, proximal hydroureter and hydronephrosis. The "fibrosed, contracted bladder" with stenosis of the ureteric orifices was described by Girges (1934) while Ragheb (1939) commented on the radiological appearances of ureteric involvement.

Makar (1948) reviewed the surgical pathology of ureteric disease and described hyperplastic and hypoplastic lesions.

He/...

He classified papillomata, ureteritis cystica and ureteritis glandularis as hyperplastic lesions, and sandy patches undergoing ulceration with deposition of urates and oxalates, as hypoplastic lesions. The end result of both types of lesion was either stenosis with fibrosis or a rigid dilated ureter with subsequent uretero-vesical reflex. He noted that the lower ends of the ureters and especially the intramural part, were most frequently involved. Kirkaldy-Willis (1948) from East Africa reported on the frequency of ureteric bilharzial disease with secondary hydronephrosis. More recently, Forsyth & Bradley (1964) in Tanganyika demonstrated similar ureteric changes in children with asymptomatic bilharziasis. Edington (1957) from Ghana also reported the finding in autopsy material of severe upper renal tract pathology in association with bilharziasis.

Gelfand (1948) from autopsy studies in Southern Rhodesia revealed the high incidence of ureteric disease in bilharziasis. He noted, however, that stricture of the ureter was uncommon, and that hydroureter resulted from the active stage of bilharzial involvement. Subsequently (1950) he reported that in his series 31% had evidence of gross ureteric lesions and 20% had hydroureter but only 3.1% had strictures. Honey & Gelfand (1960) in a clinical study of both African and European bilharzial patients, demonstrated the high incidence of upper renal tract disease. They noted that the lesions in the African were more severe than in the European and ascribed this to the heavier and more prolonged infection in the African. In their study they recorded that stricture of the ureter was the most common lesion (31% in Europeans and 42% in Africans) with hydronephrosis a common sequel.

More recently, Gregory (1964) in contrast to Gelfand

(1950)/...

(1950) reported that stricture formation was the most common manifestation of the disease in Southern Rhodesia. Earlier Marcks (1956) had described the ureteric pathology as "ureterectasia" produced by direct bilharzial involvement of the wall. Whether the lesion subsequently became stenotic or dilated depended on the quantity and quality of the fibroblastic reaction.

Describing the pathology of bilharziasis in South Africa, Pijper (1934) considered ureteric disease so rare as to be a curiosity, but Vermooten (1937) a few years later, from clinical and radiological evidence, revealed the frequency of severe upper renal tract disease. Vermooten (1937), like Fairley (1920), Dew (1923) and Makar (1948), emphasised the common blood supply of the bladder and lower ureters and stated: "It (also) makes one realise that with the involvement of the bladder, one must necessarily assume infestation of the pelvic portion of the ureter". He described the pathognomonic radiological appearances of ureteric bilharziasis.

Campbell Begg (1944) described the cystoscopic appearances of bilharziasis and warned that the lack of symptoms in the early stage may mask the disease which might only present later with vague non-specific symptoms of the complications. He noted, surprisingly, that: "In most cases of chronic Bilharzia pyelograms are normal". Kisner (1952) however, from a study of both European and African patients in Johannesburg, demonstrated all grades of ureteric disease.

Kark (1960) and Chapman (1964) from Durban, described the late ureteric lesions as complications of bilharzial cystitis and noted that these were commoner in the Indian than the African.

From/...

From this review, it is apparent that ureteric damage in vesical bilharziasis is common. With the exception of Fairley (1920), Dew (1923), Makar (1948) and Kisner (1952), authors have considered that ureteric damage is a late complication of vesical bilharziasis.

PRESENT STUDY

Results.

Correlation of the morbid and histopathological study of autopsy cases with the I.V.P. and cystoscopic appearances of clinical cases demonstrated the extent, severity and stage of the ureteric lesions.

STAGES OF URETERIC BILHARZIASIS

From this study it became apparent that the ureteric lesions were basically of 2 types; (1) early and (2) late. The early lesions correspond with the acute stage of vesical bilharziasis whilst the late lesions are a progression of the acute lesions to the subacute and chronic stages.

1. EARLY ACUTE LESIONS

Macroscopic and histological examination of autopsy specimens revealed typical flat-topped granulomatous lesions and acute pseudotubercles similar to those described in the bladder. The only histological difference was the more widespread involvement of the ureteric wall. Muscle

destruction/...

destruction with early fibrosis was prominent and egg deposition extended even to the serosal surface (Figs. 32, 33 & 34).

The proliferative lesions intruded into and narrowed the lumen. The marked oedema in all the tissue layers must have aided in the narrowing of the lumen.

The early acute ureteric lesions are evident on I.V.P. by the ragged and irregular or beaded appearance of the lower end (Figs. 35, 36 & 37). There is never a complete hold-up of the dye, and a minor degree of dilatation at the site of the lesion is common.

At cystoscopy, the ureteric orifices may be completely obscured by the surrounding proliferative granulomata. If the granuloma is in the intramural portion of the ureter (Fig. 34), the acutely inflammed orifice will be pouting and appear to be sitting on a mound. Attempts at catheterisation usually fail, the catheter being arrested at the 2-3 cm. mark with a "concertina-like" invagination of the distal ureter thereafter. Withdrawal of the catheter is followed by a bloody efflux, a result of trauma to the friable, acute granuloma in the ureter.

A "therapeutic trial" also confirms the acute nature of this lesion. Following a course of antimony treatment, not only does the I.V.P. appearance revert to near normal (Figs. 61 - 63), but subsequent catheterisation (2-3 weeks after treatment) is usually effected with ease. As has been experienced with bladder lesions, acute ureteric granulomata rapidly resolve on treatment. However, as emphasised by Kisner (1952) treatment does not eliminate the subsequent development of stenotic lesions.

2./...

2. LATE CHRONIC LESIONS

The late ureteric lesions have been recognised by most workers and have received much more prominence in their reports.

In the present study macroscopic examination of autopsy specimens revealed that the entire length or segments of the ureter may be involved. The affected part was dilated and rigid and was related to sites of bilharzial lesions, usually "coarse" or "fine sandy-patches". A fairley constant observation was that bilharzial lesions of the ureter proximal to the intramural segment, produced hydroureter whilst similar lesions in the intramural portion itself gave rise to narrowing and obstruction.

Histopathology of the lesions revealed the typical features of the subacute (Fig. 38 & 39) and chronic stages (Figs. 40 - 45) described in the bladder lesions. Calcified eggs were distributed throughout all layers with extensive muscle destruction and subsequent fibrosis. Dense whorls of collagen (Figs. 44 & 45) were evident only in the intramural portion of the ureter with a consequent likelihood of stricture.

Although macroscopic lesions were not evident, histology of the middle and upper thirds of the ureter frequently revealed bilharzial involvement (Figs. 42 & 43). The entire length of the ureter is more frequently involved by bilharzial disease than has been generally recognised.

The I.V.P. pattern in the late stage is typical and has been described by Vermooten (1937), Kisner (1952), Honey & Gelfand (1960) and James (1963) amongst others. The earliest changes described are delay in the empyting of

the/...

the dye (beyond 25 mins.) followed later by evidence of stricture formation with proximal dilatation and tortuosity of the ureter. A still later stage reveals gross hydroureter with prominent tortuosity of the ureter and varying degrees of hydronephrosis.

What has not been adeuqately appreciated is that I.V.P. studies frequently reveal direct evidence of bilharzial lesions in the ureters. Frequently the dilated segment of the ureter reveals focal hazy areas best described as a "sand-blown" appearance (Figs. 35 - 37 & 55). Correlation with histology indicates that these lesions represent focal sandy-patches with calcified ova (Fig. 40), but the concentration of ova is not sufficiently dense to appear as true calcification. When egg deposition is extensive (Figs. 41 & 42) the affected segment or even the entire ureter may be seen on x-ray as a calcified tube (Figs. 52 - 54).

Cystoscopy reveals a deformed and rigid ureteric orifice, whether this is affected directly or indirectly by adjacent bladder involvement. When the lesion is in the intramural portion, it produces a "golf-hole orifice", the result of retraction of a scarred ureter. When the ureteric orifice or the surrounding bladder is involved, the deformity is a "pin-hole meatus". In both instances, there is lack of a good efflux from the affected ureter. The urine may be seen to dribble through the orifice with no activity at the ureteric lips. Attempts to catheterise the ureters in such cases are almost always unsuccessful. In contrast to the acute lesion a "therapeutic trial" in these cases is of no avail.

INCIDENCE/...

INCIDENCE OF UPPER RENAL TRACT INVOLVEMENT

Although most authors have commented on the frequency of upper renal tract involvement, few have assessed the incidence of such lesions in a random bilharzial population. Vermooten (1937) cautioned that disease of the lower ends of the ureters should be assumed in all cases of vesical bilharziasis. Fairley (1920) and Dew (1923) merely made the suggestion.

Gelfand (1950) from autopsy studies reported that 31% of cases with vesical bilharziasis had ureteric disease. He limited the investigation to the age group 15-55 years as: "It was presumed that an adult Native would have contracted the disease by the age of 15 and would have probably had it for a number of years by the time maturity was reached". As selection is implicit, it may be claimed that his studies did not give a true incidence of ureteric involvement at all stages of the process.

Kisner (1952) from a clinical study of both African and European patients, reported an incidence of 35.5% of ureteric pathology in his series. Judging from the presenting symptomatology of his patients, it is apparent that there was selection. Similarly, Honey & Gelfand (1960) admit that in their clinical series, selection was unavoidable. They reported an incidence of 31% in European and 42% in African patients.

More recently, however, Forsyth & Bradley (1964) in Tanganyika investigated a group of school children between 10 - 16 years old, amongst whom the S. haematobium infection rate by urine testing was shown to be 84%. They reported that the incidence of ureteric lesions in this group was 16%.

It/...

It was reported earlier that in the present study what amounts to a random group of bilharzial patients were chosen for study. The only criteria for selection was:

(i) Evidence of an active S. haematobium infection.
(ii) Ability or willingness of patients to report back.

The results of the present study are compared with the reports of previous authors in Table VI.

TABLE VI

INCIDENCE OF UPPER RENAL TRACT DISEASE IN URINARY BILHARZIASIS

AUTHOR:	YEAR	MATERIAL	NO. OF CASES:	URETERIC LESIONS		HYDRONEPHROSIS	
				NO.	%	NO.	%
Gelfand	1950	Autopsy	178	55	31	10	6
Kisner	1952	Clinical	181	64	35	18	10
Honey & Gelfand	1960	Clinical	300 E	94	31	42	14
			100 A	42	42	58	58
Forsyth & Bradley	1964	Clinical	252	39	16	-	-
Personal	1964	Clinical	108	43	40	19	17
		Autopsy	30	22	73	6	20

E = European A = African.

It is evident from Table VI that the incidence of upper renal tract involvement is uniformly high in all series. In the present clinical study of unselected cases 40% of patients with

vesical/...

vesical bilharziasis have ureteric involvement. Even in patients under 20 years old, 31/77 (40%) had ureteric lesions. This demonstrates that even in early acute bilharziasis, there is a high incidence of ureteric pathology.

The present autopsy study reveals that 73% (22/30) had histological evidence of ureteric disease and demonstrates that absence of macroscopic evidence of lesions does not exclude ureteric disease. The autopsy study confirms the views of Fairley (1920), Dew (1923), Makar (1948) and Vermooten (1937) that vesical bilharziasis is almost invariably accompanied by involvement of the ureters.

In the present study, there was no evidence of racial difference (Table VII).

TABLE VII

URETERIC LESIONS DEMONSTRATED ON I.V.P. IN AFRICAN AND INDIAN BILHARZIAL PATIENTS

EXTENT	INDIAN		AFRICAN		TOTAL	
	NO.	%	NO.	%	NO.	%
Unilateral	16	35	13	21	29	27
Bilateral	4	9	10	16	14	13
TOTAL	20/46	44	23/62	37	43/108	40

On clinical examination 27% had unilateral and 13% bilateral lesions. The autopsy group however, showed not only a higher incidence, but that 50% had bilateral as against 23% with unilateral pathology.

NATURE/...

NATURE OF THE URETERIC LESIONS

FROM I.V.P. STUDIES

The nature of the I.V.P. lesions is shown in Table VIII.

TABLE VIII

NATURE OF URETERIC LESIONS ON I.V.P. IN 108 PATIENTS WITH ACTIVE BILHARZIASIS

NATURE OF LESION:	INDIAN	AFRICAN	TOTAL / URETERS	%
Irregularity only	15	5	20/216	9
Irregularity with dilatation	8	16	24/216	11
Calcification	1	12	13/216	6

It is evident from Table VIII that calcification of the ureter was commoner in the African than in the Indian.

As irregulairty of the lower end of the ureter (ragged or beaded) is indicative of an acute lesion, it is evident from Table VIII that these are by no means uncommon. The findings confirm the nonconformist views of Fairley (1920), Dew (1923) and others.

FROM AUTOPSY MATERIAL

Further confirmation that ureteric lesions may occur

in/...

in the early stages is evident from the autopsy studies (Tables IX & X).

TABLE IX

MACROSCOPIC NATURE OF BILHARZIAL URETERIC LESIONS IN AUTOPSY CASES

(30 CASES - 60 URETERS EXAMINED)

NATURE OF LESION*	NO.	%
1. Hydroureter	22	37
2. Bilharzial lesions	27	45
3. Stricture	6	10
4. No lesions	25	42

* 1. Hydroureter : either segmental or total.
2. Bilharzial lesions : sandy patches, coarse sandy patches or acute granulomas.
3. Stricture : lower end of the ureter.

BY HISTOLOGY EXAMINATION

The nature of the histopathological lesions are summarized in Table X.

It is evident from Tables IX and X that active bilharzial lesions of the ureters were common. Acute lesions were present in 13% of the ureters. Histology revealed lesions

identical/...

identical to those described in the bladder. In 2 cases acute lesions involved primarily the upper third of the ureter.

TABLE X

HISTOLOGICAL NATURE OF BILHARZIAL URETERIC LESIONS IN AUTOPSY CASES

(30 CASES - 60 URETERS EXAMINED)

NATURE OF LESION	NO.	%
Acute	8	13
Chronic	27	45
Fibrotic	2	3
No Lesions	23	38

AT CYSTOSCOPY

The cystoscopic evidence of damage of the ureteric orifices and the intramural segment is presented in Table XI.

Of the 65 cases on whom cystoscopy was performed 67% had abnormalities around either or both ureteric orifices (granulomata and deformed orifices). Attempts at catheterisation failed in 45% of all cases, and if this be accepted as evidence of ureteric pathology, then no less than 70% of cases examined had deformed ureteric orifices.

TABLE XI/...

TABLE XI

CYSTOSCOPIC NATURE OF URETERIC ORIFICES IN 65 BILHARZIAL PATIENTS

NATURE OF LESION	INDIAN	AFRICAN	TOTAL	%
Granulomata	6	6	12	18
Deformed orifice	13	19	32	49
Failure to catheterise	13	16	29	45
No. of cases affected	21	25	46	70
No. of cases examined	31	34	65	

SITE OF THE URETERIC LESIONS

The site of the ureteric lesions in both clinical and autopsy cases is summarised in Table XII.

TABLE XII

SITE OF URETERIC LESIONS IN CLINICAL (I.V.P.) AND AUTOPSY CASES OF BILHARZIASIS

SITE	CLINICAL		AUTOPSY	
	NO.	%	NO.	%
Lower Third	40	19	14	23
Lower Two-Thirds	9	4	7	12
Whole Length	7	3	16	27
No. of Ureters Examined	216	-	60	-

Though/...

Though both the autopsy series and clinical I.V.P. studies demonstrate that the lower third of the ureter is commonly involved, microscopy of the autopsy material indicates that the entire length of the ureter is affected much more commonly than expected from I.V.P. results.

RENAL PATHOLOGY

The incidence of hydronephrosis in clinical and autopsy studies has been summarised in Table VI.

I.V.P. studies revealed only mild to moderately severe degrees of pelvi-calyceal hydronephrosis. No severe or gross examples were encountered. This is no doubt due to the relatively short duration of disease in the cases investigated. Vermooten (1937), Kisner (1952), Marcks (1956) and Honey & Gelfand (1960) amongst others, all regard severe renal pathology as a late sequel. The present observations would appear to support these observations.

The incidence of hydronephrosis was higher in African (13%) than in Indian (6%) patients. This is probably related to the more chronic nature of the lesions in the African (as evidenced by bladder and ureteric calcification) than the Indian.

Of the 30 autopsy cases, 6 had renal lesions and these are summarised in Table XIII.

TABLE XIII/...

TABLE XIII

RENAL LESIONS IN AUTOPSY CASES WITH BILHARZIASIS

RACE	SEX	AGE	NATURE OF RENAL LESIONS	URETERIC PATHOLOGY
A	M	8	Bilateral severe hydronephrosis	Bilateral severe hydroureters
A	M	9	Bilateral severe hydronephrosis	Bilateral severe hydroureters
A	F	16	Bilateral suppurating pyelonephritis	Nil
A	M	34	Bilateral focal chronic pyelonephritis	Bilateral hydroureters
A	M	40	Moderate hydronephrosis with bilateral focal acute pyelonephritis	Bilateral hydroureters
I	M	43	Moderate hydronephrosis with bilateral suppurating pyelonephritis	Bilateral hydroureter with stricture on left side

Not only is the renal pathology associated with Bilharziasis severe, but it can reach its full development in the very young.

The renal pathology in the one case without evidence of ureteric pathology is probably unrelated to the vesical bilharziasis. In 5 cases the renal lesions were almost certainly related to the bilharzial infection. However, in 84% of autopsy cases, there was no evidence of renal pathology. Gross evidence of renal damage was also lacking in the clinical study. Blood urea estimations were normal in all patients.

DISCUSSION/...

DISCUSSION

The present study has demonstrated the frequency of ureteric lesions in acute bilharziasis. The cystoscopic and I.V.P. features of the different stages of the disease have been demonstrated and these have been correlated with the histopathology in autopsy cases.

Whilst most workers have recognised the serious import of ureteric damage, most of these workers regard this as a late complication. Thus the "golf-hole" ureteric orifices recognised by Fairley (1919b) and Dew (1923), and the descriptions of Ibrahim (1923), Girges (1934) and Campbell Begg (1944), all suggest late lesions. Vermooten (1937) believed that the ureteric lesions only became manifest about 8 - 10 years after the initial exposure. Similarly, Sayegh (1950), Marcks (1956) and Honey & Gelfand (1960) emphasised the chronicity of the ureteric lesions.

Despite the early observations by Fairley (1920) and Dew (1923) of acute bilharzial ureteritis, ureteric obstruction in the early stages of the disease have only been described by Makar (1948) and Kisner (1952).

The present study has indicated that ureteric lesions sufficiently severe to result in hydroureter and late hydronephrosis are not only a late sequel to stricture, but that ureteric proliferative granulomata may give rise to the syndrome early in the disease and in the very young.

PATHOGENESIS OF BILHARZIAL HYDROURETER & HYDRONEPHROSIS

Gelfand (1950) reported the common finding of a

segmental/...

segmental hydroureter in the absence of established stenotic lesions in his autopsy cases. Subsequently, Honey & Gelfand (1960) and Gregory (1964) from clinical experience, suggested that stricture of the lower end of the ureter was the cause of the proximal hydroureter.

Vermooten (1937), both from experimental evidence and from clinical experience, postulated that if a segment of the ureter was the seat of infection, that segment would undergo dilatation either due to distal partial obstruction or to vesico-ureteral reflux. Marcks (1956) suggested a similar mechanism when he defined "ureterectasia".

Most authors consider that the major cause of a cephalad dilatation of the ureter is a stenotic lesion. They concede that in a small minority vesico-ureteral reflux may be the prime cause (Dew, 1923; Makar, 1948; Kirkaldy-Willis, 1948; Honey & Gelfand, 1960 and Gregory, 1964).

From the present clinical and autopsy studies it became evident that several different pathological processes may give rise to hydroureter and consequent hydronephrosis. These conclusions support the opinion of Marcks (1956) that an understanding of the pathogenesis is essential for the subsequent management.

The various causes of hydroureter in association with Bilharziasis may be summarised as follows:

1. <u>Obstructive:</u>

   (a) Acute proliferative granuloma in the lumen or at the ureteric orifice.
   (b) Stricture of the ureter.
   (c) Secondary ureteric calculi.

2./...

2. Functional:

(a) Uretero-vesical incompetence
(b) Paralytic megaloureter.

1. OBSTRUCTIVE LESIONS

(a) Acute Granulomata:

It has been demonstrated earlier that an acute proliferative granuloma in the narrow confines of the ureter (Fig. 32) or the orifice (Fig. 34) will result in partial, if not complete, obstruction. The diagnostic features have already been presented.

(b) Stricture of the Ureter:

Stricture of the ureter is one of the commonest causes of a hydroureter. It has been shown that healing of bilharzial lesions results in fibrosis (Figs. 38, 40, 44 & 45). Depending on the site of the initial lesion, the amount of subsequen scarring determines the extent of stricture formation. The commonest site of a stricture is in the intramural portion where it may either be due to damage in the wall with subsequent fibrosis or result from a healing peri-ureteritis (Fig. 39) initiated in the bladder wall around the ureter. Stricture of the upper ends of the ureter is extremely rare (Simpson, 1963).

(c) Ureteric Calculus:

Ureteric calculi secondary to bilharzial disease may

theoretically/...

theoretically produce obstruction and hydronephrosis. In the present study, as mentioned earlier, no case of calculosis was encountered. Makar (1948) noted that this is a complication of bilharzial ureteritis and described the genesis of calculosis.

2. FUNCTIONAL CAUSES

(a) Uretero-vesical Incompetence (U-V Incompetence):

Talbot & Bunts (1949), Hunter (1954), Hutch (1954), Paquin (1959), Hutch et al. (1961), Zinner (1963) and Mathiesen (1964) have demonstrated the anatomical relationships and the physiological function of the junction between the ureter and bladder. They emphasised the importance of the "sphincteric" function and its dependence on proper anatomical relationships.

Mathiesen (1964) reported that chronic inflammatory fibrosis, surgical trauma to the ureteric orifice, loss of elasticity of the intravesical ureter or a neurogenic bladder all irreversibly damage the U-V valve mechanism and precipitate reflux.

Histopathology in the present study of bladder and ureteric bilharziasis has revealed gross disturbance consequent on fibrosis of the ureter and bladder, and especially in the U-V area. This area, as has been shown earlier in this study, is especially prone to bilharzial disease. Permanent damage to the U-V mechanism is implicit, and in the absence of an obstructive lesion proximally, will result in reflux of urine (Makar, 1948; Sayegh, 1950; Marcks, 1956 and

Honey /...

Honey & Gelfand, 1960). If there is no extravesical ureteric muscular damage, the resultant back pressure manifests itself as a dilatation and tortuosity at the pelvi-ureteric junction (Figs. 61 & 62) with hydronephrosis (Benjamin, 1956) but if there is damage to the ureteric wall as may occur in bilharziasis, the result will be a segmental hydroureter (Figs. 49 - 52) at the damaged site (Vermooten, 1937).

(b) Paralytic Megaloureter:

Beach (1931) and Bobbit (1937) believed that neuromuscular disturbance of the ureter could lead to atony with secondary hydroureter and hydronephrosis. Benjamin (1956) demonstrated that an obstructive lesion also eventually resulted in an atonic ureter. More recent work reveals that the peristaltic wave in the ureter can move in both directions and is dependent on the pressure gradient. The conduction of the peristaltic wave is considered to be a myogenic impulse conducted locally and independent of the nervous system (Mathiesen, 1964).

It is apparent that a segmental destruction of the ureteric musculature could result in a failure of transmission of the myogenic impulse. Such focal muscular destruction and atrophy is not uncommon, as has been demonstrated histologically, in ureteric bilharziasis. Occasionally, too, the entire length of the ureter is transformed by mural calcification into a rigid tube (Fig. 54). It is apparent that such a ureter will be incapable of initiating or propagating a peristaltic wave. It would also explain

the/...

the cystoscopic appearance described earlier - of urine dribbling through a widely patent orifice. Furthermore, a minimal obstructive element (common in the intramural segment), or uretero-vesical reflux, will result in back-pressure and consequent dilatation of the diseased segment of the ureter. It is suggested that the most descriptive term for such a condition is Paralytic Megaloureter.

It is apparent from this discussion that the pathogenesis of hydroureter and hydronephrosis in bilharzial disease is multifactorial and treatment ought to vary accordingly.

PROGNOSIS

The significance of hydroureter and hydronephrosis in the ultimate prognosis is difficult to evaluate. It has been suggested that in themselves they are not incompatible with long life (Kisner, 1952). Certainly the lack of symptoms and evidence of ill health in this study (admittedly no severe cases were encountered) would support this view. Gibson (1956) reported that hydronephrosis is not necessaily progressive and may become arrested in a certain phase. Nesbitt (1954) demonstrated that hydronephrotic kidneys may retain good function in spite of radiographic appearances. Spjut & Nicolai (1961) reported that a non-visualising kidney (non-fuctional by I.V.P. studies) of several months duration due to obstruction will return to near normal if the obstruction is relieved.

Radwin et al. (1963) and Platts & Williams (1963), however, have reported definite impairment of renal function, whilst Ross & Thompson (1963) demonstrated the greater

susceptibility/...

susceptibility of such kidneys to chronic pyelonephritis. In the presence of obstruction and stagnation, ascending infection and pyelonephritis are recognised complications (Makar, 1948). Forsyth & Bradley (1964), whilst concluding that the natural history of bilharzial disease was still obscure, commented that: "Almost inevitably the lives of all of them (school children with upper renal tract involvement) will be shortened".

From observations in the present study, the author cannot but endorse the opinion of Forsyth & Bradley.

SUMMARY

In this study, the incidence of upper renal tract involvement in a random group of young patients with symptoms of acute active urinary bilharziasis has been demonstrated to be of the order of 40%. Histopathological studies in the autopsy series revealed an incidence of ureteric involvement as high as 70%, demonstrating that the ureter is more frequently involved than is generally accepted, not only in the generally accepted site (lower third), but frequently throughout its entire length.

The nature of the ureteric lesions from I.V.P., cystoscopic and histopathological studies, have revealed the nature of the ureteric lesions and it has been shown that in urinary bilharziasis, acute lesions of the ureter are common.

The subsequent renal pathology in both clinical and autopsy material has been demonstrated and compared with reports of other authors. The occurrence of only mild to moderately severe lesions in the clinical study is believed to be due to the short duration of the illness.

The/...

The theories of the pathogenesis of hydroureter and hydronephrosis in bilharziasis have been examined and the probable mechanisms operative have been elucidated from the pathological studies.

Note : The summaries of the three aspects of Urinary Bilharziasis are presented at the end of each section.

PLATE VI

Fig. 32 Acute bilharzial granuloma involving the lower third of the ureter. All layers of the ureter are involved.
HE x 20

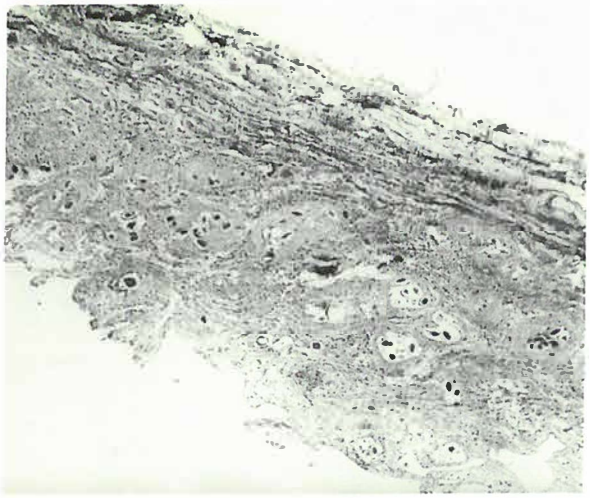
Fig. 33 Acute bilharzial granulomatous lesion involving all layers of the middle third of the ureter. The complete desturction of the normal architecture is evident.
HE x 20

Fig. 34 An acute granuloma abutting into the lumen in the region of the ureteric orifice. The pronounced epithelial hyperplasia and inflammatory reaction (eosinophils predominating) is apparent. HE x 20

Fig. 35 I.V.P. demonstrates the ragged outline of the right ureter due to involvement by acute bilharzial granulomata (confirmed by cystoscopy and ureteric catheterisation).

Fig. 36 The left lower ureter shows a segmental dilatation. Filling defects, denoting acute bilharzial granulomata, are evident in the bladder. The ureteric pattern is due to an acute bilharzial ureteritis.

Fig. 37 The lower ends of both ureters reveal a "beaded" appearance - the third form of ureteric deformity evident on I.V.P. due to acute bilharzial ureteritis.



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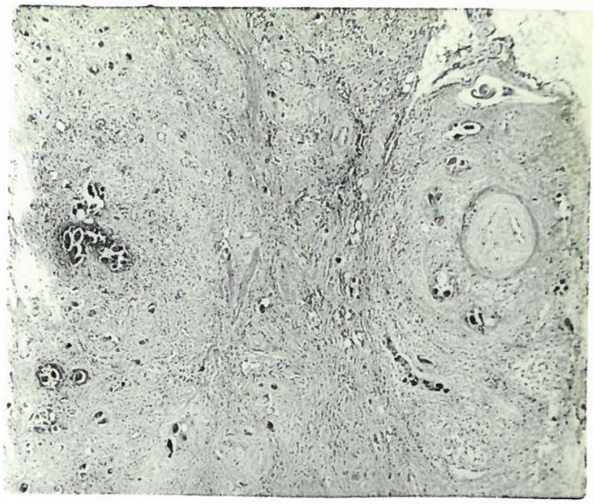

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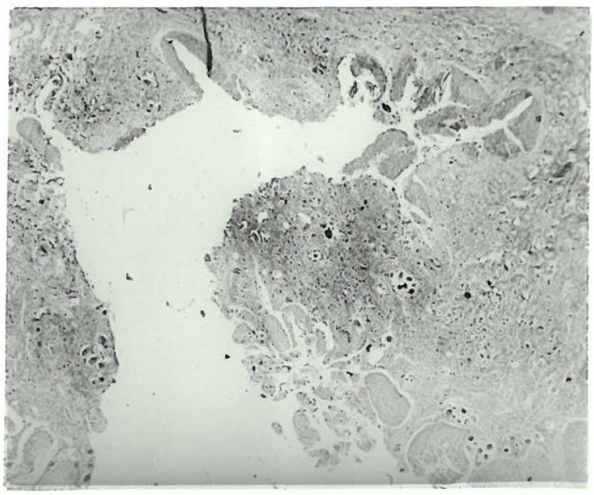

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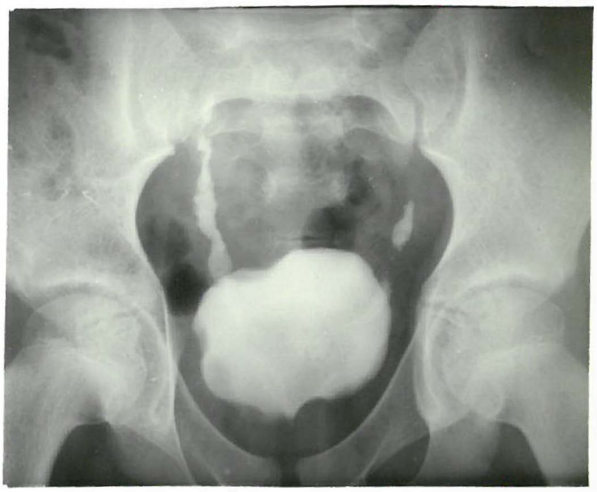

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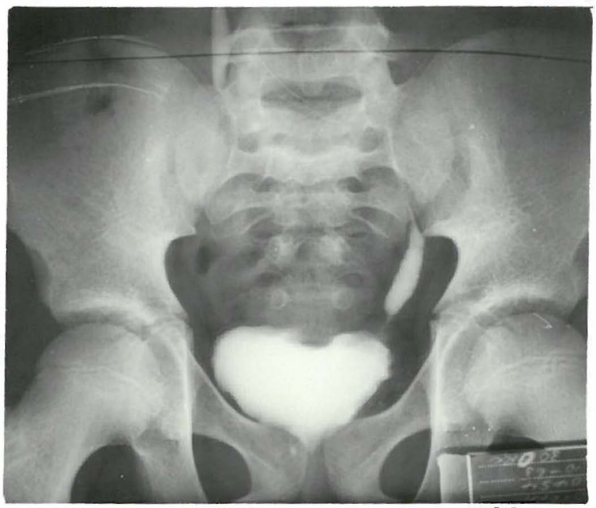

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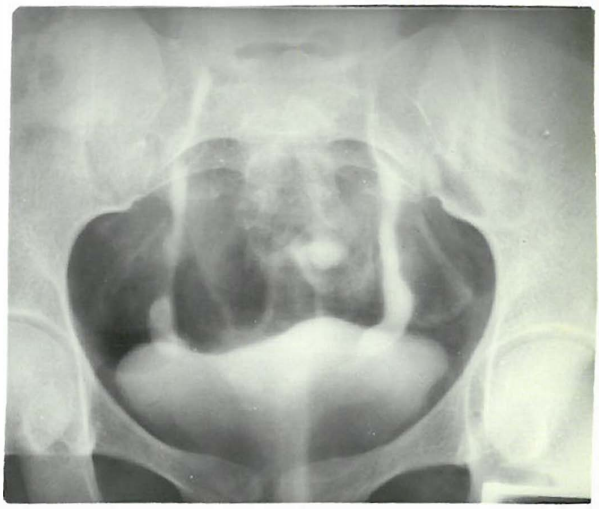

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PLATE VII

Fig. 38 A subacute lesion of the ureter (lower third). The healing pseudotubercles with concentric fibrosis are evident. HE x 20

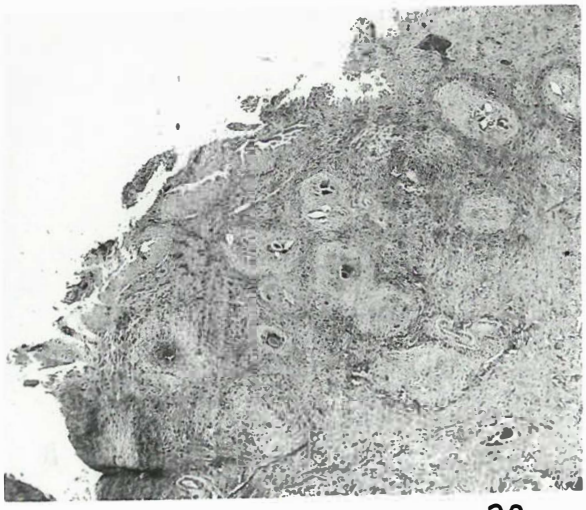
Fig. 39 A subacute lesion around the ureteric orifice. The epithelial hyperplasia is still evident and the extensive inflammatory reaction has resulted in the destruction and fibrosis of muscle fibres. HE x 20

Fig. 40 The chronic stage of bilharzial ureteritis with clusters of calcified ova, prominent fibrosis and atrophic epithelium. The muscle is intact and the bilharzial lesion was confined to the submucosa. HE x 20

Fig. 41 Myriads of calcified ova confined to the mucosa and submucosa protruding into, with consequent narrowing of, the ureteric lumen. HE x 20

Fig. 42 Segment of lower end of ureter reveals widespread deposition of ova (mainly calcified) in all layers with extensive destruction of the muscle coat and replacement by fibrous scar tissue. HE x 20

Fig. 43 Segment of upper third of the ureter (pelvi-ureteric junction) reveals a pattern similar to that of Fig. 42. HE x 20



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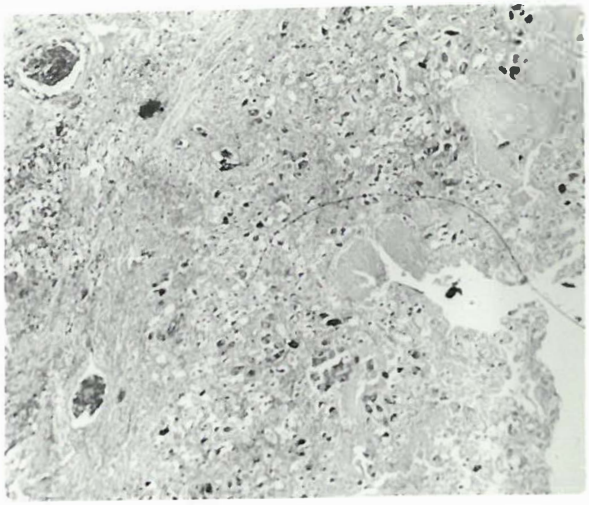

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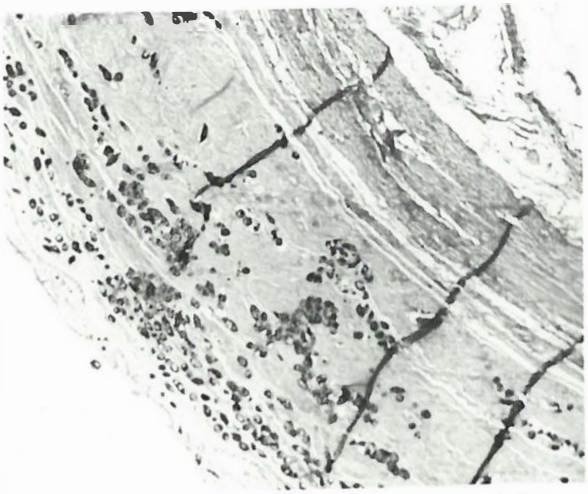

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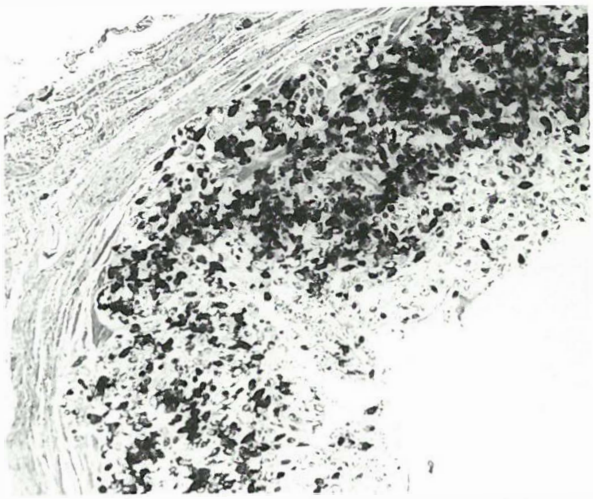

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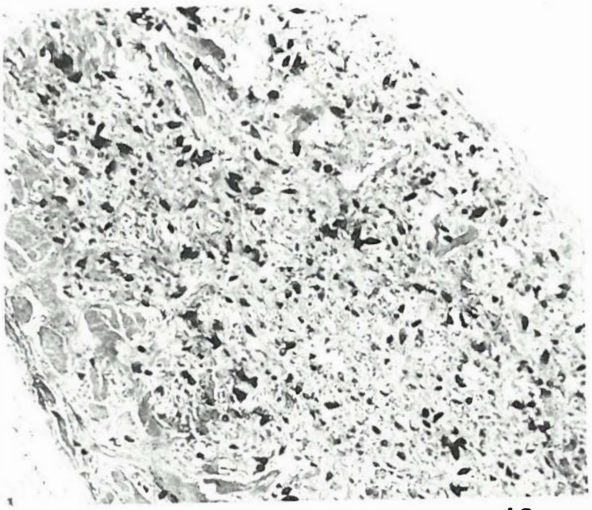

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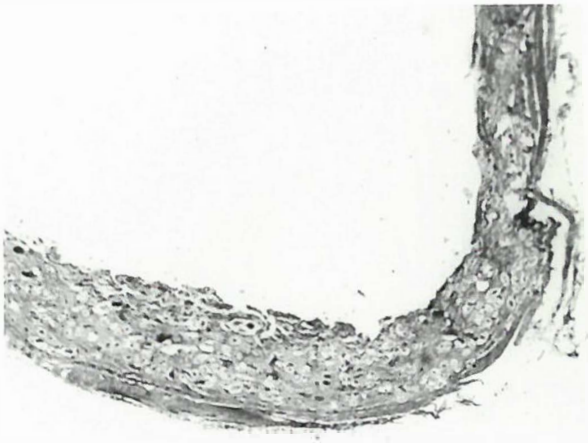

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PLATE VIII

Fig. 44 Histology of a stenotic lesion at the ureteric orifice reveals whorls of dense scar tissue formed around clusters of calcified ova. The muscle is atrophic and replaced by fibrous tissue. HE x 20

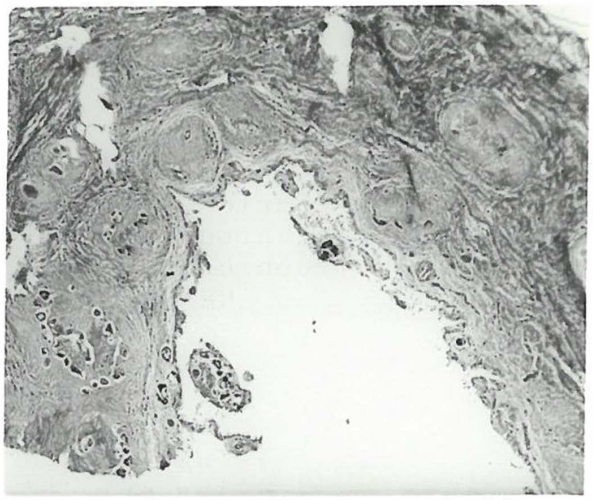
Fig. 45 Another example of a stenotic lesion with whorls of mature collagen around degenerate and calcifying ova. The epithelium is atrophic and there is striking evidence of muscle destruction. HE x 20

Fig. 46 The narrowing of the ureteric lumen due to epithelial hyperplasia is evident. Calcified and occasional ghost forms of ova may be discerned and there is atrophy and focal destruction of the muscle layer. Focal areas of urate deposition suggest a possible nidus for calculus formation. HE x 20

Fig. 47 Autopsy specimen reveals bullous cysts of both ureters - ureteritis cystica associated with fine sandy-patch lesions of late bilharziasis.

Fig. 48 Histological appearance of early ureteritis cystica with down growth of epithelial nests (lower border) into the submucosa. Occasional calcified ova are seen. HE x 20

Fig. 49 I.V.P. revealing ureteric lesion associated with late bilharziasis - with segmental hydroureter and early tortuosity. This is a later lesion than that shown in Fig. 37.



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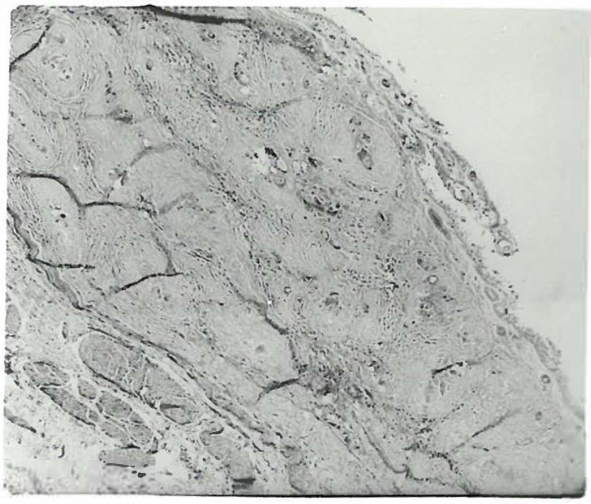

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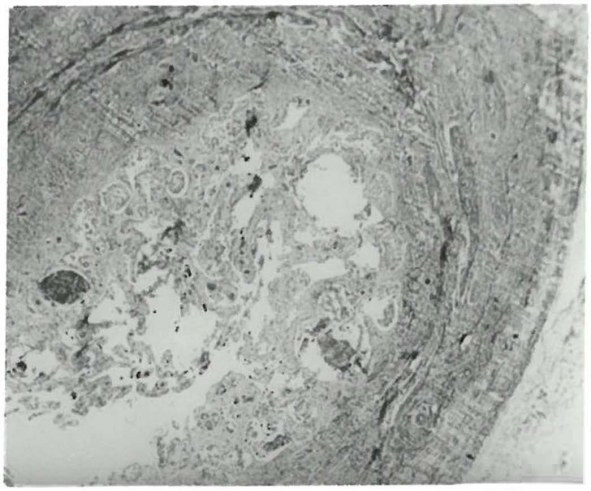

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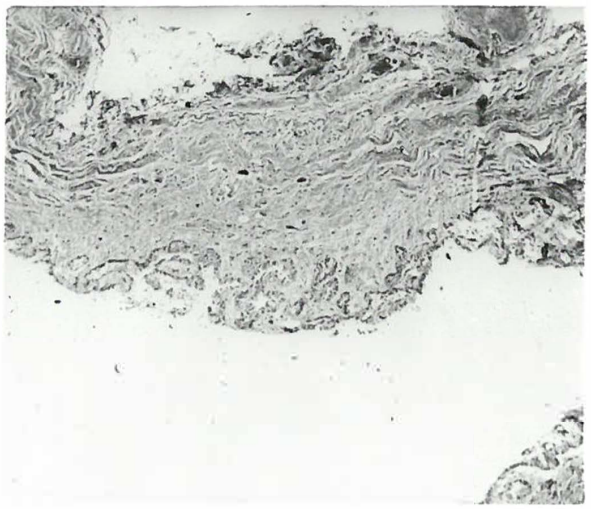

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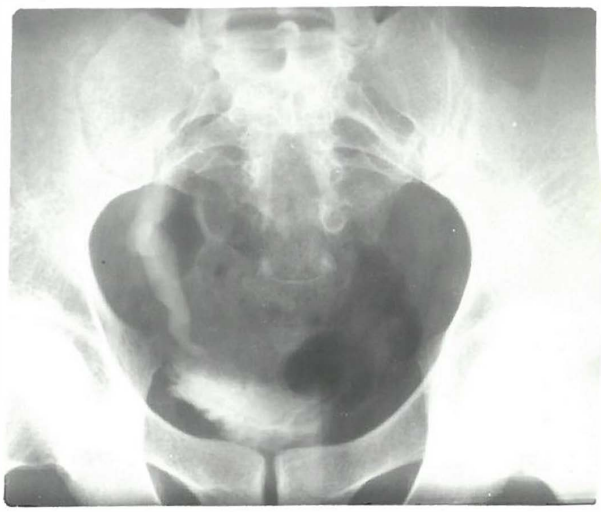

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PLATE IX

Fig. 50 A more advanced ureteric lesion associated with stricture of the lower end of the left ureter. There is a segmental hydroureter with tortuosity.

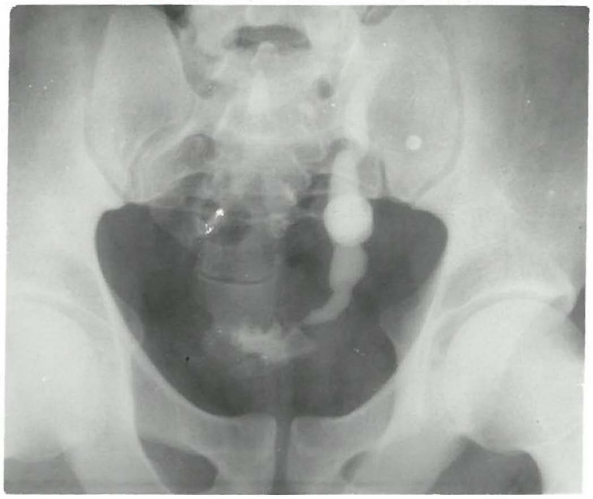
Fig. 51 Advanced bilateral hydroureter and tortuosity of the lower ends of the ureters associated with stenotic lesions.

Fig. 52 An example of advanced hydroureter and tortuosity of the left lower ureter with apparent stenosis of the intramural portion.

Fig. 53 Scout x-ray reveals advanced calcification of the bladder and calcification of the lower third of both ureters. The histology of the ureteric lesions has been demonstrated in figs. 41 and 42.

Fig. 54 Scout x-ray demonstrates a completely calcified bladder, calcification of the entire length of the right, and focal calcification of the left ureters.

Fig. 55 I.V.P. reveals a patch of haziness (late bilharzial granuloma) opposite the right spine of the third lumbar vertebra with early tortuosity of the ureter. There is a mild degree of hydronephrosis involving the kidney of the same side.



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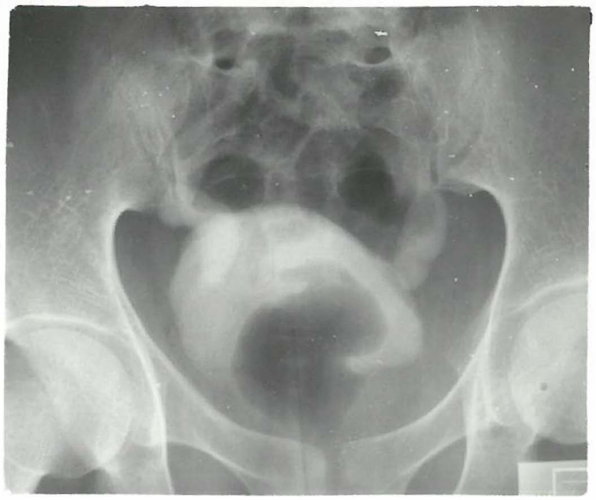

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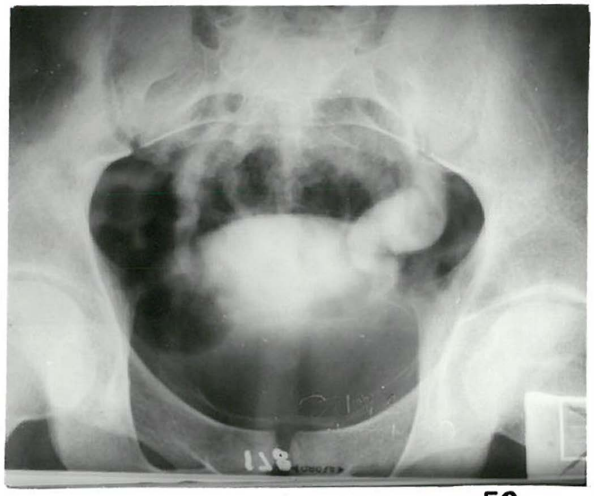

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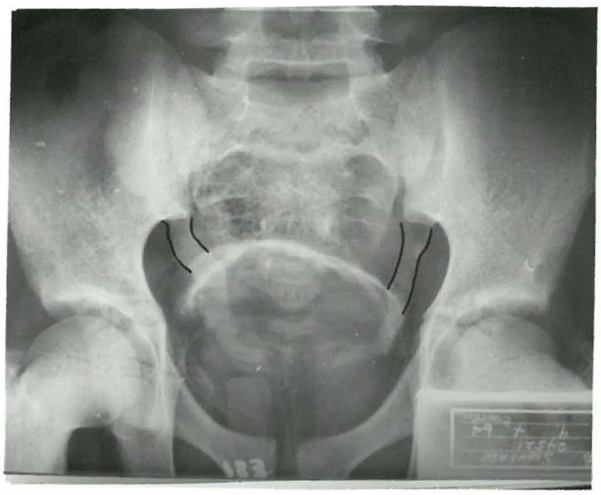

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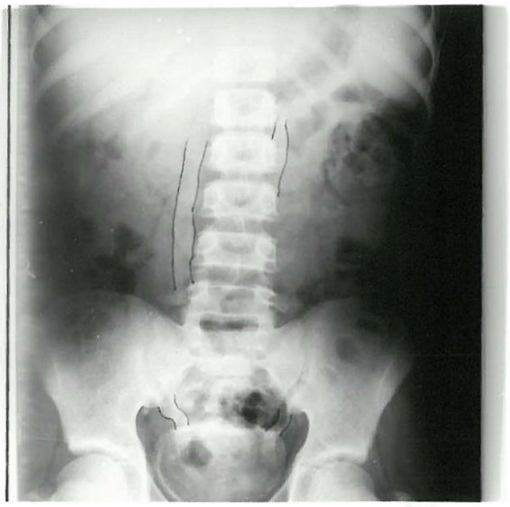

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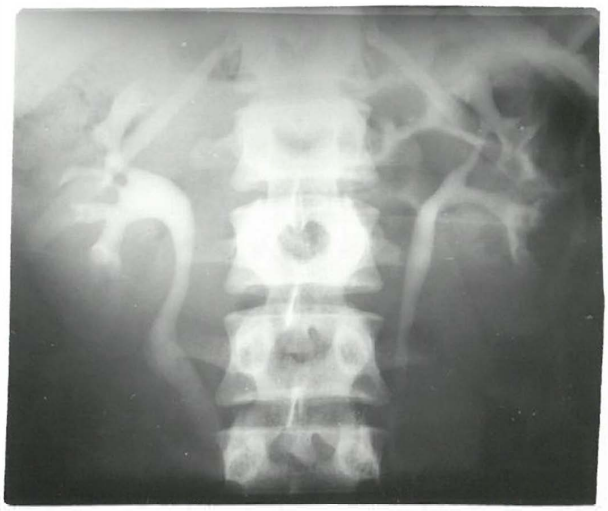

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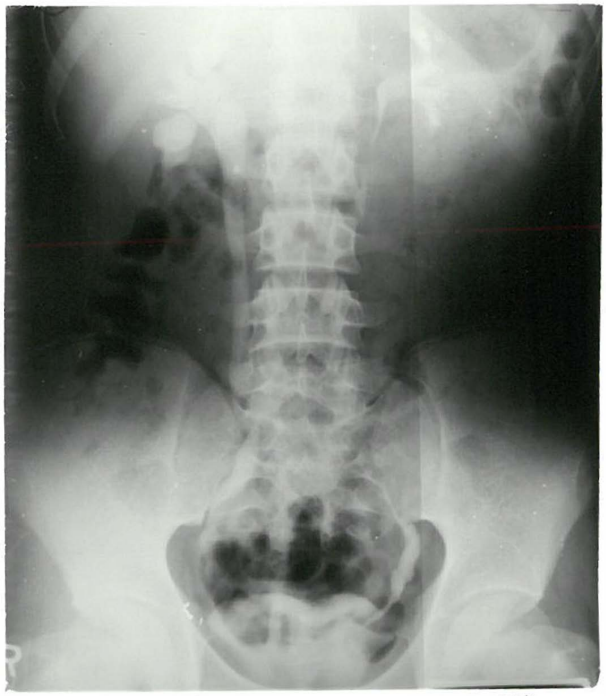
PLATE X

Fig. 56 I.V.P. demonstrates the beaded appearance of both lower ureters, a mild degree of hydroureter of the right ureter and a moderate degree of hydronephrosis of the right kidney.

Fig. 57 Reveals bilateral hydroureters with marked tortuosity of the right ureter and apparent multiple strictures. There is bilateral, moderately severe degree of hydronephrosis.

Fig. 58 Demonstrates severe bilateral hydronephrosis. The left ureter is markedly dilated.

Fig. 59 Reveals a severe left hydroureter and hydronephrosis. Only the terminal end of the right hydroureter is evident. (Not included in clinical study).



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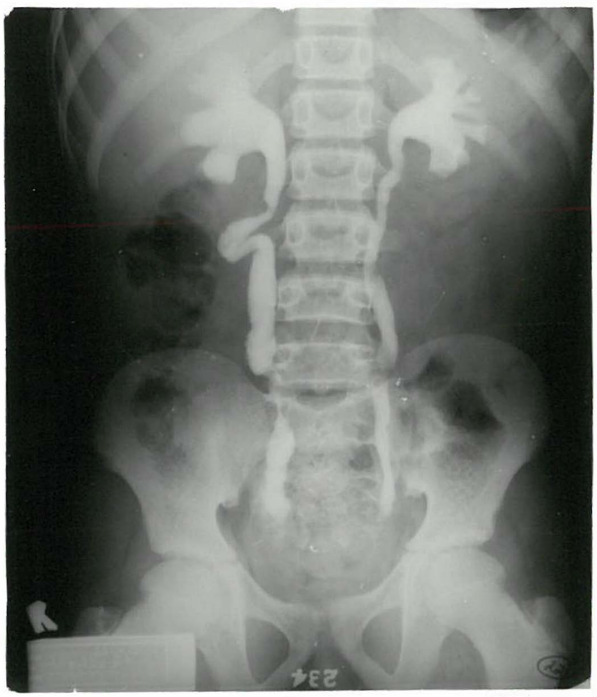

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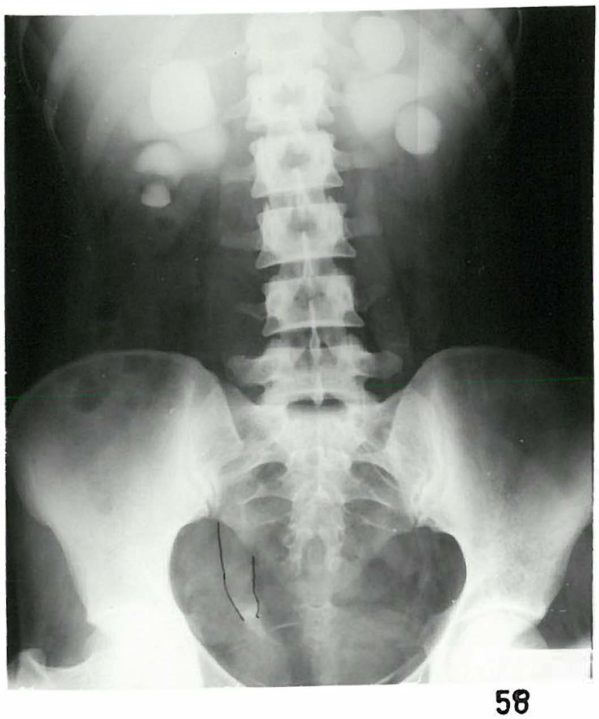

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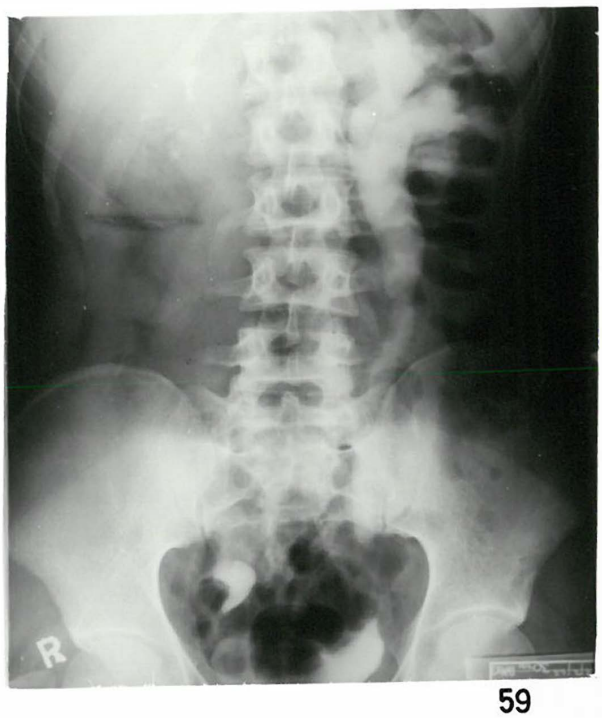

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PLATE XI

Fig. 60 An example of the very late stage of ureteric bilharzial involvement in an Indian female aged 21 (by kind permission of Professor D.S. Chapman). There is gross bilateral hydroureters and hydronephrosis.

Figs. 61 - 63 I.V.P. appearances of a patient (Indian male, 21 years) at intervals of 6 weeks to demonstrate the resolution of hydroureter and hydronephrosis on antimony treatment alone.

Fig. 61:

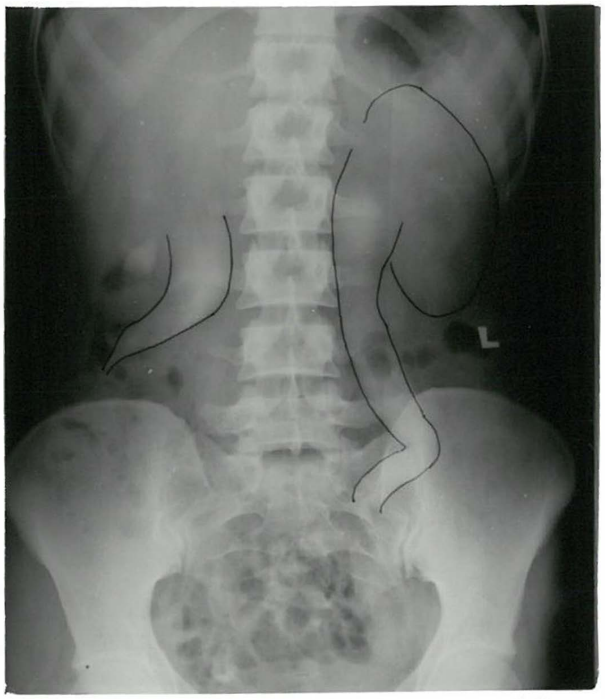
Before treatment there was marked right hydronephrosis and hydroureter with tortuosity. Cystoscopy revealed severe acute bilharziasis with involvement of the right ureteric orifice.

Fig. 62:

There is very little improvement 6 weeks after treatment. (Cystoscopic examination, however, revealed rapid improvement of the bladder lesions).

Fig. 63:

A further 6 weeks later, following a second and third course of antimony treatment, there is a remarkable resolution of the hydronephrosis and even of the hydroureter. There is no evidence of tortuosity although the lower end of the right ureter is still irregular and slightly dilated.



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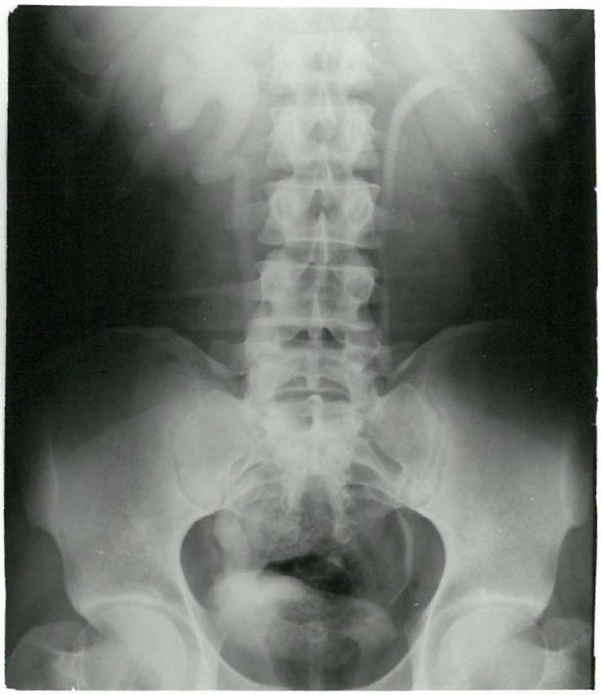

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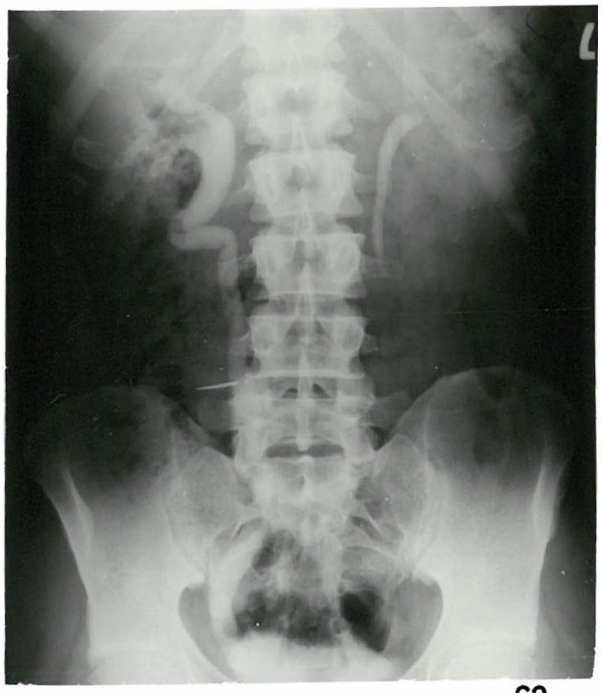

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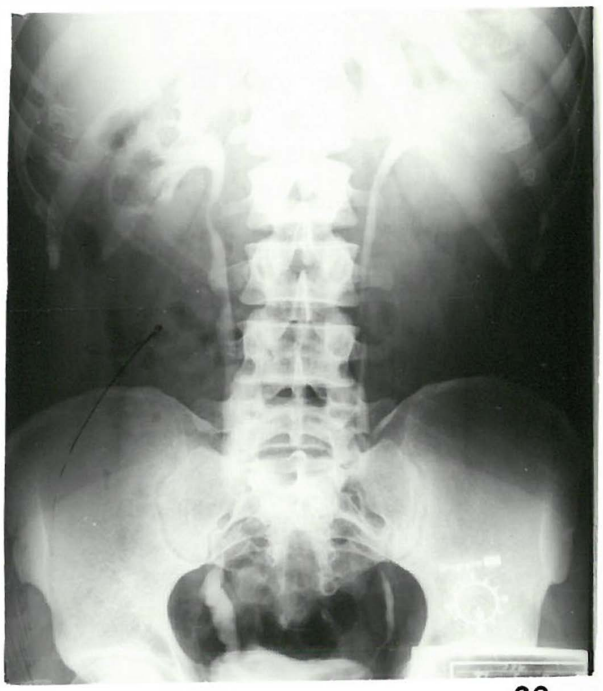

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CHAPTER V

S C H I S T O S O M I A S I S
A N D
C A R C I N O M A O F T H E B L A D D E R

INTRODUCTION

In 1911, Professor Ferguson, Professor of Pathology in Cairo, first noted the common association between bilharziasis and carcinoma of the urinary bladder, and concluded that bilharziasis was aetiologically related to the cancer.

Fairley (1920) described the vesical lesions in experimental bilharziasis in monkeys and observed that :

> "Although actual malignancy does not occur in early papillomata formation, it is, nevertheless, a very real danger at a later period, in long standing vesical bilharziasis, as Professor Ferguson (1911) has so ably demonstrated.

Some observers have accepted this to mean that the clinical observations of Ferguson (1911) had found experimental corroboration. Indeed, following the reports of Ferguson (1911) and Fairley (1920) most workers from Egypt have, until recently, accepted the concept of a bilharzial etiology of carcinoma of the bladder and numerous papers have been published on this subject.

Sorour/...

Sorour (op. cit. Afifi, 1947) analysed the autopsy records in Cairo between 1905 and 1930 and stated that the incidence of carcinoma of the bladder supervening on bilharziasis was 20.6% thus demonstrating the high incidence of malignancy in bilharzial bladders. Barsoum (1939) similarly commented on the high incidence of carcinoma in bilharzial bladders. Dolbey & Mooro (1924) stated that carcinoma of the bladder formed 23% of all malignancies in Egypt.

In a comparison of the incidence of cancer in 5 different organs from 3 Cairo hospitals, Makar (1952) demonstrated the high incidence of Cancer of the Bladder (Table I).

TABLE I

INCIDENCE OF CARCINOMA OF THE BLADDER
IN 3 CAIRO HOSPITALS DURING 9 YEARS (1932-1940)
COMPARED WITH THAT OF OTHER CANCERS*

	KASR-EL-AINY HOSPITAL	ITALIAN HOSPITAL	GREEK PRIVATE HOSPITAL
Carcinoma Tongue	210	2	1
Carcinoma Stomach	131	37	8
Carcinoma Colon & Rectum	463	26	3
Carcinoma Breast	720	88	47
Carcinoma Uterus	652	45	15
Carcinoma Bladder	1696 (4.3%) BILHARZIAL	6 (3%) NON-BILHARZIAL	10 (11%) NON-BILHARZIAL

* Abstracted from Makar (1952).

Amongst/...

Amongst the reasons he advanced for subscribing to the bilharzial aetiology of carcinoma of the bladder in Egypt were:

(1) Non-bilharzial cancer of the bladder was less common in Egypt than in Europe and America whereas "Bilharzial" vesical cancer was more frequent in Egypt than vesical cancer in Europe. In fact, bilharzial carcinoma of the bladder was the commonest cancer in Egypt.

(2) The common geographical distribution of vesical bilharziasis and cancer in Egypt.

(3) Carcinoma of the bladder was always associated with a history of previous vesical bilharziasis of up to 10 years duration.

(4) The common occurrence of leukoplakia in chronic vesical bilharziasis and the high incidence of squamous carcinoma.

(5) The younger age of onset of cancer of the bladder in Egypt as compared to the usual age incidence in non-bilharzial areas.

Dimmette et al. (1956) reported on the histological type of 90 bilharzial bladder tumours (Table II) and demonstrated that squamous carcinoma was the commonest variety.

Hashem (1961) reviewed the autopsy material at Kasr-el-Ainy Hospital between the years 1933-1958 and found that the incidence of bilharziasis was 33.6%. He encountered 518 cases (16.3%) of malignancy of which 65 (1.45% of total autopsies or

12.6%/...

12.6% of total malignancies) had carcinoma of the bladder and of these 83.1% were associated with bilharziasis. He further reviewed 207 autopsy and biopsy cases of cancer of the bladder and reported on the histological features (Table III) confirming the findings of Dimmette et al. (1956).

TABLE II

HISTOLOGICAL TYPES OF BLADDER CARCINOMA ON EGYPT*
(Classification according to Dukes & Messina)

	TYPE	NO.	TOTAL	%
i	Papillary transitional cell carcinoma	21		
ii	Solid (non-papillary transitional cell carcinoma)	12		
iii	Transitional cell carcinoma with metaplasia	1	34	37.8
iv	Pure squamous cell carcinoma	50	50	55.5
v	Pure adenocarcinoma	6	6	6.7
vi	Anaplastic sphroidal cell carcinoma simplex	0	0	-
			90	100.0

* Abstracted from Dimmette et al. (1956)

Hashem also stressed the fact that age-distribution for carcinoma of the bladder with bilharziasis was younger than that for non-bilharzial vesical cancer. He noted a sex ratio of 16 males to 1 female at autopsy and 9 : 1 on biopsy.

TABLE III/...

TABLE III

HISTOLOGICAL TYPES OF BLADDER CARCINOMA IN EGYPT WITH INCIDENCE OF BILHARZIASIS*

TYPE	AUTOPSIES (%)		BIOPSIES (%)		COMBINED (%)	
	TOTAL %	BILHARZIASIS %	TOTAL %	BILHARZIASIS %	TOTAL %	BILHARZIASIS %
Squamous Carcinoma	71.0	92.0	58.0	51.3	62.3	67.4
Transitional Cell Carcinoma	22.2	50.0	39.3	32.0	53.5	37.6
Adenocarcinoma	4.0	100.0	0.7	0	1.8	75.0
Sarcoma	2.8	100.0	2.0	0	2.6	40.0

* Abstracted and modified from Hashem (1961)

Aboul-Nasr et al. (1962) considered that, due to selection, the incidence quoted by earlier workers of carcinoma of the bladder in Egypt was erroneously high. Employing the comparative method of Makar (1952), they reported an incidence of 11.3% and in relation to total malignancies over a ten year period, the figure was 5.8%. The authors quoted corrected figures of Dolbey & Mooro (1924) as 7.7% (previously 23%) and of Makar (1952) as 17% (previously 43%). However, they (Aboul-Nasr et al.) noted that of their 652 cases of vesical carcinoma, 97% were associated with bilharziasis, whilst, of 299 cases examined histologically, 61% were of the squamous-celled variety

thus/...

thus confirming the findings of earlier observers. They also confirmed the previous observations that the age of onset of bilharzial vesical carcinoma was much younger.

This brief review of some of the more important contributions on bilharzial vesical cancer from Egypt suggests that, if bilharzia is not a direct cause of bladder cancer, at least there must be some link between the two diseases. The experience of investigators in endemic bilharzial areas outside Egypt seems to be more equivocal.

The earliest reference to cancer of the bladder in association with bilharziasis in Southern Africa is probably that of des Ligneris (1927 & 1936) who reported 15 cases from a rural hospital in Mozambique and stated that in the African, carcinoma of the bladder appeared to be associated with bilharziasis. He doubted, however, whether bilharziasis was the direct cause of the malignancies. Surprisingly he could not find a single case of bladder cancer in Lourenco Marques itself.

Strachan (1934) demonstrated the low incidence of cancer of the bladder in Africans of South Africa. He found 5 cases of vesical carcinoma out of a total of 1901 autopsies in Africans, compared to 9 cases out of 1622 autopsies in Europeans. He subsequently reported that 2 of the 5 African cases were associated with bilharziasis (Strachen, op. cit. Gelfand, 1950). Berman (1936) from two series of autopsy studies in Johannesburg Africans, gave figures of 2% and 3% of all malignancies for carcinoma of the bladder. No mention was made of the presence of bilharziasis.

More recently, Higginson & Oettle (1960) stated that the incidence of bladder carcinoma in Johannesburg Africans was

lower/...

lower than the expected figure for U.S.A. whites and closer to that for U.S.A. negroes. They found that the incidence was higher in rural Africans (5.1%) than in urban Africans (3.3%). They also noted that approximately 65% of these tumours belonged to the squamous-celled variety and that of all these tumours almost 50% were associated with bilharziasis. They suggested that the higher incidence of carcinoma of the bladder in the rural population might be due to the higher incidence of bilharzial infection but concluded that - "if schistosomal infection is a carcinogen, its influence on incidence is relatively small under our conditions".

Subsequently (1962) they reported that of 26 consecutive bladder cancers, 58% were associated with bilharziasis. They noted that, since digestion of tissues revealed higher incidences of bilharzial infection than any other method, the true incidence of bilharziasis in association with bladder cancer would be still higher if this method had been applied to the tumours. By using the autopsy digestion technique they revealed an incidence of 24% for bilharziasis in the Johannesburg male African. They concluded that - "In general, therefore, the findings would support the view that Schistosoma haematobium is found more frequently in persons with bladder cancer than in autopsy material from the same hospital, even although the latter is more intensively examined".

Wainwright & Roach (1957) in a comparative study of neoplastic diseases in the Africans, Indians and Europeans of Natal, combining autopsy and biopsy material for the years 1950-1956, reported incidences of carcinoma of the bladder of 3.7% in Europeans, 2.8% in Africans and 5.6% in Indians. They made the observation that "Despite the prevalence of urinary

bilharziasis/...

bilharziasis in the African and the Indian, there is no great increase in cancer of the bladder in these races, suggesting that bilharziasis is not an important factor in its pathogenesis".

Kisner & Fine (1958), however, reported a high incidence of squamous carcinoma in African bladder cancers and indicated that a high proportion of these were associated with bilharziasis. They suggested that a more detailed investigation of this problem be undertaken.

Thus, in comparison to the reports from Egypt, South African investigators consider the role of schistosomiasis in the pathogenesis of carcinoma of the bladder to be of doubtful significance.

Reports emanating from other regions of Africa also provide conflicting evidence.

Fairley (1931) reported a case history of a person who became infected with bilharzia in South Africa and who returned to England where he died 18 years later from carcinoma of the bladder. Kirkaldy-Willis (1946) commented on the common complication of cancer of the bladder supervening on urinary bilharziasis in East Africa.

Gelfand (1950) reporting from Central Africa stated that the incidence of cancer of the bladder was 4.4% of all malignancies in biopsy material in Africans. Seven of his ten cases had concomitant bilharzial infection. He commented, however, that "Although 7 of 10 Africans with carcinoma of the bladder had bilharziasis (70%) it does not necessarily follow that there is any connection between the two diseases".

Marcks (1956 & 1958) reported that of all malignancies

in/...

in Africans, 13% were carcinoma of the bladder. Of these 50% were associated with concomitant bilharziasis. However, he considered this to be slender evidence for ascribing a bilharzial aetiology to cancer of the bladder.

Davis & Wilson (1954) reported that carcinoma of the bladder and schistosomiasis were both uncommon in Uganda. Dodge (1962), also from Uganda, reported that 3.4% of all malignancies were in the bladder. He emphasised that bilharziasis was rare in Uganda and noted that of the 76 bladder tumours examined histologically, only 3 showed bilharzial infection. At the same time he reported that although the commonest carcinoma was the transitional-cell carcinoma (40%), no less than 35% were of the squamous-celled variety, a much higher incidence than that found in bladder tumours in non-bilharzial areas.

Edington (1956) reported a low incidence of carcinoma of the bladder (2.5% of total malignancies) in Ghana. He noted, however, that the age-distribution for bladder tumours was not unlike that described in Egypt and that 71% of autopsy material and 30% of biopsy material from carcinoma of the bladder had concomitant bilharzial infection. Bilharziasis is known to be widespread in Ghana (Edington, 1957). Consequently, from the above facts, he concluded that bilharziasis could not be excluded as a possible aetiological agent.

The African Conference on Bilharziasis (Anon, 1957) crystallised the views of several investigators by concluding that: "After a review of the published data on the subject, it was agreed that there is no valid evidence of a relationship between S. haematobium and cancer of the urinary bladder in Africa south of the Sahara".

Shortly/...

Shortly after this, and in contrast to the earlier opinions of Gelfand (1950) and Marcks (1956), Honey & Gelfand (1960) reported that whereas carcinoma of the bladder in the European was not associated with bilharziasis, the two conditions were not uncommonly associated in the African of Rhodesia. Moreover, they agreed with authors from Egypt that carcinoma of the bladder occurred in a younger age-group in the African and suggested that the racial difference in the disease was probably due to a much heavier infestation of vesical bilharzia in the African.

Whereas des Ligneris (1936) had been unable to find a single case in Lourenco Marques, Prates (1958 & 1962) reported an unusually high incidence of carcinoma of the bladder in the African from Mozambique, giving an incidence of 7.9% for males and 7.2% for females. He felt that the true incidence in the African females was probably much higher, ascribing this to the fact that in Mozambique the women worked in the fields more than did the men and were more exposed to schistosomal infection.

Subsequently Prates & Gillman (1959 & 1962) reviewed a hundred cases of bladder cancer in Mozambique Africans and demonstrated similar trends as regards histologic type, age-distribution and association with vesical schistosomiasis as those described from Egypt. Although realising the common association between schistosomiasis and bladder cancer, they concluded that " - whatever the role of schistosomiasis, it was by no means direct, and that the evidence available was not sufficient to exclude schistosomiasis as an important etiological factor in bladder cancer".

PRESENT/...

PRESENT STUDY

Materials & Methods

The present study is a review of all vesical tumours encountered at the Central Histopathological Laboratory of the Natal Provincial Administration and the Department of Pathology of the University of Natal from January 1959 to July 1964. As the laboratory served numerous hospitals for varying periods of time the material cannot be used to estimate either incidence or morbidity rates in the different racial groups.

It is however possible to compare the incidence and distribution of the histological types of bladder tumours in the African, Indian and European groups and to review the incidence of bilharzia in tumour and non-tumour groups. Only proven primary bladder cancer have been considered and "metastatic" tumours and cases where doubt existed as to the primary source of the tumour, have been excluded.

The source race and sex distribution is given in Table IV.

Histology sections from all 193 cases were available for study and an independent review of all slides was conducted. The classification of Dukes & Messina (1949), subsequently accepted as the basis of histological classification for vesical tumours by the Institute of Urology, London (Pugh, 1959), was

employed/...

employed but modified in that for purposes of comparison all transitional-cell cancers were included in one group.

TABLE IV

RACE & SEX DISTRIBUTION OF 193 BLADDER TUMOURS

RACE	SEX	SURGICAL BIOPSY	AUTOPSY	TOTAL	GRAND TOTAL
AFRICAN	M	47	17	64	86
	F	12	10	22	
INDIAN	M	15	5	20	25
	F	5	0	5	
EUROPEAN	M	67	*	67	82
	F	15	*	15	
TOTAL		161	32		193

* Records not available.

Results.

BLADDER PAPILLOMATA

Included in the 193 bladder tumours were 46 tumours classified as "papillomata" (Table V).

In all the above cases the tumours had been fulgurated by diathermy with consequent distortion and fragmentation of the

tissues/...

tissues in most instances. Though histological features suggested transitional cell papillomata either benign, or of Grade I malignancy, in the large majority of tumours a definite opinion could not be expressed. The unreliability of histologic diagnosis based on such insufficient and distorted tissue obtained by fulguration has been repeatedly demonstrated.

TABLE V

RACE & SEX DISTRIBUTION OF "PAPILLOMATA" OF BLADDER

RACE	MALE	FEMALE	TOTAL	% OF ALL BLADDER TUMOURS IN RACE GROUP
AFRICAN	5	1	6	6.96
INDIAN	9	1	10	40
EUROPEAN	23	7	30	36.5
TOTAL	37	9	46	-

Various authorities have commented on the difficulty of histological grading of so-called papillomata of the bladder (Dukes & Messina, 1949; Pugh, 1959; Mostofi, 1962 and Pessin, 1961).

An interesting observation from Table V is the presence of 6 papillomata in Africans (approximately 7% of all tumours). Higginson & Oettle (1959) reported on the rarity of this lesion in the African. The incidence of papillomata in the Indian (40%) corresponded with that of the European (36.6%).

None/...

None in the present series were associated with bilharziasis.

Realising the inadequacy of material from this group these tumours have been classified as belonging to the group with "indefinite histology", and have consequently been excluded from further consideration.

MALIGNANT TUMOURS

The source, age, sex and race distribution of these tumours are given in Table VI.

TABLE VI

TOTAL BLADDER MALIGNANCIES

RACE	SEX	BIOPSY	AUTOPSY	TOTAL	GRAND TOTAL	MALE/FEMALE RATIO
AFRICAN	M	42	17	59	80	2.8
	F	11	10	21		
INDIAN	M	6	5	11	15	2.5
	F	4	0	4		
EUROPEAN	M	44	0	44	52	5.5
	F	8	0	8		
TOTAL		115	32		147	

HISTOLOGICAL/...

HISTOLOGICAL TYPES OF TUMOURS

The various histological types and their association with bilharziasis are shown in Table VII and Figs. 65-75.

Approximately 83% of the malignant tumours in the European were of the transitional cell variety of which only one was associated with bilharziasis. There were only 4 (7.7%) cases of squamous carcinoma of which one was associated with bilharziasis, being a well differentiated keratinising squamous carcinoma. These figures for Europeans are comparable with those reported from non-bilharzial areas by Payne (1959) and Willis (1963).

In contrast to the European group, 60% of the tumours in the African belonged to the well-differentiated squamous-celled variety of which 67% were associated with bilharzia. This forms the largest single group of malignant bladder tumours in the African. Of the 21 (26%) classed as transitional cell carcinoma, 11 (52%) were associated with bilharzia and 8 (3 with bilharzia) showed definite evidence of squamous metaplasia.

The Indian group occupied an intermediate position between the European and African with 60% classified as transitional cell carcinoma and 40% as squamous cell. The figures for the Indian group should be interpreted with caution as they are based on a very small number. Nevertheless it is significant that 4/6 of the squamous celled variety were associated with concomitant bilharzial infection (all necropsy specimens). It will be noted that there were no cases of adenocarcinoma or anaplastic carcinoma in the Indian.

INCIDENCE./...

TABLE VII

HISTOLOGICAL TYPES OF BLADDER CANCER AND INCIDENCE OF BILHARZIA

RACE	TRANSITIONAL CELL CARCINOMA			ADENOCARCINOMA			ANAPLASTIC CARCINOMA			SQUAMOUS CARCINOMA		
	NO.	%	% WITH BILHAR-ZIASIS	NO.	%	% WITH BILHAR-ZIASIS	NO.	%	% WITH BILHAR-ZIASIS	NO.	%	% WITH BILHAR-ZIASIS
AFRICAN	21	26.25	52.4	6	7.5	33.3	5	6.25	40	48	60.0	66.6
INDIAN	9	60.0	22.2	0	0	0	0	0	0	6	40.0	66.6
EUROPEAN	43	82.7	2.3	4	7.7	0	1	1.9	0	4	7.7	25.0

INCIDENCE OF BILHARZIASIS IN MALIGNANT TUMOURS

The incidence of Bilharziasis in all malignancies of the bladder in the 3 different race groups is shown in Table VIII.

TABLE VIII

INCIDENCE OF BILHARZIASIS IN CASES WITH CARCINOMA OF THE BLADDER.

RACE	NO. WITH CARCINOMA	NO. WITH BILHARZIASIS	%	% BILHARZIASIS P.M. CANCER CASES	% BILHARZIASIS C SQUAMOUS CARCINOMA - P.M. CASES
AFRICAN	80	47	58.75	63	78
INDIAN	15	6	40.00	100	100
EUROPEAN	52	2	3.8	-	-

The incidence of bilharziasis in the European population is not known but the impressions of a parasitologist, physician, paediatrician, pathologist and urologist are that the overall incidence in the European is low, if not uncommon (Elsdon-Dew, 1964; Adams, 1964; Mann, 1964; Fine, 1964 and Roach, 1964). Earlier in this work the incidence of bilharzia in the Indian and African race groups, as determined by digestion of tissues from autopsy material, was shown to be of the order of 28% in both African and Indian groups.

Comparison/...

Comparison of this control group with those with vesical malignancies reveals that in the African with carcinoma of the bladder, bilharziasis is twice as common and in the Indian the cancer group also has a much higher incidence.

The assessment of the incidence of bilharzia in the cancer group was far from satisfactory in that sample tissues for histology were selected and not representative of the whole organ. Surgical biopsy material was even less representative and in some instances consisted only of bladder washings. The figures for the control group were based on digestion of the whole bladder. Nevertheless, the results reveal that the incidence in the cancer group is double that of the control. If one considers only those bladder tumours which subsequently came to autopsy, then 63% of these in the African had concomitant bilharzial involvement, whilst no less than 78% with squamous carcinoma in the autopsy group were associated with bilharziasis. Of the 5 cases with cancer encountered in Indians at autopsy, all were associated with bilharziasis. Had adequate sampling been possible, the incidence of bilharziasis in association with carcinoma would have been still higher, especially in those cases based on biopsy.

The probability of cancer of the bladder with concomitant bilharzial infection being merely coincidental seems to be over-ruled by the far higher incidence of bilharziasis in the cancer group in comparison with the controls.

AGE DISTRIBUTION OF MALIGNANCIES

The age distribution in the different races for carcinoma of the bladder is shown in Table IX and Fig. 64.

TABLE IX/...

TABLE IX

AGE DISTRIBUTION FOR CARCINOMA OF BLADDER

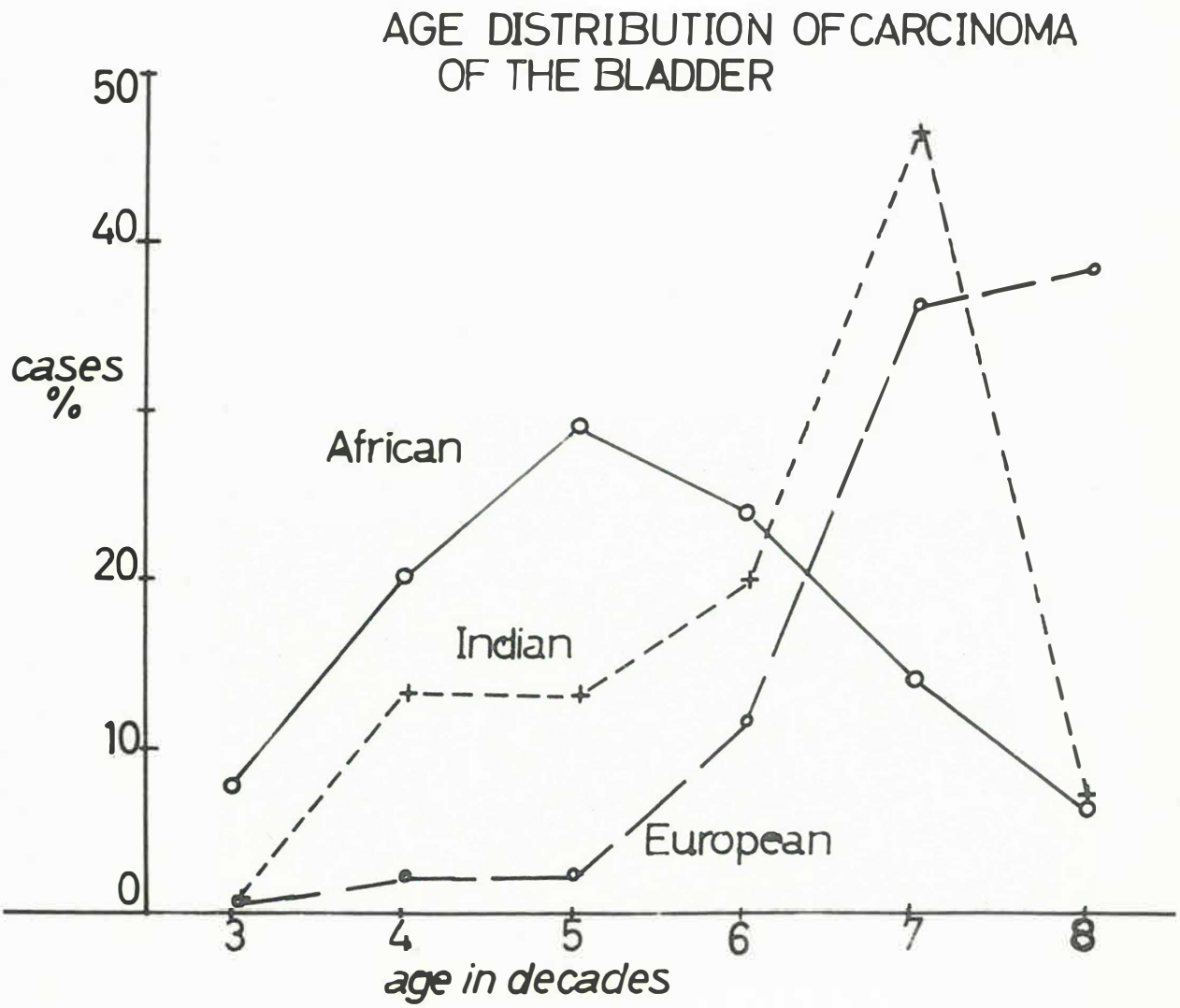
AGE	AFRICAN		INDIAN		EUROPEAN	
	NO.	%	NO.	%	NO.	%
21 - 30	6	7.5	0	0	0	0
31 - 40	16	20.0	2	13.3	1	2.0
41 - 50	23	28.75	2	13.3	1	2.0
51 - 60	19	23.75	3	20.0	6	11.5
61 - 70	11	13.75	7	46.7	19	36.5
71+	5	6.25	1	6.7	20	38.5
Unknown	-	-	-	-	5	9.5
TOTAL	80		15		52	100

The differences in the age-distribution for the different races are immediately apparent. The peak-incidence of cases in the African group occurs between the 4th and 6th decades, that in the Indian between the 6th and 7th decades and that in the European between the 7th and 8th decades.

The age-distribution of tumours for Europeans is in general agreement with that reported by Payne (1959) from England. By contrast, in the African a much younger age group is afflicted. This finding is similar to those quoted by Makar (1952 & 1957); Hashem (1961) and Aboul-Nasr et al. (1962) from Egypt.

Prates/...

Fig. 64


AGE DISTRIBUTION OF CARCINOMA OF THE BLADDER
50
40
20
10
0
cases %
African
Indian
European
3
4
5
6
7
8
age in decades

Prates & Gillman (1959) reporting from Mozambique, and Edington (1956) from Ghana (both endemic areas of bilharziasis) also emphasised the younger age distribution. On the other hand, Dodge (1962) from Uganda, a reputedly non-bilharzial (S. haematobium) area, reported that the age-distribution in Africans was similar to that of the local European.

The age distribution for the Indian is intermediate in position.

SEX DISTRIBUTION OF MALIGNANCIES

The sex-ratio for the different racial groups in the present study is demonstrated in Table VI and compared with the findings of other authors in Table X.

The present finding in Africans is similar to that of Wainwright and Roach (1957), working in the same area, but that for Indians differs (2.5 : 1 as against 10 : 1). The sex ratio of the incidence of bilharziasis in the African by autopsy digestion technique was found to be 1.2 : 1.

While it is generally agreed that males have a much higher incidence of cancer of the bladder, there is variation in the figures quoted by different authors. The lowest ratios are those of Prates & Gillman (1959) - 1.75 : 1, and Prates (1962) was the only author who reported a preponderance of females (0.94 : 1).

DISCUSSION/...

TABLE X

SEX INCIDENCE FOR CANCER OF BLADDER

AUTHOR	COUNTRY	MALE/FEMALE RATIO	BILHARZIASIS
Wynder et al (1963)	England & Wales	2.19	Nil
	Denmark	2.2	Nil
	U.S. White	2.7	Nil
	U.S. Negro	1.6	Nil
Dodge (1962)	Uganda	7.3	Occasional
Hashem (1961)	Egypt	9	Hyperendemic
Aboul Nasr et al. (1962)	Egypt	5	Hyperendemic
Prates and Gillman (1959)	Mozambique	1.75	Hyperendemic
Prates (1962)	Mozambique	0.94	Hyperendemic
Edington (1957)	Ghana	10	Endemic
Kisner and Fine (1958)	Johannesburg (S.A.)	4.6	Endemic*
Higginson & Oettle (1960)	Johannesburg (S.A.)	3.6	Endemic*
Wainwright & Roach (1957)	Natal - African	2.4	Endemic
Wainwright & Roach (1957)	Natal - Indian	10	Endemic
Present Study (1964)	Durban - African	2.8	Endemic
	Durban - Indian	2.5	Endemic

* African labourers migrate from endemic areas. Johannesburg itself is a non-endemic area.

DISCUSSION

THE ROLE OF BILHARZIASIS IN THE PATHOGENESIS OF CARCINOMA OF THE BLADDER

INTRODUCTION

The report of Ferguson (1911) from Egypt of the common association of carcinoma of the bladder and vesical bilharziasis has led to much discussion on a possible aetiological relationship. There are two schools of thought, the one favouring and the other sceptical, of the bilharzial aetiology of cancer of the bladder.

The protagonists of this theory that bilharzia is causal were largely confined to Egypt where vesical schistosomiasis is hyperendemic and results in severe urinary tract complications (Dolbey & Mooro, 1924; Sorour, 1928; Makar, 1952 & 1962; Dimmette et al., 1956; Sayegh et al., 1956; Hashem, 1961; Aboul-Nasr et al., 1962; Mousa, 1962). More recently, however, Prates & Gillman (1959) and Prates (1962) have reported a high incidence of cancer of the bladder in Mozambique - which is also a hyperendemic area. These authors demonstrated similarities as regards age-distribution and histologic type between their material and that from Egypt and concluded that the importance of schistomiasis in relation to cancer of the bladder could not be excluded.

On the other hand, as mentioned earlier, Gelfand (1950) and Marcks (1956) were sceptical of the role of bilharziasis in cancer of the bladder. Gelfand (1950) argued that, if schistosomiasis was carcinogenic in the bladder, it ought to, but did not, behave similarly in other sites - the rectum for instance. Moreover, he argued that the incidence of carcinoma of the

bladder/...

bladder in the Rhodesian African was no higher than that quoted from non-bilharzial areas and finally that in Egypt itself though both sexes were apparently equally exposed to bilharzial infection, the incidence was much higher in males.

The fact that bilharziasis does not produce similar lesions in different organs may be partly explained by the differences in tissue reaction to identical stimuli as has been shown in animal experiments by many authors. Recently Bonser (1962) in attempts to produce bladder tumours experimentally in animals, found not only species differences in response to similar carcinogens but also strain differences within the same species. Dunning et al. (1950) reported that simple dietary differences altered the host-response to the same carcinogen.

In more recent years, a third school of thought has emerged which, though not denying a possible link between vesical bilharziasis and carcinoma, is doubtful of the specific aetiological agent (Kirkaldy-Willis, 1946; Edington, 1956; Kisner & Fine, 1958; Prates & Gillman, 1960; Higginson & Oettle, 1960; Aboul-Nasr et al., 1962).

RELATION OF ENDEMICITY TO INCIDENCE OF CARCINOMA OF THE BLADDER

The incidence of carcinoma of the bladder in various countries is shown in Table XI.

From this table and from earlier discussion it is apparent that the incidence of carcinoma of the bladder is

high/...

TABLE XI

INCIDENCE OF CARCINOMA OF THE BLADDER IN VARIOUS COUNTRIES

(expressed as a percentage of total malignancies)*

AUTHOR	YEAR	COUNTRY	INCIDENCE %	BILHARZIA
Hashem	1961	Egypt	≠ 2.66 (total) 12.6 (autopsy)	Hyperendemic
Aboul-Nasr [i]	1962	Egypt	11.3	Hyperendemic
Aboul-Nasr [ii]	1962	"	5.8	Hyperendemic
Prates [+]	1962	Mozambique	7.55	Hyperendemic
Edington	1956	Ghana	2.51	Endemic
Gelfand [++]	1950	Rhodesia	4.40	Endemic
Higginson & Oettle	1960	Johannesburg	3.3	Endemic
Wainwright & Roach	1957	Natal	2.8 (African)	Endemic
Dodge	1962	Uganda	3.4	Occasional
Pessin	1961	America	2.0	Nil

* Abstracted from authors quoted.

≠ Total autopsy and biopsy material.

[i] Aboul-Nasr - Author's figures.

[ii] Aboul-Nasr - quoting Alexandria Hospital - biopsy material for 1951.

\+ Combining male and female figures.

++ Quoted incidence in biopsy material only.

high in Egypt (Barsoum, 1939; Makar, 1952; Hashem, 1961 and Aboul-Nasr et al., 1962) and in Mozambique (Prates, 1958 & 1962). Both these countries have hyperendemic foci of S. haematobium. By contrast, the incidence of carcinoma of the bladder in areas of lower endemicity is not dissimilar from that reported by Dorn (1962) and Pessin (1961) in non-bilharzial areas. There is also a wide variation in the figures quoted in the same country, for example in Egypt itself, Hashem (1961) gives an incidence of only 2.66% (compare Makar, 1952).

From the literature one can conclude that in both Egypt (Makar, 1952; Hashem, 1961; Mousa, 1962; Nagaty, 1962) and Mozambique (Prates & Gillman, 1950) the native people are exposed to bilharzial infection for the greater part of their productive lives. Mousa (1962) remarked that bilharziasis in Egypt was an occupational disease, contracted by the people working in swampy fields. Such high exposure rate must lead to heavy worm burdens and geater severity of the disease. Prates & Gillman (1960) reporting from Mozambique stated that: "There can scarcely be any doubt, however, that schistosomiasis occurs at an early age and that its incidence increases sharply over the age of 10 years and is maintained at an elevated rate until senescence. By the time the incidence of cancer of the bladder rises steeply between the ages of 30 and 50, many of the sufferers have already been exposed to the irritating effects of the schistosomes and their eggs for 25 - 45 years".

In the Durban population under study, the factor of repetitive infection over prolonged periods does not apply. As agriculture is not a regular avenue of employment for the local non-European population, the opportunities afforded the parasite

to/...

to invade man are relatively infrequent. Consequently, it is the belief of the author, that with uncommon exceptions, infection with S. haematobium in the local population is accidental, incidental and avoidable, and the severity of the infection, consequently, light.

Using digestion technique on autopsy material, the present study has shown that in most instances the egg load is light to moderate. If one presupposes the aetiological activity of bilharziasis in carcinoma of the bladder, one may postulate that it is the difference in worm load, in repetition of infection and in duration and severity of the lesions, which accounts for the lower incidence of such malignancy in the local population in an endemic area by contrast with that found in hyperendemic areas. The relative mildness of the renal tract complications in both clinical and autopsy material in the present study by comparison with the picture reported from Egypt, lend further support to this view. The severe vesical complications of contracted fibrosed bladder (Sayegh, 1950; Sayegh et al., 1956), bladder neck obstruction (Makar, 1952; Badr et al., 1958; Aboul-Nasr et al., 1962) and calculosis (Afifi, 1934 and Bitschai, 1950) reported from Egypt, were not encountered in the present study.

INCIDENCE OF BILHARZIASIS IN CARCINOMA OF THE BLADDER

A common finding in endemic areas has been the high incidence of bilharziasis in cases of cancer of the bladder (Table XII).

TABLE XII/...

TABLE XII

CARCINOMA OF THE BLADDER WITH BILHARZIASIS IN DIFFERENT COUNTRIES

AUTHOR	YEAR	COUNTRY	TOTAL NO. OF CA.	% WITH BILHARZIASIS	
Makar	1952	Egypt	1696	100	Autopsy
Dimmette et al.	1956	Egypt	96	94	Autopsy
Hashem	1961	Egypt	65 196	83 41	Autopsy Biopsy
Aboul-Nasr et al.	1962	Egypt	652	97	?
Edington	1956	Ghana	30	30 71	Biopsy Autopsy
Gelfand	1950	Rhodesia	10	70	Autopsy
Prates and Gillman	1960	Mozambique	100	33	Autopsy
Higginson and Oettle	1962	Johannesburg	26	58	Biopsy
Dodge	1962	Uganda	76	4	Autopsy
Present Author	1964	Natal (S.A.)		COMBINED	AUTOPSY
		African	80	59	63
		Indian	15	40	100
		European	52	4	*

* Records not available.

In the present study it has been shown that there is a much higher incidence of bilharzia in cases of carcinoma of

the/...

the bladder than in a control group. Similarly Hashem (1961) noted that the overall incidence of bilharzia in 3183 autopsies was 33.6% in contrast to 83.1% in the cancer group.

An interesting observation from Table XII is the lower incidence revealed by biopsy in comparison with autopsy material. This confirms the earlier opinion that inadequate sampling inherent in biopsy lessens the likelihood of demonstrating bilharzial infection.

The lowest incidence of bilharziasis in carcinoma of the bladder in Africans is that quoted by Dodge from Uganda, a country which is relatively free from S. haematobium, whilst the lowest incidence in the total series is that quoted for Europeans by the present author. Only 2 cases of the total of 52 cases of bladder cancer in Europeans showed evidence of bilharziasis. The incidence of bilharziasis in Europeans locally is believed to be as stated, comparatively low.

AGE INCIDENCE OF CARCINOMA OF THE BLADDER IN ENDEMIC AREAS

Attention has already been drawn to the lower age distribution of carcinoma of the bladder in bilharziasis. Table XIII gives a comparison of the present findings with those reported elsewhere.

TABLE XIII/...

TABLE XIII

AGE DISTRIBUTION (IN %) OF CARCINOMA OF THE BLADDER*

AUTHOR	DECADES						OTHER & UNKNOWN	PLACE	BILHARZIA
	3	4	5	6	7	8			
Makar (1952)	10	31	30	23	5	-	1	Egypt	Hyperendemic
Hashem (1961)	13	44.4	21.4	16	5.2	-	-	Egypt	Hyperendemic
Aboul-Nasr et al (1962)	8	25	39.4	18.4	7.7	1	.5 3	Egypt	Hyperendemic
Prates & Gillman (1959)	4	24	33	17	17	4	(?) 1	Mozambique	Hyperendemic
Dodge (1962)	2.6	9.3	24	40	14.6	9.3	(?) 1	Uganda	Uncommon
Payne (1959)	.7	2.3	9.2	22.3	35.5	29.2	(?) 7	England	Nil
Present Author: (1964)									
African	7.0	20	29	24	14	6	-	Natal	Endemic
Indian	0	13	13	20	47	7	-	Natal	Endemic
European	0	2.0	2.0	11.5	36.5	38.5	? 9.5	Natal	Uncommon

Higginson & Oettle (1960) from Johannesburg and Edington (1957) from Ghana, both made the observation that cancer of the bladder occurs in a younger age-group in bilharzial areas. That it is not a racial characteristic may be deduced from the report of Dodge (1962) from Uganda, where the age-distribution is nearer that of the European of South Africa and England.

HISTOLOGICAL TYPES OF TUMOURS IN ENDEMIC AREAS

Reference has already been made to the striking differences in the histological types of bladder carcinoma in bilharzial and non-bilharzial areas. Table XIV compares these incidences of histologic types in relation to geographical region and presence or absence of bilharziasis in these areas.

The preponderance of squamous-cell carcinoma in bilharzial areas is well demonstrated in Table XIV. It is shown that in populations with no significant bilharzial infection (Uganda, England and Natal Europeans) the incidence of squamous carcinoma is low, transitional cell carcinoma being the commonest variety. The reverse is true in bilharzial areas.

PRE-NEOPLASTIC BILHARZIAL VESICAL LESIONS

Numerous authors have reviewed the vesical epithelial changes produced by bilharziasis in an attempt to correlate possible pre-neoplastic and neoplastic lesions.

Ferguson/...

TABLE XIV

GEOGRAPHICAL COMPARISON OF HISTOLOGICAL TYPES OF BLADDER TUMOURS

(Expressed as %)

Author	Transitional	Adenocarcinoma	Anaplastic & other	Squamous	Place	Bilharzia
Payne (1959)	96.6	0.6	0.3	2.4	England	Nil
Dodge (1962)	44.1	7.4	10.3	38.2	Uganda	Uncommon
Dimmette et al. (1956)	37.8	6.7	0	55.5	Egypt	Hyperendemic
Hashem (1961)	33	1.8	2.6	64	Egypt	Hyperendemic
Aboul-Nasr et al (1962)	33	5	0	62	Egypt	Hyperendemic
Prates & Gillman (1959)	28	0	13	59	Mozambique	Hyperendemic
Higginson & Oettle (1962)	8.7	4.3	17.3	69.6	Johannesburg	Endemic
Present Author (1964)						
African	26.25	7.5	6.25	60	Natal	Endemic
Indian	60.0	0	0	40	Natal	Endemic
European	82.7	7.7	1.9	7.7	Natal	Endemic

Ferguson (1911) notedthe frequent association of bilharziasis with Brunn's nests, cystitis cystica and cystitis

glandularis/...

glandularis. He concluded that these changes were exclusively bilharzial in origin. However, observers from non-bilharzial areas reported similar lesions following chronic cystitis associated with urolithiasis and obstructive renal tract disease (Patch & Rhea, 1935; Aberhouse, 1943; Fagerstroem, 1948; Nesbit, 1956 and Morse, 1928).

Patch & Rhea (1935) gave a classic description of the genesis and histological appearances of these lesions and concluded that these changes were due to vesical epithelial metaplasia as a result of chronic irritation following on urinary stasis and infection. They also demonstrated the possible relationship of cystitis glandularis and adenocarcinoma. Mostofi (1954) discussed the metaplastic potentialities of the bladder epithelium and demonstrated the variability of response to apparently similar stimuli. Johnson (1957) confirmed the observations of Patch & Rhea (1935) and of Mostofi (1954) by producing similar lesions in experimental animals. More recently, Mende et al. (1957) and Mostofi (1962) have reported that the different layers of the vesical epithelium possess differing enzyme properties - the surface cells having a high phosphatase content and the deeper cells showing succinic dehydrogenase. Metaplasia, therefore, entails not merely a cellular morphological alteration, but also promotes a cytochemical and physiological change in the cell.

Makar (1952, 1957 & 1962), Hashem (1961) and Aboul-Nasr et al. (1962) from Egypt have emphasised the proliferative and hyperplastic bladder lesions associated with bilharziasis and have shown their relationship to cystitis cystica and cystitis glandularis. They reported that similar lesions were not uncommon in the ureters. Prates & Gillman (1959) reported somewhat

similar/...

similar lesions in bilharzial bladders from Mozambique.

These findings have been confirmed in an earlier chapter. The natural history of the hyperplastic and proliferative acute lesions of bilharziasis has been recounted and it has been demonstrated that in the absence of further infection these lesions regress to the stage of an atrophic epithelium. The ingression of epithelium into the submucosa, will, however, result in cystitis cystica and glandularis. Whereas the acute hyperplastic phase of bilharziasis may simulate a pseudo-malignant histological appearance, the end result is in fact a quiescent, benign, atrophic epithelium with rests of epithelial tissue (Brunn's nests?) in the submucosa and ingrowing epithelial glandular elements - so-called cystitis cystica and cystitis glandularis.

From the literature it is apparent that these changes are present in both non-bilharzial and bilharzial chronic cystitis.

Whilst some authors have suggested that cystitis glandularis is potentially preneoplastic (Makar, 1952; Aboul-Nasr et al., 1962; Patch & Rhea, 1935 and Mostofi, 1962), many still regard cystitis cystica as a benign lesion. Patch & Rhea (1935) considered cystitis cystica as potentially premalignant whilst Nesbit (1956) reported the origin of papillary transitional cell carcinoma from these cystic lesions and emphasised that all these lesions should be considered as potentially malignant.

Now, whereas it is probable that an adenocarcinoma may arise from cystitis glandularis (Makar, 1952) (Figs. 78 & 79) and transitional cell carcinoma from cystitis cystica (Nesbit,

1956/...

1956) (Fig. 71), the literature from endemic bilharzial areas and personal experience reveal that the commonest bladder cancer is the squamous cell variety (Table XIV). This suggests that the bladder epithelium most commonly undergoes squamous metaplasia when associated with bilharziasis.

The experience of authors has already been quoted demonstrating the wide metaplastic potentiality of the bladder epithelium - it is capable of metaplastic change from well-differentiated, mucus-secreting type of epithelium to the well-differentiated keratinising squamous epithelium (Patch & Rhea, 1935; Mostofi, 1962). All these authors are also agreed that chronic bladder sepsis with persistent irritation from whatever cause, is the probable irritating factor in metaplasia. Politano (1956) reported that in the presence of sepsis and stagnation with irritation (from calculosis), squamous metaplasia, leading to leukoplakia, would supervene even in the renal pelvis. However, Bonser & Jull (1956), Roe (1964) and Ball et al., (1964) have experimentally induced metaplastic lesions in animal bladders with chemical and foreign bodies in the absence of sepsis. These were identical to the descriptions of Patch & Rhea (1935) and Mostofi (1954). This suggests that specific irritants per se are in fact capable of stimulating these metaplastic lesions and that bacterial sepsis may potentiate the action of these irritants.

Mostofi (1962) observed that whereas glandular metaplasia arose from the surface epithelial cells, squamous metaplasia originates from the basal cells of the epithelium. Squamous metaplasia with leukoplakia, according to Mostofi, is the most frequent metaplastic form assumed by the bladder epithelium in the presence of infection and calculosis.

Numerous/...

Numerous authors from Egypt have also commented on the frequency of squamous metaplasia and leukoplakia in bilharzial bladders (Makar, 1952 & 1962; Aboul-Nasr et al., 1962; Hashem, 1961). These workers also emphasised the presence of sepsis in these chronic bilharzial bladders. Prates & Gillman (1959) demonstrated the common occurrence of squamous metaplasia progressing to leukoplakia in bilharzial cystitis in Mozambique Africans and noted that secondary bacterial sepsis was a common feature. They were of the opinion, however, that metaplasia was a direct result of irritation by the presence of large numbers of bilharzial ova and their toxins.

Squamous metaplasia with leukoplakia in parts of the bladder unaffected by tumour was present in 40% of the cases of Prates & Gillman (1959), whilst no less than 43% of all tumours showed evidence of squamous metaplasia in parts. Dimmette et al. (1936) also reported a high incidence (72%) of squamous metaplasia in unaffected parts of bladder in malignancies, whilst adenoid metaplastic changes were present in 44% of squamous carcinoma.

In an earlier chapter the changes in the bladder epithelium encountered in bilharziasis were described, attention being drawn to the rarity of squamous metaplasia and/or leukoplakia in the absence of malignancy. The clinical study also revealed the low incidence of sepsis in such cases. It has not been possible, owing to the inadequacy of the samples, to assess the frequency of metaplasia in other parts of bladders with malignant change. However, review of the available material is shown in Table XV.

TABLE XV/...

TABLE XV

METAPLASTIC CHANGES IN CANCER OF THE BLADDER IN DURBAN AFRICANS

TOTAL NO. OF CASES:	SQUAMOUS CARCINOMA		TRANSITIONAL CELL CARCINOMA	
	TOTAL	WITH KERATIN	TOTAL	WITH SQUAMOUS METAPLASIA
80	60%	85.4%	26.25%	38%

Keratinising, well-differentiated squamous carcinoma was the commonest form encountered (Figs. 68 - 70).

With such a degree of differentiation, an epidermoid type of metaplasia must have preceeded the development of malignancy (Figs. 71, 76 & 77).

The evidence that there are several important differences in bladder neoplasia in bilharzial as opposed to non-bilharzial areas, may be summarised as follows:

(1) The high incidence of carcinoma of the bladder in such hyperendemic areas as Egypt (Makar, 1952; Hashem, 1961; Aboul-Nasr et al., 1962) and Mozambique (Prates & Gillman, 1959), in contrast to that in non-bilharzial areas (Payne, 1959 and Dodge, 1962). Although Dolbey & Mooro (1924) reported that the incidence of carcinoma supervening on a bilharzial bladder was 23%, no real assessment similar to

that/...

that reported for aniline dye workers by Case et al., (1954) has been made of the increased risk of a bilharzial population to carcinoma of the bladder.

In areas of lower endemicity, review of the literature and personal experience reveal that the incidence of carcinoma of the bladder appears to differ but little from that in areas without bilharziasis (Gelfand, 1950; Edington, 1957; Higginson & Oettle, 1960; Wainwright & Roach, 1957).

(2) The much younger age-distribution of vesical malignancy in both hyperendemic and endemic areas.

(3) Whereas well-differentiated keratinising squamous carcinoma predominates in the bilharzial zones, transitional-cell carcinoma is commoner in non-bilharzial areas.

(4) The common association of carcinoma of the bladder and concomitant bilharzial infection in endemic and hyperendemic bilharzial areas.

(5) The presence of preneoplastic metaplasia in the bladder - of cystitis cystica, cystitis glandularis, squamous metaplasia and leukoplakia, in association with bilharziasis and malignancy in bilharzial areas.

CARCINOGENESIS AND VESICAL BILHARZIASIS

In spite of the fairly convincing circumstantial evidence linking bilharziasis and carcinoma of the bladder, the preciseaetiologic significance of bilharziasis in promoting

neoplastic/...

neoplasia in the bladder is not known. The theory of chronic irritation by the parasite as originally advanced by Ferguson (1911) has found many supporters. Whilst Ferguson & Diamantis (1934) believed that the ova acted as mechanical irritants, Makar (1952) and later Prates & Gillman (1959) suggested that miracidial toxins liberated from viable ova may, in fact, be a more powerful irritant to the bladder tissue and could account for the prominent hyperplastic and metaplastic changes evident in bilharzial bladders.

Dolbey & Mooro (1924) suggested that the superimposition of bacterial sepsis on chronic bilharzial cystitis might account for the preneoplastic and neoplastic changes so commonly encountered.

The reports of more than 60 years ago indicating the high incidence of vesical tumours in aniline dye workers have been confirmed by numerous authors, amongst the more recent being Goldblatt (1947), Hueper (1952) and Vigliani & Barsotti (1962). The association of these tumours with benzedine, beta-naphthylamine, alpha-naphthylamine and several other aromatic amines, has been demonstrated (Hueper, 1952; Clayson, 1953; Case *et al.*, 1954; Bonser, *et al.*, 1962). Bonser *et al.* (1952) demonstrated that 2-naphthlyamine *per se* was not carcinogenic but that its metabolite 2-amino-1-naphthol was the active agent. They postulated that as this was an ortho-hydroxyamine (ortho-aminophenol), other carcinogenic aromatic amines may similarly be active by virtue of their conversion to ortho-hydroxyamines. Clayson (1953) postulated a similar theory.

Following the reports of Bonser *et al.* (1952) & Clayson (1953), Boyland *et al.* (1955) observed that naturally occurring

ortho-aminophenols/...

ortho-aminophenols from tryptophan metabolism were normally present in the urine but in conjugated form. They postulated that the carcinogenic aminophenols might be liberated in the urine by enzymatic activity, one such enzyme probably being beta-glucuronidase. They also noted that many cases subsequently developing malignancy of the bladder, had, over varying periods, been treated for non-bacterial cystitis. They suggested that this "cystitis" might in fact have been a chemical, rather than a bacterial irritant - predisposing to neoplasia. Furthermore they suggested that cases subsequently developing spontaneous malignancy 'might have a metabolic pattern analogous to an "in-born error of metabolism" or other cause such as a vitamin deficiency associated with excretion of a carcinogenic agent'.

Earlier, Dunning et al. (1950) had reported that whereas 2-acetamido-fluorene induced carcinoma of the liver in rats, the same carcinogen, in rats on tryptophan-rich diets, induced carcinoma of the bladder. This was confirmed by Boyland et al. (1954).

Subsequently Allen et al. (1957) demonstrated that the naturally occurring aminophenols of tryptophan metabolism, 3-hydroxyanthranilic acid, 3-hydroxykyneurine and 2-amino-3-hydroxyacetophenone, behaved as carcinogens in experimental animals. They also confirmed the observation of Bonser et al. (1952) that the active carcinogen in beta-naphthlyamine-induced tumours was not the parent compound but its orthoaminophenol metabolite. Like Boyland (1955), they suggested that the active agent was released from the conjugated metabolite in the bladder probably by the enzyme beta-glucuronidase.

Working on the hypothesis that endogenous and exogenous tumours are in fact directly linked and that their irritation

might/...

might be identical, Boyland *et al.* (1955) demonstrated that bladder cancer patients had a higher beta-glucuronidase activity than normal subjects. In a more extensive study (1962), however, they failed to demonstrate any such difference.

Fripp (1960) had in the meantime, reported from Uganda that the beta-glucuronidase enzyme activity was raised in *S. haematobium* infections and that the level fell during treatment. Abul-Fadl & Metwalli (1963) reported similar findings from Egypt and noted that the urinary beta-glucuronidase activity was increased to five times the normal value. They noted too that in sediment free urines from bilharzial cases the enzyme activity tended to be low, but was raised whenever there were viable *S. haematobium* ova in the urine. This raises the probability as to whether this enzyme may have emanated from the miracidium rather than from the host. Nevertheless this would hardly explain the five-fold increase in cancer cases reported by Abul-Fadl & Metwalli (1963).

Trout *et al.* (1962) could demonstrate no appreciable difference in the excretion of ortho-aminophenols in bilharziasis in Mozambique. They noted, however, the relatively high urinary excretion of 5-hydroxyindoleacetic acid (itself a tryptophan metabolite) and its degradation products in these patients. Abul-Fadl *et al.* (1961) had made a similar observation in Egypt, reporting that with simple or complicated bilharziasis, serotonin excretion was elevated to thrice the normal value whilst it increased ten-fold in cancer of the bladder. They also reported that 3-hydroxy-anthranilic acid excretion was lower than normal in non-bilharzial Egyptians but was increased to thrice the normal value in simple or complicated bilharziasis and was increased four-fold in carcinoma of the bladder with bilharziasis.

From/...

From this brief review of carcinogenesis it is evident that there may in fact be a common carcinogen operative in the induction of neoplasia of the bladder in persons exposed to aniline dyes, bilharziasis and in those who spontaneously develop malignancy. If this is so then it is equally apparent that the role of schistosomiasis in malignancy is at most, indirect.

The theory that urinary stasis promotes carcinogenesis deserves mention. It is probable that stagnation permits not only concentration of the endogenous carcinogens but also exposes the bladder epithelium to prolonged stimulation (Boyland et al., 1955).

An interesting observation by Bonser & Green (1950), in experimental induction of tumours in rabbits, was the presence of premalignant and malignant growths in the lower ends of the ureters. Scott & Boyd (1953) observed that if, after transplanting the ureters into a colonic loop, dogs were fed beta-naphthlyamine, no tumours developed in the bladders, whereas, if the ureters were constricted during transplanation, tumours subsequently developed in the obstructed proximal ends of the ureters. This tended to confirm the observation that urinary stasis might be an important factor in promoting tumour growth.

Makar (1952) had reported that in one of his cases of bilharziasis, the proliferative bladder lesions of cystitis glandularis regressed spontaneously and dramatically following diversion of the urine by ureteric transplantation suggesting that the stimulus resided not in the tissue itself but in the urine. Hashem (1961) reported that carcinoma of the ureter and renal pelvis in bilharzial patients from Egypt was significantly higher than that reported from non-bilharzial areas and noted the relationship to urinary stasis due to ureteric strictures.

The/...

The theory of urinary stasis as a factor promoting carcinogenesis finds fresh support from the observations of Davies & Wilson (1954) and that of Dodge (1962) from Uganda. Bilharziasis in Uganda appears to be uncommon whereas urethral stricture with subsequent retention is a relatively common complication (Dodge, 1962). Many patients with urethral stricture required supra-pubic cystostomy as a permanent measure. Of the 108 cases with bladder tumours, 31 had urethral stricture with retention. In 8 of the latter cases, the tumour arose in or around the suprapubic cystostomy tract. Histological examination in 7 of the cases revealed well-differentiated keratinising squamous carcinoma (Dodge, 1962). Dodge also reported the relatively high incidence of carcinoma of the urethra in Uganda and concluded that:

> "The association between urethral stricture and bladder cancer in our patients suggests also that prolonged exposure of the bladder mucosa to urine-borne carcinogens in patients with chronic retention of urine, is important in the genesis of bladder carcinoma in Uganda Africans".

As mentioned earlier, workers in Egypt have often stressed that one of the commoner late complications of bilharzial cystitis was bladder neck obstruction (Makar, 1952; Hashem, 1961; Aboul-Nasr et al., 1962 and Sayegh & Dimmette, 1956). According to these authors secondary bacterial sepsis was also common in these cases. The present study has demonstrated that these complications are rare in local bilharzial patients.

It is obvious then that there are major differences

in/...

in bilharzial bladder pathology experienced in the present study compared with reports from Egypt. Some of these are:

(1) The absence in the local bilharzial patient of the contracted, fibrosed bladder described by Makar (1952) and Sayegh (1956) in Egypt;
(2) The rarity of bladder neck obstruction due to bilharziasis;
(3) The rarity of renal calculosis in the local African and Indian bilharzial group but common in Egypt (Afifi, 1934; Bitschai, 1950);
(4) The rarity of secondary bacterial sepsis in the local bilharzial patients; and
(5) The rariety of pronounced squamous metaplsia in the local non-malignant bilharzial bladders.

The implications of these differences may be significant in explaining the lower local incidence of malignancy in the bilharzial bladder as reported by Wainwright and Roach (1957) and Higginson & Oettle (1960).

If it is true that bilharzial infestation per se is responsible for the irritative stimulus by the presence of ova and/or, miracidial toxins, as postulated by Prates & Gillman (1959), thereby initiating metaplastic changes, then it is difficult to explain the local rarity of squamous metaplasia in the bilharzial bladders. If, however, secondary bacterial spesis, superimposed on a bilharzial bladder, is a prerequisite for the initiation of metaplasia as suggested by the observations of Patch & Rhea (1935), Mostofi (1954) and Sayegh & Dimmette (1956), then the disparity is easily explained on the basis of the rarity of secondary sepsis in the local group. Moreover, as sepsis is more likely to supervene in the presence of

stagnation/...

stagnation, which is rare in the local group, then the lack of sepsis is easily explained, and with it the disparity in the pathology of the local and Egyptian groups.

A logical sequence of events to explain the Egyptian complications could be:- repeated bilharzial infections giving rise to proliferative and regenerative bladder epithelial lesions with subsequent muscle destruction and fibrosis. Repeated episodes of infection and healing would involve the bladder to a greater degree with eventual bladder neck fibrosis resulting in obstruction and stagnation. Stagnation would favour secondary bacterial sepsis resulting in a chronic bacterial, superimposed on a chronic bilharzial, cystitis and favouring metaplastic lesions. Stagnation would facilitate the prolonged action of urine-borne carcinogens on an already damaged mucosa. The combination of all these changes might eventually culminate in malignancy.

This sequence of events is, in the author's opinion, not operative in the local population and is operative only in the exceptions. There is neither the severity of the initial lesions, nor the repetitiveness of infections prevalent to produce a similar pattern to that experienced in Egypt.

Only the exceptions in the local population, (for undoubtedly a small percentage must be exposed to severe bilharzial infections), would follow the course of events suggested as pertaining to Egyptian bilharzial sufferers. This minority group would account for that small proportion of severe complications, with carcinoma of the bladder being the most dreaded, locally encountered.

SUMMARY/...

SUMMARY

The histopathology, sex and age distribution of cancer of the bladder in the local African, Indian and European have been described and the differences discussed. The incidence of the different tumour types differed in the 3 racial groups with squamous cell carcinoma predominating in the African (66.6%). The Indian occupied an intermediate position with transitional-cell carcinoma being the commonest tumour (60%) but this group had a much higher incidence of squamous cell carcinoma (40%) compared with the European.

This local pattern was compared with reports from other bilharzial and non-bilharzial areas and it was found that the African conformed with the pattern reported in other bilharzial areas whereas the local European pattern was not unlike that reported by Payne (1959) from England.

Attention was drawn to the high incidence of bilharzial infection in association with malignancy of the bladder in Africans and Indians (58.75% and 40% respectively) and it was shown that for the African group this amounted to a twofold increase compared to a control group, whilst in the Indian it was only slightly less. Only 2 of a total of 52 European cases of vesical cancer had concomitant bilharzial infection.

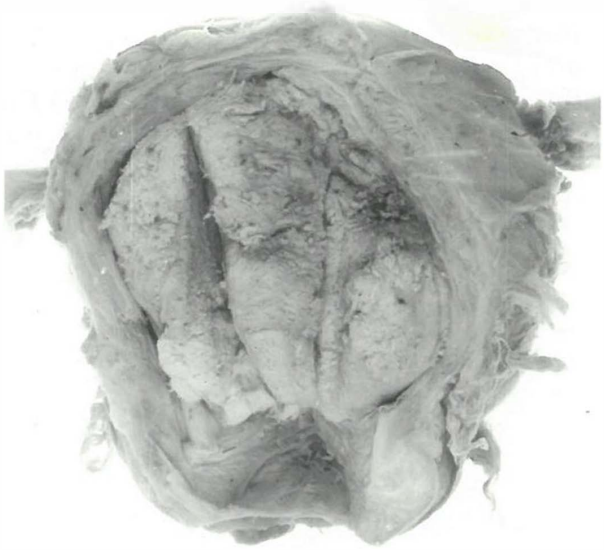
The age distribution of tumours in the various races was compared and showed that vesical cancer manifested itself in a younger age group in the African. The comparative age with the highest incidence of carcinoma being:

4th/...

4th - 6th decades in African group;
6th - 7th decades in Indian group; and
7th - 8th decades in European group.

The African distribution curve corresponded to that reported from other bilharzial areas whilst the European pattern was similar to that reported by Payne (1959). The Indian occupied a midposition.

Finally the relationship of bilharziasis to carcinoma of the bladder was critically examined in the light of reports from other bilharzial areas and the more recent advances in the elucidation of the problems of vesical carcinogenesis. It has been postulated that the lower incidence of carcinoma of the bladder in endemic areas compared to the high incidence reported in hyperendemic bilharzial areas (Egypt and Mozambique) is due to a difference in the pattern of vesical pathology. Whereas in endemic areas like Durban, complications such as bladder-neck obstruction and consequent stasis and sepsis are rare, in hyperendemic areas like Egypt, they are, due to the load and repetition of bilharzial infection, much commoner. Such stasis with the almost inevitable bacterial contamination is likely to promote the release of carcinogens in an already damaged organ. In this pattern of pathology, it is postulated that bilharziasis most probably behaves as a promoting agent in bladder carcinogenesis.



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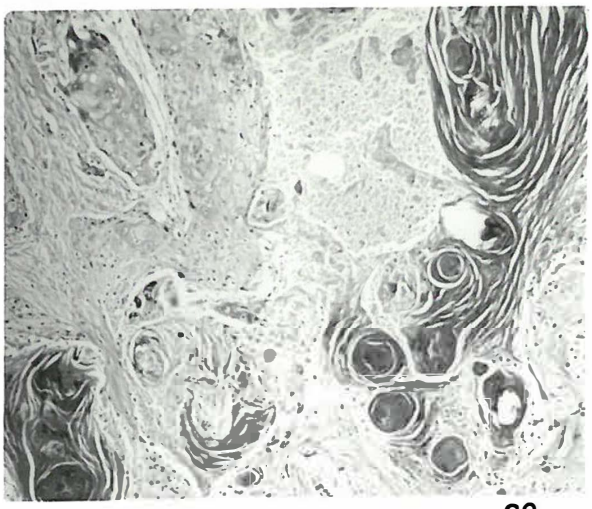

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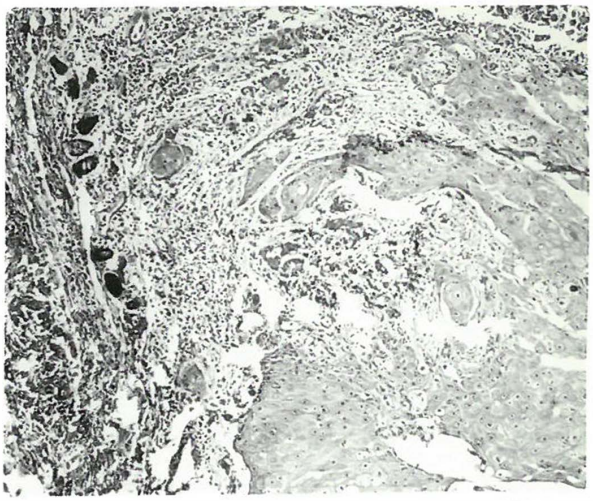

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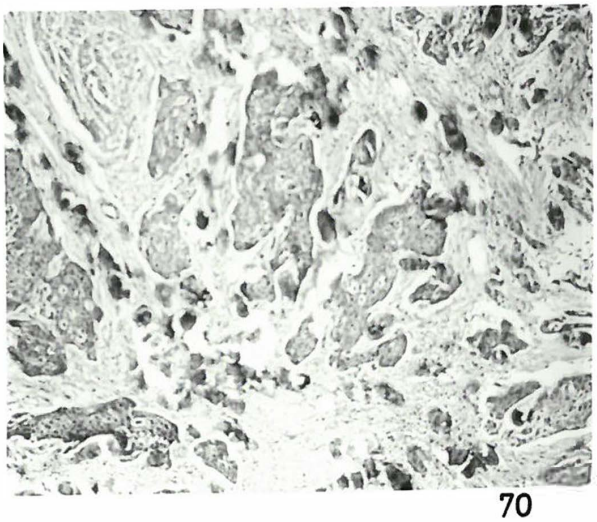

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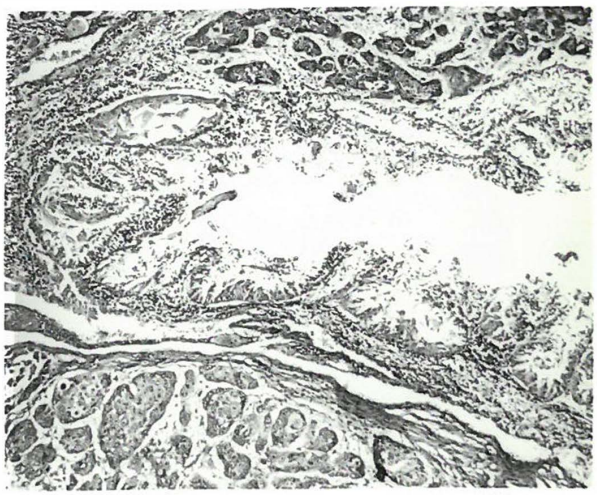

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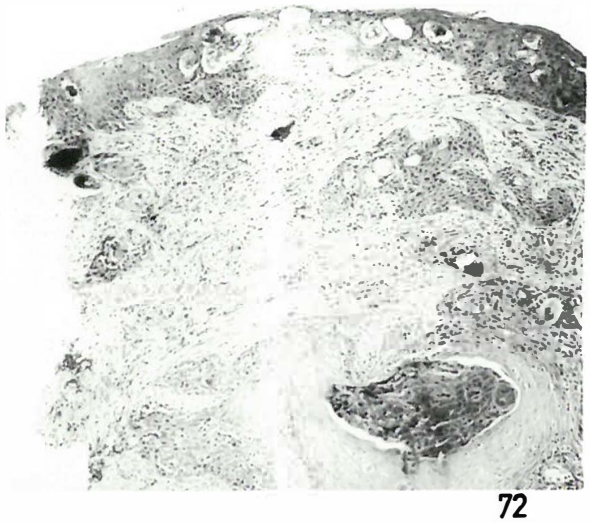

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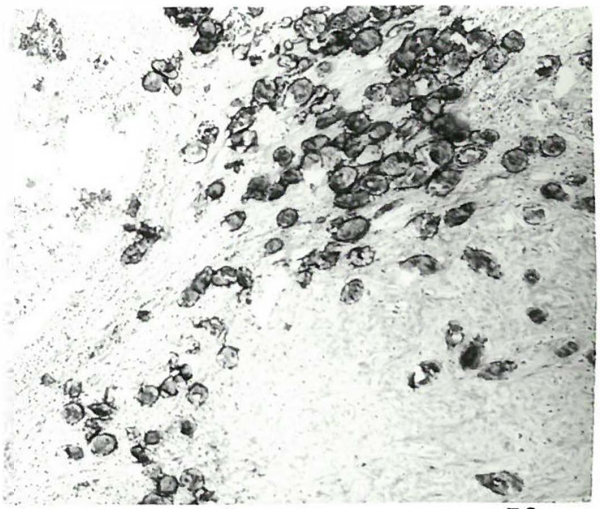

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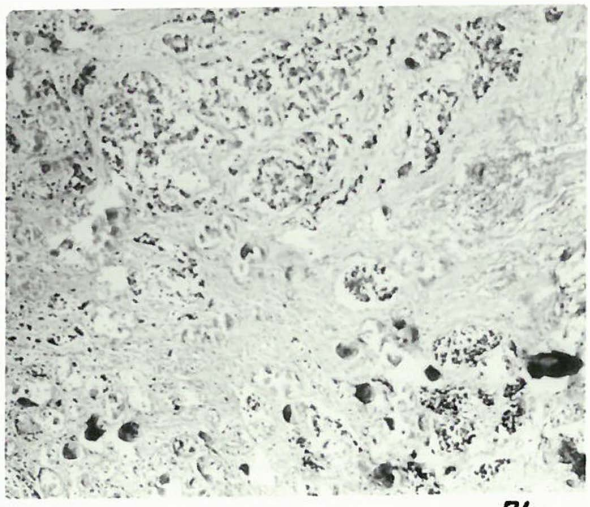

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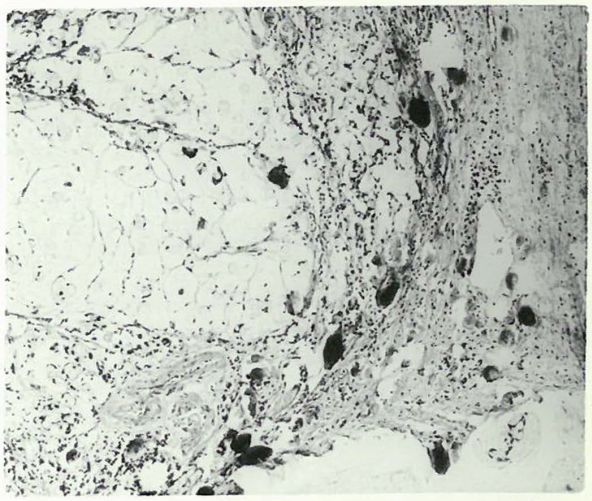

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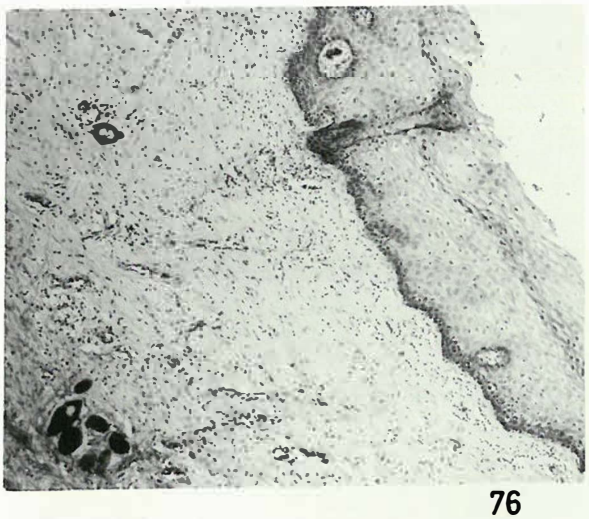

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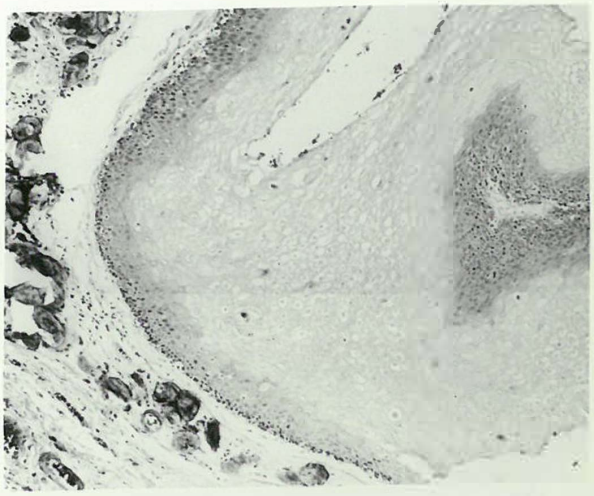

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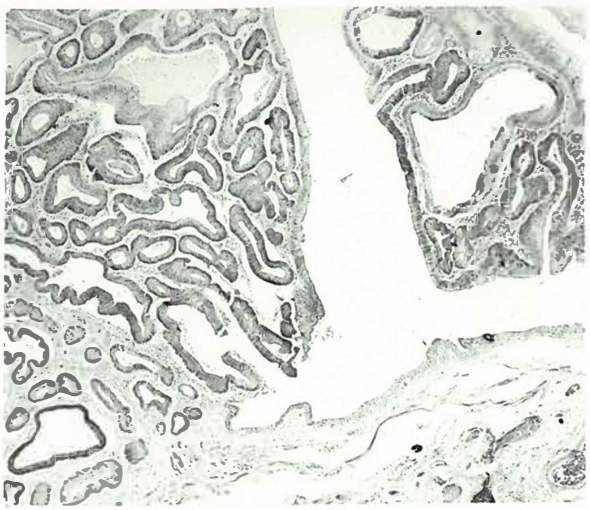

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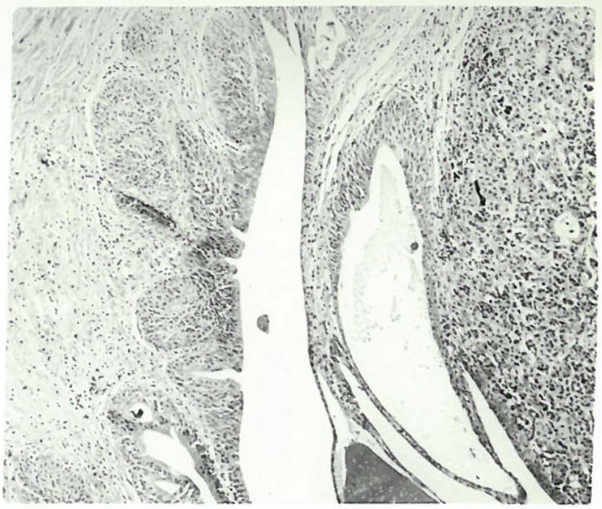

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CHAPTER VI

I N T E S T I N A L S C H I S T O S O M I A S I S

A. CLINICAL PRESENTATION

INTRODUCTION

In an earlier chapter the incidence of S. mansoni in the local Indian and African populations was shown to be of the order of 10%. The lack of symptoms in the large majority of patients makes diagnosis difficult. Fairley (1920) noted that, in spite of a high incidence in the Nile Delta, S. mansoni infections were usually latent and benign, the large majority being symptom free. He considered that this was probably due to the low egg-laying capacity of the worm. Reviewing the pathological changes associated with the infection, Dew (1923) observed that the passage of blood and mucus in the stools was related to the hyperactivity of the mucus glands and the generalised mucosal hyperaemia following on deposition of ova in the sub-mucosa. He was of the opinion, however, that the so-called "bilharzial dysentery" in Egyptians was frequently due to a mixed infection; the bilharzial ulcers, he believed, became "infected with B. dysenteria or with the Entamoeba histolytica".

Girges (1934) recognised two forms of clinical manifestation, hepatic and intestinal. He described four clinical stages of the intestinal type:

1./...

1. The febrile stage - the toxic stage of invasion by the parasite prior to egg deposition and corresponding to the "Katayama Disease" originally described with S. japonicum in Oriental Schistosomiasis (Fairley, 1919b).

2. The dysenteric stage - corresponding with the stage of egg deposition.

3. The papillomatous stage -ccorresponding to the sub-acute stage of granulomatous polypoidal lesions developing in the colon and rectum with dysentery being less frequent.

4. The stage of repair - accompanied by vague abdominal symptoms with dysentery being uncommon.

More recently Ragheb (1958) correlated sigmoidoscopic appearances and symptoms. He noted that in the earlier stages of the disease the prominent symptoms were tenesmus or discomfort at defaecation with fresh blood streaking the surface of the stools. He differed from Girges (1934) in stating that the severe dysentery was related to the presence of polypoidal lesions in the large bowel. However, in the late stage rectal bleeding and other symptoms were minimal.

Koppisch (1943) described the clinical pathology of the disease in Puerto Rico and compared his findings with reports from Egypt. He divided the disease process into the early, intermediate and late stages, and noted that while, in the early phase of invasiveness, symptoms were singularly lacking, the stage of egg deposition was accompanied by febrile attacks, "abdominal discomfort, with or without pain, which may be colicky, by nausea, vomiting, abdominal distension, dysenteriform manifestations, urticaria and cough - ". A constant, severe

eosinophilia/...

eosinophilia and bronchopneumonia-like lung changes were also described. Except for dysentery, the symptom-complex described by Koppisch (1943) as belonging to the stage of egg deposition is remarkably similar to the "Katayama Syndrome" - or the toxic phase prior to egg deposition (Girges, 1934; Belding, 1952; Walt, 1954 and Faust & Russell, 1964). It is only towards the end of this toxic phase that egg-deposition begins, followed by dysenteric symptoms. It is possible that Koppisch (1943) was in fact describing the "Katayama syndrome" with patients passing insiduously into the second, or, dysenteric stage. Koppisch (1943) reported that in the intermediate stage patients might be asymptomatic, especially if the infection was light whilst other patients might complain of diarrhoea with blood and mucus and tenesmus. In the later stage of visceral damage, there were vague abdominal symptoms including bouts of diarrhoea.

Gelfand (1950) reported that the majority of cases of S. mansoni infections in Central Africa were asymptomatic (73% in his series). The remainder had symptoms of diarrhoea, with or without blood and mucus, pain on defaecation, or only mucus and blood in their stools. He stressed the benign nature of the lesions by comparison with those reported from Egypt and South America.

The World Health Organisation Expert Committee on Bilharziasis (Anon, 1953) stated that whilst the stool may be normal in light infections, in acute (presumably severe) infections it is "frequently dysenteric in character either with an excess of blood and mucus and essentially no intact faeces, or with flecks of blood and mucus on the outside of elements of formed faeces". A similar observation was made at the African Conference of the World Health Organisation Expert Committee (Anon, 1957).

Manson-Bahr (1958) reported that symptomatology in East Africa was variable. Intestinal infection was usually symptom-free due to the high immunity of the indigenous populations and a low infectivity rate. However, the "Katayama Syndrome" was not unusual in the non-immune immigrant Asian and European. Moreover, although Wydell (1958) demonstrated severe intestinal pathology in the later stages in an isolated African population group on Ukerewe Island in Lake Victoria, and although the incidence of S. mansoni infection was high, he noted that intestinal symptoms were rare.

Similarly Jaffe (1948) from Venezuela and Pontes (1961) from Brazil reported on the relatively asymptomatic nature of S. mansoni infections.

Belding (1952) and Faust & Russell (1964) described three stages of the disease:

1. Incubation period; corresponding to the stage of invasion.
2. Period of egg deposition; with an onset approximately 5-7 weeks after exposure and presenting with typical bilharzial dysentery.
3. The stage of tissue proliferation and repair, corresponding to the late stage with onset of complications.

CLINICAL PRESENTATION OF INTESTINAL BILHARZIASIS IN SOUTH AFRICA

Little work has been done on the clinical aspects of this disease in South Africa.

Turner (1908) reported that symptoms due to intestinal bilharzia were variable and were easily mistaken for chronic

diarrhoea/...

diarrhoea or dysentery. Holland (1934) considered bilharzial dysentery to be a rare illness. King (1955) reported on the similarities in clinical presentation of amoebiasis and bilharzial dysentery. Cosnett (1957) noted that the role of S. mansoni in intestinal disorders was difficult to evaluate. Earlier Walt (1954) described the "Katayama syndrome" in European children infected with S. mansoni and with S. haematobium.

Schneider (1958) reported that, in his series of African patients with S. mansoni infection in the North and Eastern Transvaal, 42% were symptom-free whilst the reaminder had a variety of symptoms including diarrhoea with or without blood and mucus, pain on defaecation and vague abdominal pain.

From this brief review, it is apparent that the symptomatology varies, not only from endemic area to endemic area, but from author to author in the same area. Though the most severe manifestations were reported from Egypt, it was in that country that Fairley (1920) made the original observation that the disease is insiduous.

The variability of the symptoms and severity of subsequent lesions may be dependent on the host-parasite relationship. Manson-Bahr (1958) postulated three types of endemicity for Bilharziasis:

(a) Hyperendemic - wherein the infection rate is close to 100% and the immunity of the people high. He noted that the immunity may be overcome by superinfection when severe disease may result.

(b) Endemic - where the infection is less than 100% but the immunity is high and is not overcome by infection.

(c)/...

(c) Epidemic - where the infection rates are variable with low immunity. Consequently light infections may produce symptoms and severe disease.

PRESENT STUDY

The aim of the present study was to assess the clinical presentation and significance of intestinal bilharziasis in the Durban Indian and African populations.

Three aspects of the disease were investigated as follows:

(1) To determine the relationship between symptoms of intestinal disease and probable S. mansoni infection. In this study (CLINICAL GROUP I) 225 patients, with vesical bilharziasis (S. haematobium), were questioned specifically about symptoms of intestinal disease BEFORE A DIAGNOSIS OF RECTAL BILHARZIASIS HAD BEEN ESTABLISHED. A corollary of this study was to determine whether symptoms suggested intestinal bilharziasis.

(2) To determine the significance of S. HAEMATOBIUM in intestinal disease. Gelfand (1950) and Pitchford (1958a) amongst others, have shown the frequency with which S. haematobium ova are detected by rectal biopsy in urinary bilharziasis but little work has been done to demonstrate actual intestinal disease produced by this parasite.

For this study (CLINICAL GROUP II) a further 40 patients with proven active S. haematobium infections were selected and investigated specifically from the aspect of intestinal disease.

(3)/...

(3) To assess the ROLE OF S. MANSONI itself in producing intestinal disorders amongst Durban African and Indian populations. For this study (CLINICAL GROUP III), 40 cases with proven (by rectal biopsy and/or stool examination) S. mansoni infections were selected.

1. SYMPTOMS OF INTESTINAL DISEASE WITH PROBABLE S. MANSONI INFECTION - CLINICAL GROUP I

Materials & Methods.

Of the 225 patients included in this study, 150 were Africans and 75 Indians. All presented with typical symptoms of vesical bilharziasis and this was confirmed by urine examination. A detailed history was obtained. Specific questions asked were:

1. Present or past history of diarrhoea, with or without blood and mucus.
2. Present or past history of blood and/or mucus in stools.
3. Any upset in bowel habits.
4. Abdominal pain and nature of pain.
5. Pain on defaecation.

A complete physical examination was conducted and a rectal biopsy was done on every patient.

Results.

The results are tabulated in Table I.

TABLE I/...

TABLE I

RECTAL BIOPSY RESULTS AND SYMPTOMATIC INTESTINAL BILHARZIASIS

	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
No. examined:	150	-	75	-	225	-
Rectal biopsy (S. haematobium	117	78	48	64	195	67
Rectal biopsy (S. mansoni	25	17	20	23	45	20
Symptomatic S. mansoni	3/25	12	1/20	5	4/45	9

The results reveal that 45 (20%) patients with S. haematobium had concomitant S. mansoni infection but that only 4/45 (9%) with S. mansoni infection had related symptoms. None of the patients had clinical findings related to intestinal bilharziasis.

No less than 67% had rectal involvement by S. haematobium but this was always asymptomatic.

These results demonstrate the asymptomatic nature of both S. mansoni and S. haematobium infections of the bowel.

2./...

2. ROLE OF S. HAEMATOBIUM IN INTESTINAL DISEASE - CLINICAL GROUP II

Materials & Methods.

40 patients (27 African and 17 Indian) in the age group 6-22 years, with proven active urinary bilharziasis (viable S. haematobium ova in urine) were investigated in a similar manner to that of Clinical Group I. In addition, the proctoscopic appearances of the rectum were recorded and rectal biopsy done in all cases.

Symptoms

The main presenting symptom in all 40 patients was related to urinary bilharziasis (terminal haematuria and related symptoms).

When questioned specifically about gastro-intestinal symptoms, 8 patients (20%) admitted to having had bouts of diarrhoea with some blood in stools less than 4 months prior to the present complaint of haematuria. The diarrhoea was never severe amounting to no more than 2-4 semi-formed stools per day with flecks of blood on the surface. Abdominal pain, confined to the hypogastrium was a prominent complaint in 2 (5%) other patients. Thus, in all, 25% had some gastro-intestinal symptoms.

Clinical examination failed to reveal any significant findings. None of the patients had visceromegaly.

Proctoscopic/...

Proctoscopic examination

Mucosal punctate haemorrhages with focal areas of hyperaemia were present in 34 (68%). No other significant features were observed.

Stool and Biopsy Results

The stool and biopsy results are summarised in Table II.

Note : All 40 patients had viable ova of S. haematobium in the urine.

The results indicate that 9/40 (27.5%) had concurrent S. mansoni infection whereas no less than 24/40 (60%) had proctoscopic evidence of rectal involvement. All these 24 patients had S. haematobium on rectal biopsy and of these 9/24 had viable ova on biopsy. In 4/9 of these viable ova of S. haematobium were also recovered from stools. Of the 9 cases 3 with viable ova of S. haematobium had concomitant S. mansoni infection. An interesting observation was that in only 2 of the 9 cases of S. mansoni were ova of S. mansoni recovered from the stools.

In the group with no proctoscopic evidence of rectal involvement none had viable ova, whilst 10 had calcified ova of S. haematobium in the rectal mucosa. S. mansoni was not found.

It is obvious then that punctate haemorrhages in the rectal mucosa are not related exclusively to S. mansoni but may be due to active S. haematobium infection (as shown by the presence of viable ova not only in the rectal mucosa, but also in

stools/...

TABLE II

STOOL & RECTAL BIOPSY RESULTS IN
40 PATIENTS WITH KNOWN
S. HAEMATOBIUM INFECTIONS

With Rectal Involvement on Proctoscopy TOTAL 24					With No Rectal Involvement on Proctoscopy TOTAL 16			
S.H.		S.M.			S.H.		S.M.	
RECTAL		STOOL	RECTAL	STOOL	RECTAL		STOOL	RECTAL	STOOL
V	NV	V	V	V	V	NV	V	V	V
9*	15	4	9	2	0	10	0	0	0

V = viable
NV = non-viable (mainly calcified)

S.H. = S. haematobium
S.M. = S. mansoni

* 6 pure S. haematobium and 3 with S. mansoni.

stools). Moreover, 3 of the patients with pure S. haematobium infection in the bowel (all had viable ova on rectal snip) had noticed blood-flecked stools, suggesting that mild intestinal symptoms may be related to pure S. haematobium rectal involvement. It is also apparent that S. haematobium infections not uncommonly involve the rectum.

Using/...

Using symptomatology as a basis, all the infections in this group may be classified as being mild.

3. INTESTINAL DISEASE AND S. MANSONI - CLINICAL GROUP III

Materials & Methods.

40 patients were selected with known S. mansoni infection (proven by rectal biopsy). The same procedure was adopted as in the Clinical Group II. In addition liver biopsy was performed on 20 of these patients.

The results of the liver biopsies will be presented in the next chapter.

All the patients were males and the race and age groups are summarised in Table III. Only 2 patients were over 25 years of age.

TABLE III

AGE & RACE DISTRIBUTION OF CLINICAL CASES OF S. MANSONI INFECTIONS

RACE	NO.	AGE RANGE	AVERAGE AGE
AFRICAN	25	8 - 49 yrs.	15.8 yrs.
INDIAN	15	11 - 25 yrs.	16.6 yrs.
TOTAL	40	8 - 49 yrs.	16.1 yrs.

Results/...

Results.

The stool, urine and rectal biopsy examination results are summarised in Table IV.

TABLE IV

STOOL, URINE & RECTAL BIOPSY RESULTS OF 40 CASES WITH S. MANSONI INFECTIONS

RACE	STOOL	RECTAL SNIP		URINE
	SM+	SM+	SH+	SH+
AFRICAN	12/20	25	17	21
INDIAN	7/10	15	11	14
TOTAL	19/30	40	28	35

The results reveal that 35/40 had concomitant S. haematobium infections and that S. mansoni was recovered from the stool of no less than 19/30 by the Zinc Sulphate Floccula-tion method. Pure S. mansoni infections were present in 4 African and 1 Indian.

Symptomatology

The symptoms of the 40 patients are summarised in Table V.

TABLE V/...

TABLE V

SYMPTOMS OF 40 PATIENTS WITH S. MANSONI INFECTIONS

MAIN COMPLAINT	AFRICAN		INDIAN		TOTAL	
	NO.	%	NO.	%	NO.	%
Diarrhoea with blood and mucus	6	24	1	7	7	17.5
Diarrhoea only	1	4	0	0	1	2.5
Diarrhoea and haematuria	1	4	0	0	1	2.5
Haematuria and blood-flecked stools	1	4	2	13	3	7.5
Abdominal pain	2	8	1	7	3	7.5
Haematuria and other symptoms of S. haematobium infection	14	56	11	73	25	62.5
TOTAL	25	-	15	-	40	-

Diarrhoea with blood and mucus was the commonest symptom related to intestinal bilharziasis. All the patients had more than one symptom, the commonest accompanying symptom being vague hypogastric pain (in 10 cases), whilst in 2 this was the major presenting symptom. None of the patients complained of pain on defaecation. Definite symptoms related to the intestinal infection were present in 15 (11 African and 4 Indian). The dysenteric group had fairly severe diarrhoea with frequent loose stools (all more than 6 stools per day) associated with some degree of tenesmus.

Of/...

Of the cases with S. mansoni infection, 25 were asymptomatic. These patients complained primarily of symptoms related to vesical schistosomiasis.

Duration of Symptoms

In the 15 patients with symptoms directly related to the S. mansoni infection, the history varied from 3 days to 4 months: 10 had symptoms of under one week; 4 of under 1 month; 3 of under 2 months and 2 of under 4 months. The 2 cases with histories of 4 months duration both complained of intermittent diarrhoea.

Clinical Findings & Case Reports

All 40 patients looked well and were apyrexial on the first examination. 14 had liver enlargement (Table VI) but only 4 had associated splenic enlargement. In no case was the spleen grossly enlarged.

In all except one case with hepatomegaly, the liver was firm and non-tender. In 1 patient (CASE I - vide infra) there was a three-finger, tender hepatomegaly and a tentative diagnosis of amoebic liver abscess was made

The following case reports illustrate the clinical presentation of the disease:

Case I : L.N. : African male, 14 years old; when first seen in the out-patient clinic complained of a dull

aching/...

TABLE VI

HEPATOMEGALY ASSOCIATED WITH
S. MANSONI INFECTIONS

SIZE*	AFRICAN	INDIAN	TOTAL	%
0	14	12	26	65
1	3	3	6	15
2	4	0	4	10
3	4	0	4	10

* Finger breadth below costal margin.

aching pain in the right hypochrondrium and generalised weakness with joint pains. He admitted to having had diarrhoea with mucus but no blood, 3 months previously and to having had haematuria a year previously. He had no treatment for either complaint.

The pertinent findings on examination were: a soft but moderately distended abdomen with a tender hepatomegaly (3 finger) and a palpable spleen. A diagnosis of hepatic amoebiasis was entertained.

Proctoscopic examination before any therapy revealed an oedematous mucosa with punctate haemorrhages but no amoebic ulceration. Biopsy from a bleeding spot revealed viable ova of S. mansoni and non-viable ova of S. haematobium. Urine

examination/...

examination showed viable ova of S. haematobium. He had a haemoglobin of 13.8G%; a white cell count of 17,000 and an absolute eosinophilia amounting to 50% of the white cell series.

There was no improvement after a course of anti-amoebic therapy. Liver biopsy was performed, revealing hepatic bilharziasis. The patient improved considerably on anti-bilharzial therapy, the liver size regressing to 2-fingers and the spleen no longer being palpable.

A more detailed comment on the liver biopsy, haematological pattern and liver function tests will be given in the chapter on Hepatic Bilharziasis.

Case II : B.S. : African male, 12 years old; initially complained of diarrhoea with blood and mucus and abdominal pain of a week's duration. As stool examination on three occasions failed to reveal amoebae, he had been treated for bacillary dysentery for a month without success when the author saw him. The patient still complained of diarrhoea with blood and mucus and some tenesmus. The stool examination on this occasion showed viable ova of S. mansoni and proctoscopy revealed an oedematous mucosa with clusters of punctate haemorrhages. Rectal snip revealed large numbers of viable S. mansoni eggs (Fig. 3). Physical examination revealed a firm hepatomegaly (2-fingers) and a palpable spleen.

The liver biopsy findings will be presented in a later chapter on Hepatic Bilharziasis.

Case III : J.M. : African male, 16 years old; presented with terminal haematuria, frequency of micturition

and/...

vague epigastric pain but no history of diarrhoea or of blood and/or mucus in the stools could be obtained. Examination revealed a tender hepatomegaly (2-finger). On proctoscopy the mucosa showed punctate haemorrhages and a patchy granular appearance not unlike the sandy-patches in a chronic bilharzial bladder. By rectal snip viable ova of S. haematobium and S. mansoni and large numbers of calcified S. haematobium ova were demonstrated (Fig. 6). Viable ova of S. haematobium were found in the urine.

This case also formed one of the liver biopsy series.

Case IV : M.S. : Indian male, 20 years old; complained of intermittent attacks of terminal haematuria over the past three years and had noticed blood-flecked stools for 1 week. There was no history of diarrhoea, past or present.

Systemic examination was negative, but proctoscopic examination revealed punctate mucosal haemorrhages. Rectal biopsy revealed viable ova of S. mansoni and calcified ova of S. haematobium.

Liver biopsy results will be presented in a later chapter on Hepatic Bilharziasis.

The wide variability in symptomatology of intestinal bilharziasis is illustrated by these four cases.

B./...

B. PATHOLOGY OF INTESTINAL BILHARZIASIS

INTRODUCTION

From post-mortem observations, Dew (1923) described a segmental colitis with the mucosa being acutely inflammed and developing small, shallow ulcers. He believed that the number of eggs in the submucosa determined the type of polypoid lesions - moderate egg deposition giving rise to sessile pseudo-polyps and severe deposition leading to pedunculated polyps. He also described "pericolic" inflammatory masses involving focal areas of the colon and noted that the small intestine was rarely involved in intestinal bilharziasis.

Dimmette & Sproat (1958) reported on the high incidence of bilharzial polyps in Egyptian patients and noted that while these were commoner with S. mansoni, similar lesions were found with S. haematobium infections. In their series, multiple polyps were found in 91% and though these arose in any segment of the large bowel, they were commonest (61%) in the rectum.

Ragheb (1958) also from Egypt, described the progressive sigmoidoscopic pattern of intestinal involvement and divided the disease into four stages:

I : "Sandy patches" with pin-point bleeding spots being the earliest stage and present in 19.6% of his cases.

II : A granular fragile mucosa which bled easily and which he considered a sequel to stage I. Of his cases, 54.8% belonged to this group.

III/...

III : The stage of papilloma formation (22.8% of his cases). He noted that papillomata were usually multiple and involved the rectum commonly.

IV : The late stage (2.8%) with oedema of the bowel and a pale, boggy mucous membrane.

Koppisch (1943) from Puerto Rico, Jaffe (1948) from Venezuela, Warner (1956) from United States of America (describing Puerto Rican patients resident in U.S.A.) and Potes (1961) from Brazil, all described a similar pattern of intestinal pathology, the commonest lesion being hyperaemia of the bowel mucosa, punctate haemorrhages, granular mucosa and shallow, small ulcers. All reported that bilharzial papillomata were uncommon. Koppisch (1943) noted that in late stages, fistulae may develop from segments of infected colon and rectum.

Jackson (1956) described a similar pattern of pathology in Saudi Arabians, but noted that papillomata occurred in some of these cases.

Unlike Egypt and other African countries where double infections are common, the intestinal pathology in South American and Caribbean countries is related exclusively to S. mansoni infection.

Wydell (1958) reported an interesting syndrome apparently peculiar to Ukerewe Island, which has hyperendemic foci of S. mansoni. While bilharzial dysentery, papillomata and colonic abscesses were rare, there was a high incidence of hepatosplenomegaly and of bilharzial granulomata of the ileum, presenting as abdominal tumours with clinical signs of intestinal obstruction.

Gelfand/...

Gelfand (1950) from Southern Rhodesia reported minimal changes in both clinical and autopsy cases. He found no examples of papilloma or fistula-formation and noted that whilst punctate haemorrhages were not uncommonly present on sigmoidoscopy, in the large majority of patients the bowel was normal.

PRESENT STUDY

The clinical observations were correlated with the morbid anatomical and histopathological studies conducted on autopsy material.

1. CLINICAL STUDY

Results

The findings at proctoscopy of the 40 cases with S. mansoni infection (Clinical Group III) are summarised in Table VII.

All 40 cases in Group III of the clinical study had punctate haemorrhages and generally congested mucosa whilst 2 patients had patchy sandpaper areas. In addition to S. mansoni 7 cases also revealed viable ova of S. haematobium on biopsy.

Sigmoidoscopy was done on 4 cases with pure S. mansoni infection and on one with a mixed infection. In the former the

sigmoid/...

TABLE VII

PROCTOSCOPIC FINDINGS IN 40 PATIENTS WITH S. MANSONI INFECTIONS

FINDINGS	AFRICAN	INDIAN	TOTAL	%
Punctate Haemorrhages	25	15	40	100
Sandy-patch - Granular mucosa	1	1	2	5
Papillomata	1*	-	1	2.5

* on Sigmoidoscopy.

sigmoid mucosa appeared congested with punctate haemorrhages appearing in clusters, the picture being no different from that seen on proctoscopic examination.

In the fifth case, sigmoidoscopy was done because of rather persistent rectal bleeding. In this case a solitary polyp on a narrow pedicle was situated about 10 cms. up the rectum. The remainder of the mucosa was congested with crops of punctate haemrrohages. The polyp was fulgurated and was found to be approximately 1 cm. in diameter. Histology revealed a hyperplastic adenomatous pattern with large numbers of bilharzial ova in various stages of degeneration and a moderate inflammatory cellular infiltrate made up of eosinophils, lymphocytes and plasma cells (Figs. 90 & 91). It was not possible to identify the species of ova.

2./...

2. AUTOPSY STUDY

Results.

It has been reported (Chapter III) that, of the 900 autopsy cases studied, 277 (31%) were shown to have bilharziasis by digestion technique. Snips taken at autopsy revealed rectal involvement in 165 (18.3%). Of these 107 (12%) had pure *S. haematobium* infections, 37 (4%) had pure *S. mansoni* infections and 21 (2.3%) mixed infections.

MORBID PATHOLOGY

Of the 165 cases with rectal involvement (including 58 (6.4%) with *S. mansoni* infections) gross intestinal lesions were present in only 3 cases.

One of the patients had a pure *S. haematobium* infection but died from acute peritonitis following perforation of a typhoid ulcer. This patient had "sandy patch" lesions in the rectum. In addition to typical vesical bilharziasis there was bilateral hydroureter and hydronephrosis. The second case had a mixed bilharzial infection and died of acute bilharzial dysentery. The third case also had a mixed infection but died of Cor Pulmonale due to pulmonary bilharziasis complicated by bilharzial hepatic fibrosis.

A few months prior to this survey the author conducted an autopsy on a case who died from acute bilharzial dysentery.

Brief/...

Brief case reports and relevant autopsy findings of the two cases who died from acute bilharzial dysentery are presented to demonstrate the morbid anatomical intestinal pathology.

Case V : M.N. : African male, aged 9 years; presented with a history of intermittent bouts of diarrhoea with blood and mucus over five months. On admission the patient was shocked and a diagnosis of fulminating amoebic dysentery was made. He died shortly after admission.

Post-mortem examination was conducted two days after death and except for the pallor of all the organs, the significant findings were limited to the gastro-intestinal tract.

The lumen of the small and large bowel contained moderate quantities of altered blood and mucus. The mucosa of the terminal ileum and of the colon was intensely congested with myriads of punctate haemorrhagic or pin-point-like ulcers. These alternated with normal mucosa. Neither papillomata nor large ulcers were present.

The liver and spleen were only slightly enlarged and no macroscopic changes were noted.

Case VI : C.M. : African male, aged 8 years; presented with a history of diarrhoea with blood and mucus of two months duration. Three weeks prior to the onset of dysentery, the patient had generalised body aches and "swelling of the whole body". There was no history of haematuria.

The patient was admitted in a state of collapse. A 2-finger breadth hepatomegaly was present. In spite of resuscitative measures, the patient died shortly after admission.

Post-mortem/...

Post-mortem examination revealed a picture in the terminal ileum and colon similar to that described in Case I. The liver and spleen were moderately enlarged. The urinary bladder showed typical acute bilharzial lesions.

The records of the Department of Pathology were consulted and an additional two cases of death from acute bilharzial dysentery, were discovered. One was an African male aged 7 years and the other his sister, aged 5 years. In both these cases terminal ileum and colon were described as being congested with large numbers of pin-point mucosal haemorrhages. Histological material from these two cases was available and is considered together with that of the two cases from the present series.

HISTOPATHOLOGY OF THE BOWEL IN FATAL CASES

Sections from the terminal ileum and colon in all 4 cases revealed large numbers of bilharzial ova, some apprently viable, large numbers calcified and still others as "ghose forms".

Those ova in the mucosa excited no proliferative tissue response (Figs. 80 - 85) although the mucosa had a "feathery" appearance (Figs. 84 & 88). The apparently viable ova were present in clusters in and around mucosal glands with surrounding areas of moderate eosinophil infiltration (Figs. 81 - 83). Only the superficial mucosal glands had been shed in these areas and the surface had an exudate of red blood cells, mucoidal material and some eosinophils. No true ulceration was evident. The

appearance/...

appearance suggested that the ova deposited in the mucosal vessels escaped into the lumen by evoking local necrosis of the mucosa (Figs. 82 & 83) probably by the secretion of toxic metabolites. These focal, microscopic areas are the focal "pin-point" ulcers or punctate haemorrhages seen proctoscopically.

Those ova trapped in the submucosa and muscular layers, however, evoked a typical pseudo-tuberculoid reaction with the ovum, or remnants of the ovum, in the centre attacked by foreign-body giant cells and surrounded by epitheloid cells, eosinophils, fibroblastic reaction and a rim of plasma cells and lymphocytes (Figs. 86 & 87). There were large numbers of these pseudo-tubercles in the submucosa and lesser numbers in the muscle layers.

Histological examination of sections of the bowel in the one case with sandy patches (S. haematobium infection) revealed an atrophic mucosa with large numbers of degenerate ova in the mucosa. The striking feature, however, was a dense plaque of calcified ova in the submucosa without any inflammatory response (Fig. 89). The appearance was identical to that described in late, healed bilharziasis of the bladder. Moreover, in the clinical cases with "sandy patch" lesions of the rectum, rectal snip revealed, in addition to viable ova, a preponderance of calcified ova. It seems reasonable to conclude then that the "sandy patch" lesions in the rectum, as in the bladder, are the late stage of bilharziasis with myriads of calcified ova layered predominantly in the submucosa with minimal tissue response. The atrophy of the overlying mucosa contributes to the typical naked-eye appearance.

HISTOPATHOLOGY/...

HISTOPATHOLOGY OF THE RECTUM IN AUTOPSY SERIES

Of the 165 cases of rectal bilharziasis in the autopsy series demonstrated by the snip method, histology was positive in 98 (60%) cases.

The histopathological features are summarised in Table VIII.

TABLE VIII

HISTOPATHOLOGICAL FEATURES OF RECTAL BILHARZIASIS

HISTOLOGICAL FEATURES	NO.	%
Ova only (mucosa and submucosa)	69	70
Pseudo-tuberculoid reaction (submucosa)	27	28
Acute bilharzial colitis	2	2
Total positive	98	-

Of the 98 positive cases, histological examination revealed only ova or their remnants in 70%. These were present in the mucosa and submucosa and were accompanied by little or no inflammatory or fibroblastic response.

In 28% the typical pseudo-tuberculoid type of granulomatous reaction was excited by the ova. All these pseudo-tubercles were confined to the submucosa. In no case was there severe lesions, the large majority showing only a few pseudo-tubercles.

In/...

In many cases of pure S. haematobium infections, the submucosa harboured, not infrequently, a large number of calcified ova. The striking feature was, however, the almost total absence of any tissue response.

It would seem that the two species of schistosomes evoke different tissue responses in the rectum. This is probably related to the viability of the eggs. In the clinical cases where biopsies were fresh, eggs of S. mansoni were usually viable while those of S. haematobium were more often calcified or degenerate.

One may postulate that the proliferative lesions of bilharziasis are provoked by the release of toxic metabolites from viable or recently dead eggs. On the other hand, if the eggs are already non-viable when deposited tissue response will be minimal. Prates & Gillman (1959) suggested that bilharzial toxins were responsible for the pronounced tissue response and more recently Cameron & Gangulay (1964) demonstrated that by comparison with the intact ova of S. mansoni, clean egg shells evoked little or no tissue response.

The rectal mucosa may be considered an ectopic site for S. haematobium and may explain the greater numbers of immature, deformed and dead eggs lacking the potential to stimulate proliferative lesions such as are evoked by the mature viable eggs of S. mansoni.

DISCUSSION/...

DISCUSSION

It is apparent from both the clinical and autopsy observations that intestinal pathology produced by bilharziasis in the Durban population is minimal by comparison with reports from other endemic areas. Two fatal cases were encountered in the present study and search of the records revealed a further two cases who died as a result of acute intestinal bilharziasis.

Contrary to the belief of Dew (1923) and Dimmette and Sproat (1955) that acute bilharzial dysentery might be a result of secondary bacterial or amoebic invasion, these four cases proved to be pure S. mansoni infection confirmed by histopathological studies. Acute bilharzial dysentery is undoubtedly a clinico-pathological entity and almost certainly related to overwhelming infection as revealed by the widespread involvement of the bowel, liver, and to some extent, of the lungs, and mesenteric lymph nodes.

Clinical study of 40 patients with known S. mansoni infection demonstrated that 37.5% had symptoms directly related to the infection. Liver biopsy results (to be presented later) also revealed that the apparent benignity of the intestinal lesions (shown by proctoscopic examination) does not exclude visceral involvement.

Nevertheless, judging by the clinical and autopsy studies, intestinal bilharziasis is, in the majority of Durban patients, a mild, relatively asymptomatic disease, a conclusion supported by the minimal rectal involvement observed both clinically and histopathologically. The punctate haemorrhages

revealed/...

revealed by proctoscopy are not true ulcers but focal areas of superficial mucosal necrosis.

Following the classification of Ragheb (1958) all the clinical cases in this study would fall into Stage I - the earliest manifestations of the disease.

Bilharzial polyps in the large bowel were not encountered in the autopsy series, though, prior to this study, one case had been found with an associated "pipe-stem" cirrhosis of the liver (Bhagwandeen, 1964). A solitary bilharzial rectal polyp was discovered in one of the clinical cases.

The pathological findings in Durban contrast with those reported by authors from Egypt, East Africa, South America and Caribbean countries, where intestinal pathology associated with S. mansoni is more severe. Reports suggest that the disease is most virulent in Egypt and less so in the other endemic areas. The picture in Durban is similar to that described by Gelfand (1950) in Rhodesia.

SUMMARY

The symptomatology, clinical and pathological findings of Intestinal Bilharziasis in the Durban Indian and African populations are presented and compared with those reported by authors from other endemic areas of S. mansoni.

Four groups of cases were studied:

(1) Cases of S. mansoni infection encountered in the rectal

biopsy/...

biopsy of 225 cases of known S. haematobium infections. Of the 45 cases, only 4 (8.8%) had symptoms related to the intestinal infection.

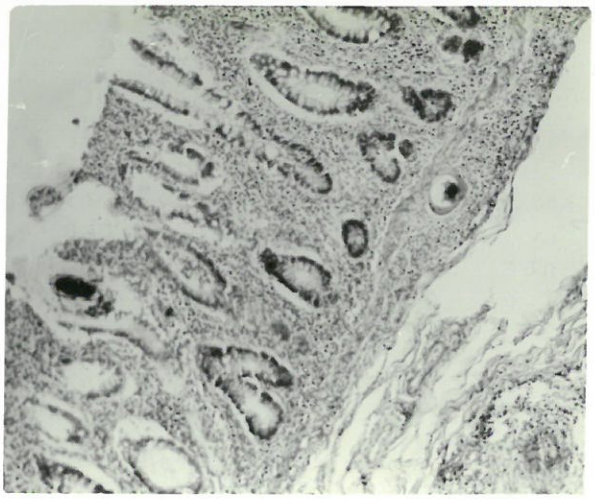
(2) The role of S. haematobium in producing intestinal disease was studied in 40 cases with proven S. haematobium infection. Of the 24 cases with proctoscopic evidence of rectal involvement, 15/24 (62.5%) had pure S. haematobium infection and in 9/24 (37.5%) viable eggs were shown in rectal biopsies. Intestinal involvement by this parasite is usually asymptomatic.

(3) The symptomatology, clinical manifestations and rectal and sigmoidoscopic features of S. mansoni infection in 40 cases are also presented and discussed. 5 had pure S. mansoni infection. Symptoms directly related to S. mansoni infection were present in 15/40 (37.5%). The commonest presenting symptom was diarrhoea with blood and mucus with associated abdominal pain.

(4) Of 164 autopsy cases shown by snip to have rectal involvement, histopathology revealed the condition in 30%.

In addition, 4 fatal cases of acute bilharzial dysentery are reported and the morbid anatomical and histopathological findings discussed.

The histopathology of intestinal bilharziasis is described and the genesis of punctate haemorrhages is contrasted with that of the sandy-patch lesion.



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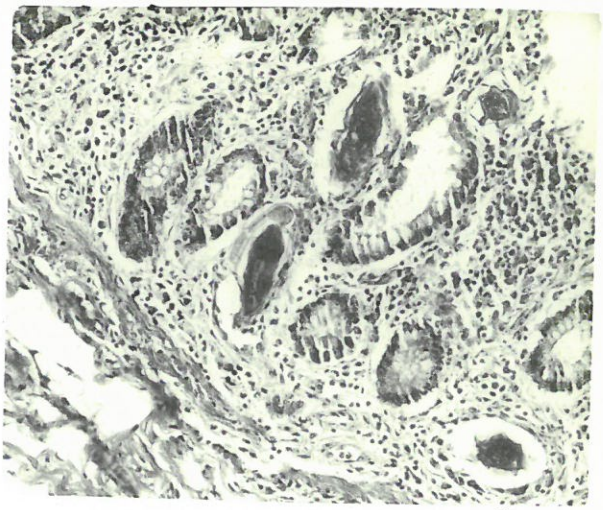

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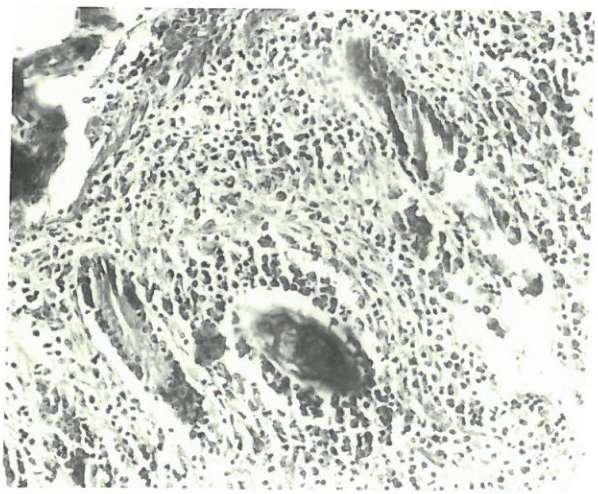

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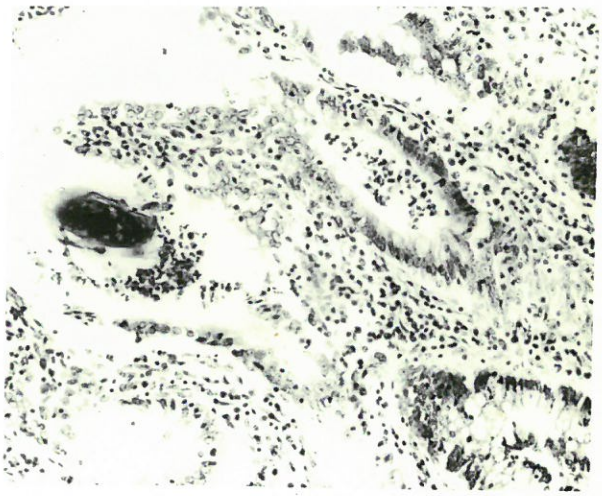

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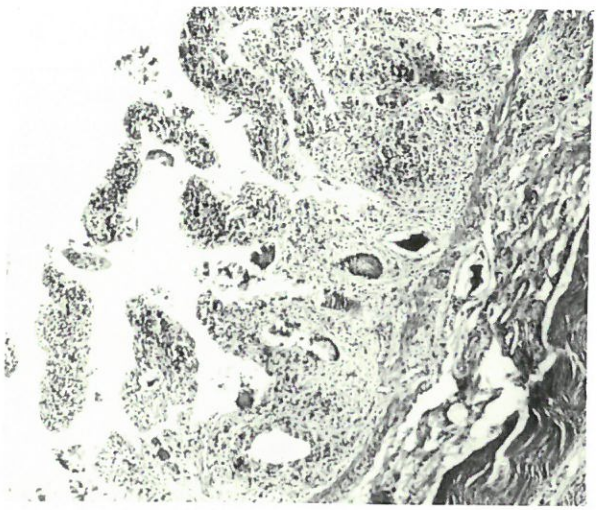

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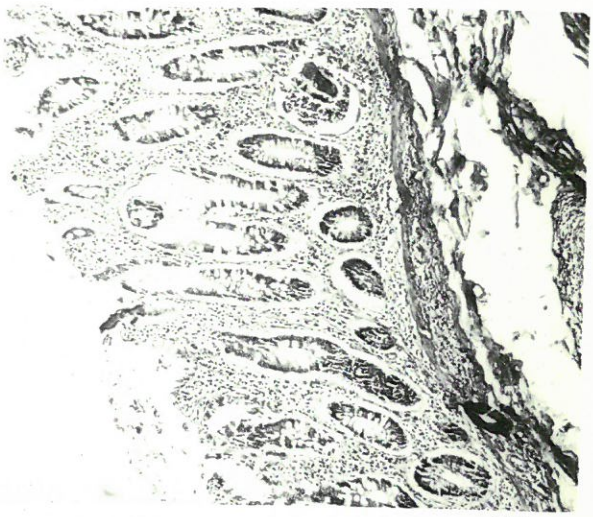

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PLATE XVI

Fig. 86 The prominent, proliferative pseudotuberculoid response evoked by ova in the submucosa is evident. HE x 20

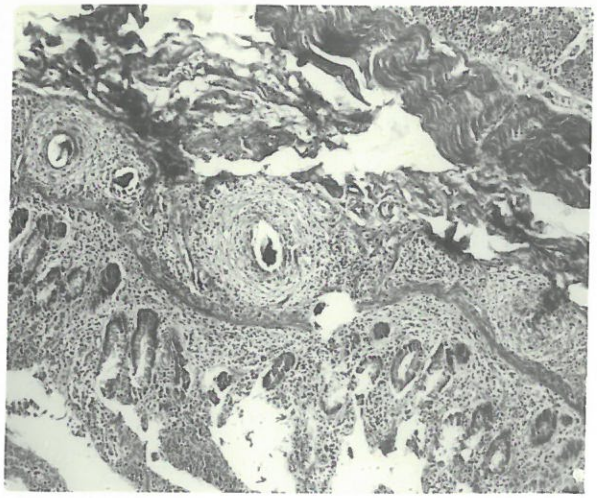
Fig. 87 Typical pseudotubercles in the outer muscle coat. HE x 50

Fig. 88 Reveals mature ova in the mucosa with cellular infiltrate (eosinophils predominating) and pronounced vascularity. HE x 20

Fig. 89 Histology of a sandy-patch lesion of the bowel with pure S. haematobium infection. Myriads of calcified ova in the submucosa and mucosa with minimal inflammatory reaction. HE x 50

Fig. 90 A bilharzial colonic "polyp" reveals an adenomatous pattern with clusters of ova. HE x 20

Fig. 91 A higher power view of the same lesion reveals the intense inflammatory reaction and occasional bilharzial ova. HE x 50



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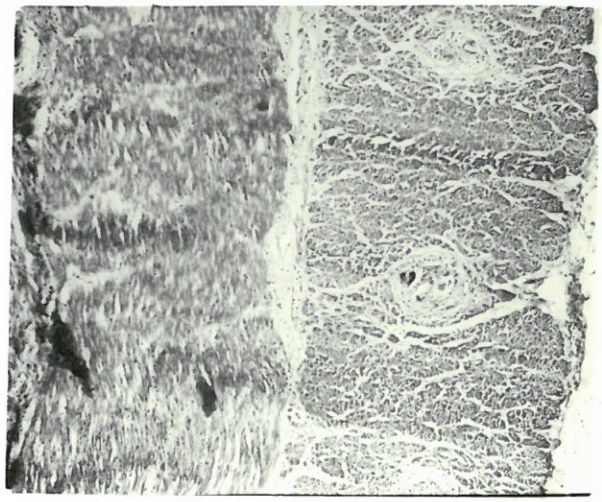

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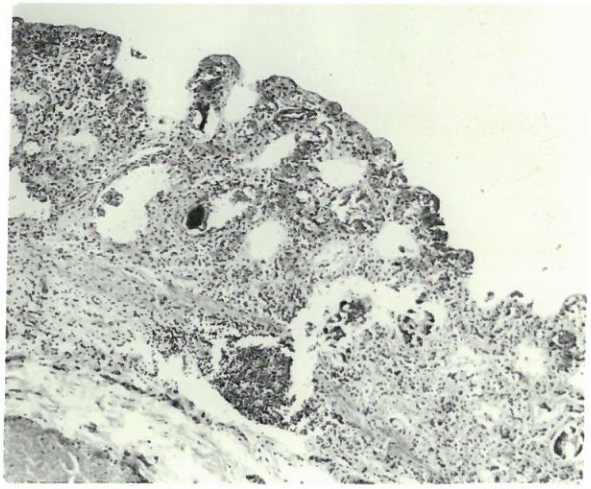

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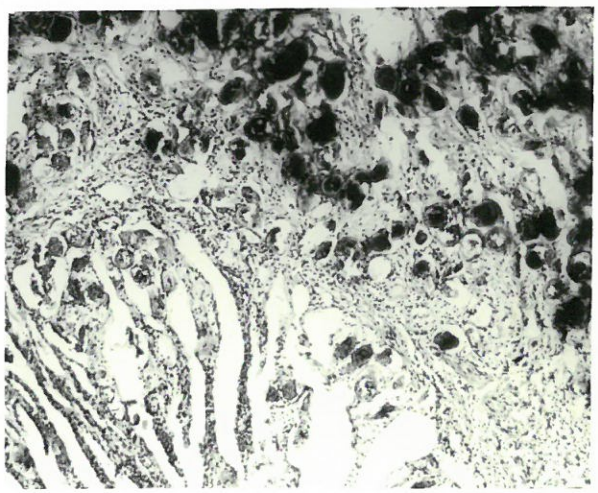

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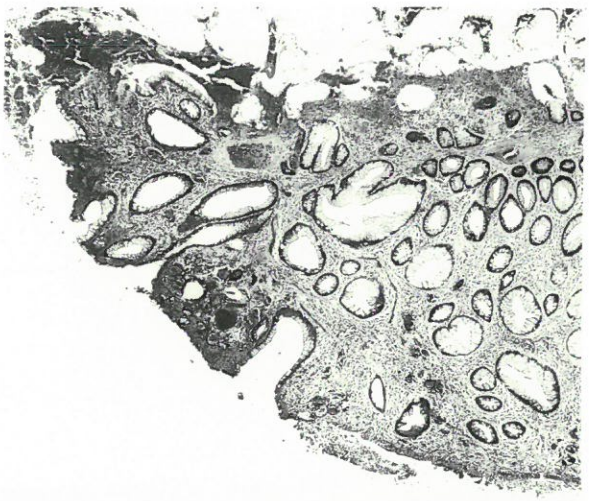

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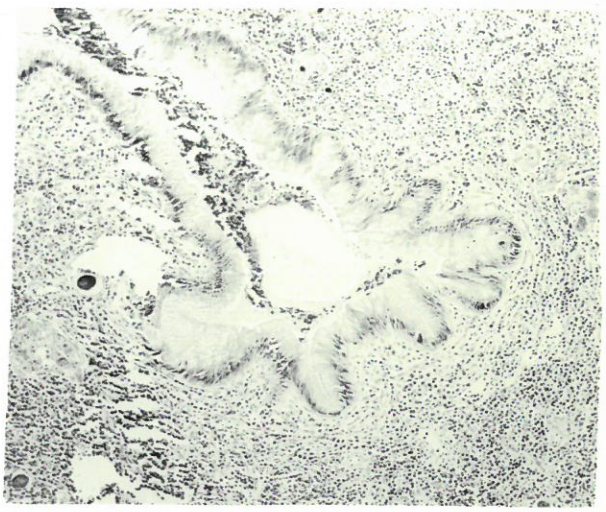

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CHAPTER VII

H E P A T I C B I L H A R Z I A S I S

INTRODUCTION

In 1904, Symmers St. Clair reported on a peculiar pattern of hepatic fibrosis in Egyptians, describing the macroscopic findings as - "the cut surface of the liver looks as if a number of white clay pipe-stems had been thrust at various angles through the organ". He noted that : "The microscopic examination of several of these has satisfied me that there is, in these cases, a constant concomitance of Bilharzia ova and periportal fibrosis" (Symmers, 1904).

Hamilton Fairley (1920) in collaboration with Ferguson examined the hepatic lesions produced experimentally in monkeys in the light of observed human pathology and concluded that " - the human liver is much more constantly involved, even in the finer grades of cirrhosis, than has been previously supposed". They realised that the pipe-stem cirrhosis of Symmers (1904) represented the most advanced and late stage of prolonged and repeated infection with S. mansoni but noted that: "Many intermediate stages exist associated with the presence of either lateral- or terminal-spined ova; such lesions, though plain enough in microscopic sections, may be missed on naked-eye examination". These findings were subsequently confirmed from

study/...

study of human material by Dew (1923) who also observed that S. mansoni produced more severe hepatic lesions than S. haematobium.

Following these observations there has been much discussion and controversy regarding the role of bilharziasis in the production of hepatic fibrosis. Workers from the major endemic areas of S. mansoni (both in Africa and South America) are generally agreed that hepatic bilharziasis is a definite pathological entity. Most of these workers, however, have concentrated on the late fibrotic stage and emphasised the frequency of these lesions.

Thus Koppisch (1943) from Puerto Rico, in a series of 100 consecutive autopsies found 75 cases of gross cirrhosis of which 26 cases (34.6%) were due to bilharzial fibrosis. Rodriquez et al. (1955) also from Puerto Rico, found that of 112 cases of gross cirrhosis, 22 (19.7%) were attributable to S. mansoni infection and a further 11 cases (9.8%) were probably due to a combined factor of S. mansoni and alcoholism. The literature reveals a large number of cases in a short period of time: from South America, Bogliolo (1957) reported 21 cases; Lichtenberg (1955) - 6 cases in 27 post mortems on patients with schistosomiasis; Polak et al. (1959) - 30 cases, and from Egypt, Ragheb (1956) - 69 cases; Hamilton et al. (1959) - 73 cases. These observations indicate that bilharzial hepatic fibrosis is a well recognised entity in these regions. Other authors have reported on the grave clinical complications of hepatic involvement (Rodriquez, 1953; Palmer & Jahnke, 1954; Rodriquez, 1956; Raffuci et al., 1958; Andrade et al., 1962 and Kloetzel, 1964). Manson-Bahr (1958) reported that bilharzial hepatic fibrosis was not uncommon in regions of Central Africa.

However/...

However, Gelfand (1950 & 1962) from Rhodesia, in 1950 and again as late as 1962, was of the opinion that bilharzial involvement of the liver resulted in occasional isolated pseudo-tubercles around ova and occasionally in a "bilharzioma" (an aggregation of pseudo-tubercles) with focal fibrotic scars which were inconsequential in the ultimate development of cirrhosis. Surprisingly, only two years later (Gelfand, 1964) working in the same population, stated: "My own attitude to this matter is that whereas portal cirrhosis has more than one cause, if schistosome ova and/or schistosomal granulation tissue are present in a needle biopsy, schistosomiasis should be accepted as the cause of the cirrhosis." This represented a complete reversal of his earlier opinions. Reviewing his 41 cases of cirrhosis reported in 1950 (none of which he attributed to bilharziasis) in the light of his present definition of bilharzial cirrhosis, no less than 56% would now be classified as bilharzial cirrhosis. However the presence of ova does not a-priori establish the aetiological basis of the cirrhosis. Bilharzial hepatic fibrosis, as demonstrated by Bogliolo (1957) has a classical morbid anatomical and histopathological pattern.

The oft-quoted report of D. Symmers (1951) rejecting the bilharzial aetiology of late hepatic fibrosis in endemic bilharzial areas was based on a review of 5 post-mortems on cases with bilharziasis. All had occasional pseudo-tuberculoid reactions around ova in the liver and 2 had Laennec's cirrhosis. On this slender evidence he concluded: "It is scarcely conceivable that relatively innocuous foreign-bodies such as ova, acting alone, are capable of causing perilobular cirrhosis of the liver - ".

Some authors, whilst accepting the concept of bilharzial cirrhosis, have confused the pathological features. Jaffe (1941)

reached/...

reached the conclusion that - "vascular congestion, biliary stasis and intoxication of different kinds, including pathological food products and toxins of parasites give a similar end result".

Prates (1961) from Mozambique, found bilharzial ova in 32.5% of 222 cases of cirrhosis. Although conceding that "pipe-stem" fibrosis is regarded as a late complication of intestinal bilharziasis, he was cautious of accepting bilharziasis as the etiologic agent of cirrhosis in his cases. In an earlier paper (1960) he had reported that of the 222 cases, 6 were of the "pipe-stem" bilharzial variety.

Observers from South Africa have generally discounted the role of bilharziasis in gross hepatic fibrosis. Gillman et al. (1945) found only 2 cases of "pipe-stem" fibrosis in 275 consecutive autopsies, whilst Higginson & de Meillon (1958) described only 2 cases in over 3000 autopsies. They concluded that mild schistosomal infection was not a significant factor in giving rise to periportal fibrosis. A similar view is shared by Gillman (1957) and contributors to the recent monograph on cirrhosis and carcinoma of the liver (Davies, 1961). Thus Becker & Chatgidakis (1961) and Higginson & Steiner (1961) found no examples of bilharzial hepatic fibrosis whilst Wainwright (1961) reported one possible example out of a total of 108 cases of gross cirrhosis.

Whereas the foregoing authors have largely concentrated on the late stages, the recent, more widespread use of needle biopsy in the diagnosis of liver disease has revealed the entire kaleidoscope of pathology --- from the earliest to the late changes in hepatic bilharziasis.

Latty/...

Latty *et al.* (1954) demonstrated the early lesions associated with *S. mansoni* and El-Gholomy *et al.* (1955) reported on the liver lesions of Egyptian children. Ragheb (1956) made a similar study of Egyptian adults whilst Dimmette (1955) compared needle and wedge biopsy results. Deschamps *et al.* (1955) demonstrated the usefulness of liver biopsy in asymptomatic *S. mansoni* infections. Rosanelli (1963) from East Africa demonstrated mild lesion in liver biopsy specimens whilst Carter & Sheldon (1959) from Nigeria reported a wide spectrum of liver pathology in apparently mild infections of *S. mansoni*. Gelfand (1964) employing the needle biopsy technique found sufficient evidence to reverse his earlier opinions (1950 & 1962).

The foregoing discussion illustrates that, with the exception of South African observers, workers in the major endemic areas of schistosomiasis recognise hepatic bilharziasis as a pathological entity. The present investigation was undertaken to examine the validity of opinions expressed by South African workers especially since Lurie *et al.* (1956) could demonstrate no differences in the pathogenicity of South African and Egyptian strains of *S. haematobium* and *S. mansoni* in laboratory animals.

PRESENT STUDY

The present study is based on:

(a) Clinical and liver biopsy studies on 25 patients with known bilharziasis; and
(b) Histopathology of post-mortem livers from 50 cases with known bilharziasis.

A. CLINICAL ASPECTS

Materials & Methods

Liver biopsy was done on 25 patients. Of these, 20 were selected from those with known S. mansoni infection (Clinical group III in Chapter VI where the clinical studies are presented). Liver biopsy was also done on 2 further cases of known S. mansoni and 3 cases of pure S. haematobium infections.

Of these, 10 were Indian patients and the remainder African patients. The only female was Indian. The ages ranged from 4 years to 50 years but the majority were in the 10-22 years age group with only 2 over 22 years (34 and 50 years respectively) and 2 under the age of 10 years (4 and 9 years respectively). The average age of the patients was 15.9 years.

A detailed history, full clinical examination including proctoscopy, rectal and liver biopsy results were recorded. Haematological and Liver-function tests (L.F.T.) were conducted on all patients.

Technique of Liver Biopsy

In all cases liver biopsy specimens were obtained under local anaesthesia by means of a Menghini needle (Menghini, 1958). The transthoracic route in the right midaxillary line of the ninth intercostal space, was used in all cases. The

usual/...

usual precautions were observed (Sherlock, 1962) and except for temporary pain at the biopsy site, no untoward effects were experienced.

A suitable core of tissue was obtained in every case. It was possible to repeat the biopsy at intervals in 2 cases.

Liver biopsy specimens were fixed in 10% formol-saline and after embedding in paraffin-wax were serially sectioned at 6 microns. All the sections were stained with H & E, a Gordon and Sweet silver reticulum stain, and a Perls reaction for iron with a Van Gieson counterstain (E.V.G.) to demonstrate mature collagen was done in every case.

Results.

The urine, stool and rectal biopsy results are summarised in Table I.

It is evident that no less than 20 had urinary bilharziasis and viable ova of S. haematobium were found in the urine in all cases. In addition, 1 patient had viable S. mansoni ova in the urine whilst in 4 cases viable ova of S. haematobium were recovered from the stools. In 12 patients viable ova of S. haematobium were demonstrated by rectal biopsy and in a further 4 cases non-viable ova were present. Only 3 cases had pure S. haematobium infections, the remaining 22 having S. mansoni with 5 pure S. mansoni infection. In all S. mansoni cases viable ova were present on rectal biopsy although only 13/20 cases had ova in stools. A double infection (S. haematobium in urine and S. mansoni on rectal biopsy) was present in 17 cases whilst a

mixed/...

TABLE I

URINE, STOOL & RECTAL BIOPSY FINDINGS IN CASES SELECTED FOR LIVER BIOPSY.

MATERIAL EXAMINED	NO. EXAMINED	S. HAEMATOBIUM				S. MANSONI	
		Viable		Non-Viable		Viable	
		No.	%	No.	%	No.	%
URINE	25	20	80	0	0	1	4
STOOL	20	4	20	1	5	13	65
RECTAL BIOPSY	25	12	48	4	16	22	88

mixed intestinal infection (S. mansoni and S. haematobium) on rectal biopsy was demonstrated in 16 patients.

SYMPTOMATOLOGY

This has been discussed in detail in the chapter on Intestinal Bilharziasis. The main presenting symptoms of those patients on whom liver biopsy was performed are summzrised in Table II.

TABLE II/...

TABLE II

PRESENTING SYMPTOMS OF PATIENTS IN LIVER BIOPSY SERIES

SYMPTOMS	NO.
Terminal haematuria	19
Diarrhoea with or without blood	10
Abdominal pain	7
Haematemesis (small)	1

Though, by selection, the majority (17/25) presented with symptoms of urinary bilharziasis, 4 of these also complained of having had bouts of diarrhoea with flecks of blood in the stool. Diarrhoea with blood and mucus was the presenting symptom in 6 patients, with one having had an episode of terminal haematuria. One patient (Indian female, aged 50 years) presented with vague and generalised abdominal pain and weakness. Rectal biopsy revealed viable ova of S. mansoni. One patient, presenting with abdominal pain, had a history of one bout of mild haematemesis and terminal haematuria; though no history of diarrhoea was obtained, rectal biopsy revealed viable ova of S. mansoni.

All the patients with prominent intestinal symptoms (diarrhoea with blood and mucus) were Africans.

CLINICAL/...

CLINICAL FINDINGS

All patients appeared in reasonably good nutritional state. None was very ill and all were apyrexial at the initial examination.

The state of the liver and spleen is summarised in Tables III and IV.

TABLE III

SIZE OF LIVER IN BIOPSY SERIES

(Size expressed as finger-breadths below costal margin)

SIZE:	INDIAN	AFRICAN	TOTAL
0	5	5	10
1	4	3	7
2	-	4	4
3	1	3	4
TOTAL	10	15	25

TABLE IV/...

TABLE IV

SIZE OF SPLEEN IN LIVER BIOPSY SERIES

(Size expressed as finger-breadths below costal margin)

SIZE:	INDIAN	AFRICAN	TOTAL
0	8	9	17
1	-	4	4
2	2	2	4
TOTAL	10	15	25

Tables III and IV show that the liver was not enlarged in 10 and the spleen in 17 cases. Hepato-splenomegaly was present in 8/25 cases. With one exception, the liver enlargement was non-tender with a firm edge. In one case there was a tender hepatomegaly (3-fingers) associated with splenomegaly. In this case an initial diagnosis of amoebic liver abscess was made (Case report I : Chapter VI - Intestinal Bilharziasis).

Hepatomegaly was present in 4 and splenomegaly in 2 of the 5 cases with pure S. mansoni in the African group. Proctoscopic examination in all cases revealed rectal involvement with hyperaemic mucosae and crops of punctate haemorrhages. The rectal biopsy results are summarised in Table I.

LABORATORY/...

LABORATORY INVESTIGATIONS

Haemoglobin:

Only 5 patients had haemoglobin values well below the normal range quoted by Wintrobe (1962). These results are tabulated in Table V.

TABLE V

HAEMOGLOBIN VALUES OF 5 PATIENTS WITH ANAEMIA AND HEPATIC BILHARZIASIS:

(compared with normal values for different ages quoted by Wintrobe, 1962)

AGE	RACE	SEX	Hb. grams/%	Normal range Hb. grams/ %
50	I	F	8.0	12 - 16
4	A	M	10.6	12.6
15	A	M	10.3	13.4
9	A	M	10.2	12.9
11	A	M	9.0	13.4

Of the 25 cases only 5 cases had mild hypochromic anaemia. Erfan (1947) noted a mild hypochromic anaemia in the early stage of liver involvement whilst Ragheb (1956) found anaemia in his late cases and considered this to be due to

constant/...

constant blood loss. El-Gholomy (1955) found no correlation between the stage of the disease and the haematological findings. Rodriquez (1953) and El Mofty (1962) described hypochromic anaemia and believed that this was due to a Banti's Syndrome in late bilharzial involvement of the spleen and liver. Bibwai & Amin (1964) have recently demonstrated masked sideropenia (an iron deficiency state) in patients with bilharzial hepatic fibrosis. The mechanism is obscure.

In the present study the anaemia cannot be explained on the basis of blood loss or Banti's syndrome. In the few cases showing anaemia, this was mild and might have been due to other causes.

White Cell Count & Eosinophilia:

A leucocytosis was always associated with an absolute eosinophilia. The eosinophil levels are summarised in Table VI.

TABLE VI

EOSINOPHIL LEVELS IN PATIENTS WITH BILHARZIASIS ON WHOM LIVER BIOPSY WAS PERFORMED

EOSINOPHIL COUNT ($\times 10^2$)	< 4	> 4	> 10	> 20	> 40
No. of cases	6	19	9	6	1

Wintrobe/...

Wintrobe (1962) quotes an absolute count of over 250 as denoting an eosinophilia. In this study 15 (60%) had an absolute eosinophilia of over 500. In this latter group the count varied from 550 to as high as 16,500 (50% of the total white cell count).

In 2 patients the eosinophil count was repeated at intervals after treatment had been instituted (Sodium antimony tartrate). The results are shown in Table VII.

TABLE VII

EOSINOPHIL COUNT IN 2 PATIENTS WITH HEPATIC SCHISTOSOMIASIS

(on treatment)

CASE	TIME (in weeks):	0	2	4	6	8
1	Eosinophil Count	456	5,335	42,000	49,000	-
	Total White cell count	9,000	17,000	72,000	68,000	-
2	Eosinophil Count	16,450	12,400	2,513	-	1,000
	Total White cell count	33,000	20,000	12,000	-	9,000

Table VII reveals that in the first case, the eosinophil count was fairly low initially, but shortly thereafter there was a trementous eosinophil response which remained at an elevated level 6 weeks after therapy had been instituted. Unfortunately the patient was lost to follow-up studies.

On/...

On the other hand, in the second example, there was a severe eosinophilia (16,450) when first seen, but this gradually diminished on therapy to a level of 1,000, eight weeks after therapy. This patient too was subsequently lost to follow-up.

These 2 cases demonstrate the wide variability over a period in the eosinophil count. Lane (1953) postulated an allergic reaction to explain the eosinophilia in early bilharziasis. In the 2 cases under consideration, it is feasible that treatment, with the subsequent death of parasites and the sudden release of large amounts of toxic metabolites, precipitated an allergic reaction.

Liver Function Tests:

The liver function tests reported by the routine laboratory is shown in Table VIII. In this series electrophoretic studies were not performed.

There was no definite pattern of derangement, a finding similar to those of Ragheb (1956), Rodriquez (1956), Popper & Schaffner (1957), Gelfand (1964) and others. The variations in the protein pattern have been discussed in Chapter IV.

TABLE VIII/...

TABLE VIII

SUMMARY OF LIVER FUNCTION TESTS OF 25 BILHARZIAL PATIENTS ON WHOM LIVER BIOPSY STUDIES WERE UNDERTAKEN:

RACE	AGE	ALB.	GLOB.	TOTAL	A. PHOS.	ZT	TT	P.I.	BIOPSY
I	14	4.4	2.3	6.7	22	8	4	96	+
I	14	4.0	2.5	6.5	18	6	2	100	O
I	13	-	-	-	-	-	-	100	+
I	11	2.9	3.6	6.5	18	7	3	96	+
I	19	3.6	3.3	6.9	7	0	1	100	+
I	14	2.5	4.2	6.7	31	-	-	94	+
I	20	3.8	3.3	7.1	8	9	2	80	O
I	16	4.2	3.0	7.2	21	9	4	100	+
I	20	5.0	2.3	7.3	9	3	1	100	+
I	50	3.2	3.9	9.0	8	7	2	100	+
A	4	2.2	4.3	6.5	16	14	7	96	+
A	12	3.6	3.7	7.3	11	-	-	73	+
A	15	4.8	3.3	8.1	20	4	1	100	+
A	16	2.6	5.0	7.6	24	6	1	100	+
A	15	4.7	2.9	7.6	19	9	3	96	+
A	13	2.1	5.1	7.1	23	20	3	87	+
A	13	3.4	3.1	6.5	15	-	-	96	O
A	34	-	-	-	-	-	-	85	+
A	16	4.9	3.1	8.0	15	5	1	95	+
A	9	3.9	3.5	7.4	18	8	1	100	+
A	11	1.3	2.8	4.1	18	1	1	87	+
A	10	3.7	3.5	7.2	17	7	3	100	+
A	12	2.6	5.4	8.0	4	2	8	100	+
A	12	3.2	3.6	6.8	12	4	1	76	+
A	15	5.2	1.8	7.0	24	8	4	99	+

RACE : I = Indian
A = African

ALB. = Albumin
GLOB. = Globulin
A. PHOS. = Alkaline Phosphatase
ZT = Zinc Turbidity
TT = Thymol Turbidity
P.I. = Prothrombin Index
+ = positive liver biopsy
O = negative liver biopsy.

B./...

B. PATHOLOGY OF HEPATIC BILHARZIASIS

INTRODUCTION

Fairley (1920) and Dew (1923) realising that the classic description of Symmers St. Clair (1904) applied only to the late stages of hepatic involvement, described the intermediate changes. Koppisch (1943) also reported a series of changes, ultimately ending in portal cirrhosis. In the later stages of hepatic involvement, Hashem (op cit Erfan, 1947) recognised two forms of fibrosis, a coarse, corresponding to the classical pipe-stem variety and a fine fibrosis confined to smaller tracts. The two forms could co-exist.

El-Gholomy et al. (1955) studied needle biopsies from 33 Egyptian children and described 4 stages:

(a) the pre-cirrhotic with cellular infiltration of the portal tracts;
(b) early cirrhosis with fibroblastic proliferation in the portal tracts;
(c) established cirrhosis with minimal cellular infiltration;
(d) advanced cirrhosis with excessive portal fibrosis.

Using wedge biopsies done at the time of splectomy on 73 patients, Hamilton et al. (1959) also described four stages of histopathology but were different from that of El-Gholomy et al. (1955).

Group I/...

Group I : Established pipe-stem cirrhosis involving mainly the largest portal tracts and with prominent pyelophlebitis of the portal vessels.

Group II : Akin to post-necrotic scarring with prominent peripyelophlebitis but with fewer ova than in Group I.

Group III : A diffuse involvement of the finer portal tracts with focal areas resembling a coarse nodular cirrhosis.

Group IV : Similar to Group III, but the lesions were focal.

Bogliolo (1957) encountered 3 forms of hepatic lesions in autopsies in Brazil:

(i) The typical "clay pipe-stem" cirrhosis;

(ii) A diffuse bilharzial fibrosis with focal involvement primarily of the Kiernan spaces and marked interlobular septation. Generally the architecture of the liver was maintained;

(iii) A "flint-liver" with morbid anatomy resembling a congenital syphilitic interstitial fibrosis with prominent periportal connective tissue proliferation resulting in loss of the normal architecture.

Polak et al. (1959) described the same number of groups as El-Gholomy et al. (1955) and Hamilton et al. (1959) but based these on macroscopic (from laparoscopy) and microscopic (needle biopsy) features:

Group I : Active granulomatous lesions with slight liver enlargement.

Group II : Similar pathology but with moderate liver enlargement.

Group III/...

Group III : Interlobular fibrosis with lobular disarray and a nodular macroscopic appearance.

Group IV : Similar pathology as Group III except that those livers had more extensive extracapsular adhesions.

Carter & Shaldon (1959), in addition to the reactions around ova, described a generalised hepatitis with prominent lymphocytic and some plasma cell infiltration - a condition earlier described by Deschamps et al. (1955), Dimmette (1955) and Ragheb (1956). Gelfand (1950), in addition to pseudo-tubercles, described a macroscopic lesion which he termed a "bilharzioma". Histologically this consisted of an aggregation of pseudo-tubercles.

Though there are differences in the terminology used by different authors, the basic pathology described is apparently similar.

Generally, four stages of hepatic involvement have been recognised. These may be summarised as follows:

STAGES OF HEPATIC BILHARZIASIS

(1) Miliary Hepatic Bilharziasis:

This represents the earliest stage of hepatic involvement. There are granulomatous pseudo-tubercles around embolic ova, which represent the microscopic pathological units of all bilharzial lesions (Fairley, 1920; Dew, 1923; Koppisch, 1943 and Deschamps et al., 1955). This early infiltrative

phase/...

phase corresponds with Stage I of El Gholomy *et al.* (1955). As the histological pattern is not unlike that of miliary tuberculosis, this stage is perhaps best termed Miliary Hepatic Bilharziasis.

(2) Diffuse Bilharzial Hepatic Fibrosis:

(Group 2, "Fine Bilharzial Fibrosis" of Hashem (1947) and Bogliolo (1957); Groups 3 & 4 of Hamilton *et al.* (1959); Groups 1 & 2 of Polak et al. (1959)).

Bogliolo (1957) describes a diffuse bilharzial fibrosis which is lobular in distribution with large areas of the liver uninvolved. In one of his cases, only half of the right lobe was involved and in another the left lobe only was affected. Hamilton *et al.* (1959) and Polak *et al.* (1959) describe similar lesions.

Microscopy in this group reveals interlobular septation, inflammatory reaction and newly-formed periportal connective tissue. Hashem (*op. cit.* Erfan, 1947) and Bogliolo (1957) emphasised that in this stage the liver portal tracts are primarily involved. No gross alteration of the architecture is present and the number of ova and active granulomata are greater than in established portal fibrosis demonstrating that the lesions are in fact an earlier phase of the disease than portal fibrosis.

(3) Coarse Nodular Bilharzial Fibrosis:

Group 2 of Hamilton *et al.* (1955), 3 & 4 of Polak *et al.* (1959) and possibly the "flint-liver" of Bogliolo (1957).

In/...

In this stage the liver has a gross appearance of nodularity and histology reveals lobular disarray with both intralobular as well as periportal fibrosis. Hamilton et al. (1959) conclude that emboli produced by successive waves of dead worms over a prolonged period could produce such a picture. Bogliolo (1957) however, describing a similar pathology, found a preponderance of bilharzial granulomata only.

(4) "Pipe-stem" Portal Fibrosis:

Workers from Egypt and South America are unanimously agreed that the anatomical picture of "pipe-stem" portal fibrosis as originally described by Symmers St. Clair (1904) is typical and pathognomonic of bilharzial liver disease and that it represents the very late stage of hepatic bilharziasis (Fairley, 1920; Dew, 1923; Koppisch, 1943; Hashem, op.cit. Erfan, 1946; Rodriquez et al., 1955; Ragheb, 1956; Bogliolo, 1957; Pucci et al., 1958; Hamilton et al., 1959 and Polak et al., 1959).

In this stage there is an unusual distribution of excess fibrous tissue limited to the ramifications of the Glisson's capsule which normally surrounds only the larger portal tracts. Unlike the gross distortion of the normal architecture accompanying other forms of cirrhosis (Laennec's, post-hepatic, biliary) there is in pipe-stem cirrhosis but minimal upset in the normal lobular architecture. Degenerative changes in the parenchyma are slight and there is no evidence of bile duct proliferation or biliary retention. There may be bilharzial pigment and a variable number of degenerate ova and pseudo-tubercles in the fibrous sheaths.

PRESENT/...

PRESENT STUDY

1. CLINICAL BIOPSY GROUP

Of the 25 cases on whom liver biopsy was done, bilharzial involvement was found in 22. All stages, from the earliest stage of focal cellular infiltrate to the late stage of established portal fibrosis, were demonstrated. The histopathological findings are summarised in Table IX.

TABLE IX

HISTOPATHOLOGY OF HEPATIC BILHARZIASIS

Liver biopsy findings in 25 cases:

NATURE OF LESION	NO.	%
No abnormal findings	3	12
Acute granuloma with ovum or ovum remnants	15	60
Acute granuloma with no recognisable ovum or ovum remnants	15	60
Healing fibrotic granulomata	13	52
Ova present	17	68
Pigment present	22	88
Eosinophil cellular infiltrate	22	88
Widening of the portal tracts	18	72
Established portal fibrosis	9	36
Evidence of liver parenchymal damage	15	60

Table/...

Table IX reveals that despite the mite of tissue examined, liver involvement was apparent in all but 3 cases.

The histopathological features revealed not only the frequency and severity of the hepatic lesions, but also indicated the probable pathogenesis of the lesions. The presence of an ovum seemed essential for the subsequent pathological changes. By a study of serial sections the development and regression of the granulomatous "pseudo-tubercles" became evident and the role of the egg in the genesis of portal fibrosis more apparent.

HISTOPATHOLOGY OF LIVER LESIONS

Evolution of the Pseudotubercle:

In the earliest stage the mature ovum which lies in a portal tract, is surrounded by an almost predominant eosinophil cellular infiltrate (Fig. 93). Koppisch (1943) in human material and Meleney *et al.* (1953) and Cameron & Gangulay (1964) in experimental animals, describe the early appearance of polymorphonuclear leucocytes. In the present study a prominent feature was the absence of neutrophils and the predominance of eosinophils.

The next stage is probably dependent on the death of the miracidium with local release of toxic material. This evokes a typical granulomatous response with an area of central eosinophilic necrosis surrounding the ovum (Fig. 94). The necrotic centre is surrounded by epitheloid cells and monocytes and this zone is, in turn, bordered by a cellular infiltrate. Though eosinophils predominate in the latter, lymphocytes and some

plasma/...

plasma cells being to appear. The tissue-response is most probably due to an antigen-antibody or hypersensitivity-like reaction (Andrade et al., 1961).

At a later stage the ovum is attacked by one or more giant cells surrounded by epitheloid cells and monocytes (Figs. 95 & 96). At the periphery of the pseudo-tubercle there is a variable amount of fibroblastic proliferation in concentric rings. This, in turn, is surrounded by a cellular infiltrate in which eosinophils are less and lymphocytes and plasma cells, more prominant. At this stage of giant cell reaction - the dead ovum is apparently acting merely as an inert foreign body and providing no further antigenic stimulus. The difference in the character of the cellular infiltrate with the appearance of more plasma cells suggests that the antigen is now either fixed or neutralised (Fairley, 1920).

Thereafter the pseudo-tubercle begins to heal with concentric proliferation of fibroblasts (Figs. 97 & 98) and the laying down of young collagen, as revealed by van Gieson stain. The peripheral cellular infiltrate becomes less prominent, and, in the late fibrotic stage, disappears. No egg remnants can be demonstrated and the site of the pseudo-tubercle is marked by a hyaline fibrotic nodule (Fig. 99).

Such pseudo-tuberculoid lesions in all stages were evident in 16 cases (64%) whilst ova or their remnants were identified in 17 cases (68%). In one case there were several viable ova (with an identifiable miracidium) in the portal tracts with a complete absence of any tissue response (Fig. 92). This patient had a pure S. haematobium infection with severe bladder

and/...

and upper renal-tract involvement. Whether the lack of reaction was determined by the species of ovum or the possible paralysis of the immune mechanism by the long-continued, severe infection, is debatable.

Role of Eosinophils

There was a prominent eosinophil cellular infiltrate in 22 cases. Though the distribution was, in most, in the portal tracts, there were, in some, focal collections of cells apparently in the parenchyma. The three dimensional wax model of Main (1963) reveals however that it is possible for biopsy to miss the main lesion.

The part played by the eosinophils is an indication of the mechanism underlying the tissue changes. Day (1911) demonstrated local tissue eosinophilia by injecting extracts of ova and worms subcutaneously. Fairley (1920) in experimental infections, demonstrated an eosinophilia in the early stages of the disease which diminished markedly in older infections. This phenomenon has been confirmed by clinical observations (Dew, 1923; Erfan, 1947; Koppisch, 1943; amongst others). Thus eosinophilia is probably an allergic response and appears to be an early manifestation of bilharziasis. If the degree of eosinophilia can be used to "date" the infection, most of the cases in the present study may be said to have active, early lesions.

Bilharzial Pigment:

The golden-brown pigment peculiar to bilharziasis (Fairley, 1920; Dew, 1923; Koppisch, 1943; Erfan, 1947; Meleney et al., 1953 and Bogliolo, 1957) was evident in variable quantities in 22 cases (Figs. 101 & 105). Whilst in some it was minimal and confined to the Kupffer cells, in others it was prominent being concentrated in the portal tracts and often lying extracellularly. There appeared to be some correlation between the amount of pigment and the severity of the lesions. As it is an excretory product of the parasite, the amount of pigment does, perhaps, give an indirect measure of the worm load.

Damage to Portal Tracts:

Widening of the portal tracts was apparent in 18 cases (72%). This was produced by a cellular infiltrate only in some cases (Fig. 100), by fibrous tissue response in others and by both in most (Figs. 100 - 111). The extent of portal fibrosis varied but definite distortion of the portal tracts due to collagen deposition was obvious in 9 cases (36%). In some of these there was early linkage of portal tracts with septation (Fig. 103) whilst in others there was definite distortion of the normal lobular architecture with pronounced septation and established periportal fibrosis (Figs. 104 - 107).

Liver Parenchymal Cellular Damage:

An interesting observation in this study was the evidence of parenchymal cell damage hitherto not described in

human/...

human livers. These changes were apparent from nuclear aberrations - of pyknosis, vacuolation, variation in size and endomitotic devision (Figs. 116 & 117). In some the cytoplasm appeared feathery and the cell borders indistinct. These cellular changes were diffusely scattered and bore no relationship to the main pseudo-tuberculoid lesion. Such cell changes were commoner in the more early phase of hepatic involvement. Numerous authors have described a "piece-meal" focal necrosis in both human and experimental material (Fairley, 1920; Erfan, 1947; Meleney et al., 1953; Ragheb, 1956; Gillman, 1957 and Bogliolo, 1957). This, however, was always associated with the main granulomatous lesions in the portal tracts. Only Gonnert (1955) described liver cell damage in experimental bilharziasis similar to that observed in the present study.

STAGES OF HEPATIC INVOLVEMENT

From this study it was possible to classify the pathology of active hepatic bilharziasis into 3 stages:

(1) Miliary Hepatic Bilharziasis - STAGE 1.
(2) The intermediate proliferative stage - STAGE 2.
(3) The late fibrotic stage - STAGE 3.

The stage of the hepatic involvement in the liver biopsy series is summarised in Table X.

The following criteria were used to determined the stage:

STAGE 1/...

TABLE X

STAGE OF HEPATIC INVOLVEMENT IN 25 LIVER BIOPSIES ON PATIENTS WITH BILHARZIASIS

STAGE	INDIAN	AFRICAN	TOTAL
No REACTION	2	1	3
STAGE I	6	4	10
STAGE II	2	5	7
STAGE III	0	5	5

STAGE 1 : Miliary Hepatic Bilharziasis

In the early stage the prominent features are the presence of acute pseudo-tubercles associated with a viable or recently deceased egg. There is a predominant eosinophil cellular infiltrate, not only around the granulomatous lesions but also in the portal tracts. Though epitheloid cells and monocytes may be seen neither giant cells nor fibroblasts have appeared round the pseudo-tubercle (Figs. 92 - 95). Any widening of the portal tracts is due to cellular infiltration and not to fibrosis. A feature of this stage is the evidence of individual liver parenchymal cell damage described earlier (present in 8/10 Stage I cases).

The number of granulomata varies and is no doubt

dependent/...

dependent on the load of infection. The severity of the involvement may be gauged from one example wherein a single liver biopsy specimen revealed 12 pseudo-tubercles. An average biopsy (by the present technique) was found to weigh approximately 12-15 mgm. whereas an average liver in a 13-year old (the age of this particular patient) weighs approximately 1,000 grams. Consequently the number of granulomata in this patient (assuming the liver to be diffusely involved) would exceed a million! It is obvious then that the insult to the liver must be considerable.

Of the 10 cases classed in Stage 1, 6 were Indian and 4 were African.

STAGE 2 : Intermediate Proliferative Stage

The second stage of the disease corresponds to the phase of tissue proliferation and repair processes initiated around pseudo-tubercles. There is a less pronounced eosinophil cellular infiltrate but lymphocytes and plasma cells are more prominent. In this stage giant cells attack the ovum and often merely fragments of the chitinous, refractile egg shell are identifiable (Figs. 96 - 99). There is widening of the portal tracts due to the laying down of young collagen (Figs. 101 & 102) and there may be early septation around the liver lobules (Fig. 108). Liver parenchymal cell damage is not prominent.

There were 7 cases in Stage 2 of which 5 were African and 2 Indian.

Stage 3/...

Stage 3 : Stage of Portal Fibrosis

This is the last stage which can be diagnosed by the needle liver biopsy. Because of the limitations of the technique, such later lesions as pipe-stem cirrhosis may only be surmised.

In this, the third stage, the most prominent feature is the established, advanced fibrosis of the finer portal radicles resulting in distortion and widening of the tracts (Figs. 103 - 107). Healing and fibrosed pseudo-tubercles are intimately associated and merge with the portal fibrosis. A variable amount of cellular infiltrate, chiefly of lymphocytes and plasma cells but with only occasional eosinophils, is present.

Co-existent early pseudo-tubercles are no doubt related to more recent egg deposition and though such early granulomata bear no temporal relation to the stage of portal fibrosis, they are apparently rare in Stage 3.

In the present study, 5 cases (20%), all Africans, were classified in Stage 3 or established advanced fibrosis. Whether these cases belong to the group of "pipe-stem" portal fibrosis of Symmers St. Clair (1904) is debatable.

Evidence from autopsy material (to follow) suggests that even in the stage of Symmers' pipe-stem cirrhosis, there are different grades of severity. Thus in the early phase of Stage 3 macroscopic features are non-specific and the ultimate diagnosis rests on histopathology. Both Fairley (1920) and

Dew (1923)/...

Dew (1923) made similar observations.

In the opinion of the author, Stage 3 may be sub-divided into three grades:

STAGE 3 : Grade (i) : where macroscopic evidence is inconclusive and diagnosis rests on the typical histopathology (Fig. 109).

STAGE 3 : Grade (ii) : where there is macroscopic evidence of fibrosis of the larger portal tracts, and which is subsequently confirmed by histology to be of bilharzial origin (Fig. 110).

STAGE 3 : Grade (iii) : the classical macroscopic and microscopic picture of Symmers' pipe-stem cirrhosis (Fig. 111).

On this basis the five cases in Stage 3 of the present biopsy study may be classified in the early stage of established "pipe-stem" portal fibrosis or Stage 3 - Grade (i). Clinical observations support this conclusion as well, for, in spite of the histopathological appearances, there were no clinical signs of advanced portal hypertension. Although a moderate degree of hepatomegaly was present, splenomegaly was unimpressive and not gross and none of these five patients had episodes of haematemesis. (The one case who had a mild haematemesis was an Indian male in Stage 2).

In one case in Stage 2 a second liver biopsy was repeated after an interval of 6 weeks following antimonal therapy. Whereas the original biopsy had revealed larged numbers of granulomatous lesions, the subsequent biopsy revealed focal

chronic/...

chronic cellular infiltrate in the portal tracts only. The apparently, almost complete resolution suggests that early lesions may be reversible. Cameron & Gangulay (1964) and Warren (1961) reported similar changes in experimental animals.

In a second patient in Stage 3, grade (i) liver biopsy was repeated on 2 occasions, the second after an interval of 4 weeks and the third 13 weeks later (i.e. 17 weeks after the initial biopsy - treatment having been completed 1 week after the first biopsy). The initial biopsy revealed established advanced portal fibrosis (Stage 3, grade (i)) with pronounced chronic cellular and some eosinophil infiltration in the portal tracts (Fig. 106). Late stage granulomata were intimately associated with the portal fibrosis. Although clinically the liver had regressed in size, a month later the histological appearances were identical to the original biopsy findings. Histology in the third specimen (17 weeks) again revealed a fibrosed portal tract with pronounced vascular involvement (Fig. 119).

The findings in these 2 cases indicate, as suggested by Erfan (1947) and Koppisch (1943) that in the more acute phase (Stage 1 & Stage 2), prior to deposition of mature collagen tissue, the lesions are reversible following treatment, whereas, once portal fibrosis has become established, complete resolution cannot occur. Cameron & Gangulay (1964) obtained contrary results in experimental animals and reported that even the late lesions were reversible.

2./...

2. AUTOPSY STUDY

Materials & Methods

Histology sections of livers taken during autopsy from 50 cases with known intestinal bilharziasis were examined. In all but 2 cases a random section was chosen by an independent observer. Multiple sections were available in 2 cases. A routine H & E stained section was exmained and wherever lesions of bilharziasis were encountered, further stains were done:

(1) Perl's reaction for iron with Van Gieson counterstain to demonstrate collagen tissue; and
(2) The Gordon & Sweet silver reticulum stain to demonstrate the reticulum framework.

The species of schistosome present was established in a snip of fresh rectal tissue.

Of the 50 cases, 44 were African and 6 Indian, whilst 36 were male.

Results.

Incidence of Hepatic Lesions

Of the 50 cases, 16 showed evidence of liver involvement. The relationship of schistosome species to the liver lesions is given in Table XI.

Table XI/...

TABLE XI

SCHISTOSOME SPECIES FOUND IN AUTOPSY CASES EXAMINED FOR HEPATIC LESIONS

SPECIES	NO.	WITH LESIONS	%
Pure S. mansoni	10	5	50
S. mansoni + S. haematobium	15	8	53
Pure S. haematobium	25	3	12
TOTAL	50	16	32

It will be seen that of the 25 cases with S. mansoni, 13 had liver involvement whereas of a similar number with pure S. haematobium, there were lesions in only 3. In this study, liver involvement is four times as common with S. mansoni as with S. haematobium.

Type of Lesions

Of the 16 cases with liver involvement only 5 had lesions of any significance (Table XII). The remainder had isolated pseudo-tubercles, variable, usually inconspicuous amount of pigment and mild focal cellular infiltrate. It was apparent from histology that in the latter these lesions were of little or no importance.

TABLE XII/...

TABLE XII

NATURE OF HEPATIC BILHARZIASIS
IN AUTOPSY STUDIES

TYPE OF LESION	NO.	%
No lesions	34	68
Occasional pseudo-tubercles	11	22
Acute severe lesions	4	8
Established pipe-stem fibrosis	1	2

Age:

The age distribution of all cases is shown in Table XIII.

TABLE XIII

AGE DISTRIBUTION OF AUTOPSY CASES EXAMINED
FOR HEPATIC BILHARZIASIS

RANGE IN YEARS	NO.
5 - 15	7
15 - 25	9
25 - 35	11
35 - 45	10
45+	13
TOTAL	50

The/...

The average age of the 50 cases studied was 33.1 years. The 11 cases (22%) with mild hepatic lesions had an average age of 32.4 years, whilst the 5 cases with severe lesions (all associated with S. mansoni) had an average age of 15.6 years, approximately half that of the whole group. The race, ages and sex of the severe cases, toghether with the cause of death were as follows:

RACE	SEX	AGE	CAUSE OF DEATH
A	M	24	Purulent Meningitis
I	M	13	Tetanus
I	M	19	Pulmonary Emphysema and Cor Pulmonale
A	M	8	Acute Bilharzial Dysentery
I	M	14	Cor Pulmonale due to Bilharzial Pulmonary Hypertension and Bilharzial Portal Fibrosis

Sex:

Though in the 50 cases a higher proportion of females showed lesions, their numbers are too small to have any significance.

Race:

Hepatic lesions, always severe, were present in 3 of the 6 Indian cases whilst 13 of the 44 African patients had lesions. Due to the small numbers, no special significance can

be/...

be attached to the above findings.

HISTOPATHOLOGY OF SEVERE LESIONS

Except for one case with established pipe-stem portal fibrosis, the other 4 cases had evidence of miliary hepatic bilharziasis.

Miliary Hepatic Bilharziasis:

Of the 4 cases with Miliary Hepatic Bilharziasis, the patient who died of acute bilharzial dysentery showed the severest hepatic involvement with large numbers of pseudo-tubercles becoming confluent and consequent linkage of the portal tracts (Fig. 108). Although a picture of septation was produced there was no evidence of established portal fibrosis. The 3 remaining cases revealed miliary pseudo-tubercles with variable quantities of pigment and cellular infiltrate in the portal tracts. None of these cases revealed adult worms in liver sections.

Liver sections from 3 other cases who died from Acute Bilharzial Dysentery prior to this study (reported under Autopsy Study in the Chapter on "Intestinal Bilharziasis") were reviewed. All 3 cases revealed Acute Miliary Hepatic Bilharziasis. Dead worms in the portal veins of one case evoked an intense peri-pylephlebitis (Figs. 113 & 114) while live worms in the same liver caused no reaction (Fig. 112).

Pipe-Stem Portal Fibrosis:

In the present autopsy study only one example of

established/...

established pipe-stem portal fibrosis was encountered in an Indian boy aged 14 years who died of Cor Pulmonale due to Bilharzial Pulmonary Hypertension. The liver did not have the characteristic macroscopic appearance of Symmers' pipe-stem cirrhosis and the true nature of the pathology became obvious only on histological examination. According to the author's criteria, this case is classified as Stage 3, grade (ii) (Fig. 110).

Three cases of typical pipe-stem cirrhosis, Stage 3, Grade (iii) encountered in autopsies previously have been reported by the author (Bhagwandeen, 1964), (Fig. 111).

CONCLUSIONS.

(1) Both the liver biopsy and autopsy studies in cases with ova on rectal snips demonstrate the high incidence of hepatic involvement of the liver (88% and 32% respectively). Of the 25 cases showing S. mansoni in the autopsy series, 13 (52%) had hepatic bilharziasis.

(2) Confirming the observations of Fairley (1920); Dew (1923), Erfan (1947) and El Gholomy (1955), the autopsy studies showed that by comparison with S. mansoni, hepatic involvement with S. haematobium is less common and much milder.

(3) Histopathology revealed that severe hepatic lesions can arise in S. mansoni infections.

(4)/...

(4) The present study, comprising both biopsy and autopsy studies, revealed the entire range of hepatic pathology from the earliest reaction around the ovum to the stage of pipe-stem portal fibrosis. The lone example of late pipe-stem portal fibrosis in this study was only demonstrated from histology sections taken at autopsy.

(5) Biopsy studies revealed not only a high incidence (22/25) of hepatic involvement in cases, with rectal bilharzia, but also that there may be very large numbers of eggs, one case having shown approximately a thousand eggs per gram of liver.

(6) Despite the high frequency of the earlier stages of hepatic involvement in asymptomatic S. mansoni infections encountered in the present series, the late stage of pipe-stem cirrhosis is uncommon.

(7) Both the clinical and autopsy series revealed the high incidence of the disease in the younger age group. This is more apparent from the atuopsy studies, wherein too, it became evident that older patients had less severe infections (dependent on level of acquired immunity ?) than younger age groups.

PATHOGENESIS OF HEPATIC BILHARZIAL FIBROSIS

Whilst there is overwhelming evidence substantiating the original observation of Symmers St. Clair that pipe-stem portal fibrosis in endemic bilharzial areas was a sequel of the

parasitic/...

parasitic infestation, there is still considerable controversy about the pathogenesis. Symmers (1904) himself merely commented on a "constant concomitance of bilharzial ova and periportal fibrosis".

SPECIES OF SCHISTOSOMES

From the time of Fairley (1920) and Dew (1923) it has been recognized that S. haematobium produces relatively milder hepatic lesions. Dew (1923) noted that: "All grades of cirrhosis were seen and the most advanced were always S. mansoni infections. No matter how severe the infection was with S. haematobium such marked cirrhosis was never met with in this type". Hashem (1947), Erfan (1947), El Gholomy et al., (1955) and Shaw & Ghareeb (1938) made similar observations.

Erfan (1947) reported that in hepatic bilharziasis, ova of S. mansoni are found four to five times as frequently as S. haematobium. Hashem (1947) noted that 15% of patients with S. haematobium infection had hepatic involvement. Though El Gholomy et al. (1955) found hepatic lesions in 66.6% of 117 children with S. haematobium infection, they concluded that the severest lesions were present in the 4 cases with S. mansoni infection. Ragheb (1956) also reported a high incidence of hepatic bilharziasis in S. haematobium infections (65.7% compared to 34.2% with S. mansoni) and did not find any qualitative differences. Shaldon & Carter (1959) from Nigeria also demonstrated the frequency of liver lesions associated with S. haematobium. Ova of S. haematobium were found twice as commonly as S. mansoni in both biopsy and post-mortem liver

studies/...

studies in Rhodesia (Gelfand, 1950) but both were associated with mild lesions. Subsequently, Gelfand (1964) reported severe hepatic involvement in S. mansoni and stated that S. haematobium infections usually gave a negative biopsy result.

The picture of hepatic bilharziasis reported from the South American and Caribbean countries, where S. haematobium does not occur, parallels that found in Egypt. This would suggest that, in Egypt, S. mansoni is the more important agent.

In an earlier publication (Bhagwandeen, 1964), the present author described 3 cases of pipe-stem fibrosis, 2 of which were related to pure S. mansoni and one to pure S. haematobium. Higginson & de Meillon (1955) from autopsy studies concluded that S. haematobium was not significant in hepatic pathology. Their one case of pipe-stem cirrhosis was related to S. mansoni infection. To explain the apparent lack of bilharzial liver involvement in South Africa, Lurie & de Meillon (1956) experimentally produced liver lesions in several laboratory animals with both Egyptian and South African strains of S. mansoni and S. haematobium. They could demonstrate no strain differences but observed that S. haematobium lesions tended to be less severe.

In the present study, the clinical group (liver biopsy series) was selected because of S. mansoni infection, only 3 having pure S. haematobium infection. All the advanced liver lesions were associated with S. mansoni infection. In the post-mortem study where there was no selection a more definite pattern emerged in that of cases with S. mansoni infection 50% had liver involvement whereas only 12% of those with pure S. haematobium showed such lesions. Moreover, whereas all the

lesions/...

lesions encountered in pure S. haematobium infections were insignificant, all the cases with severe hepatic involvement had S. mansoni.

ROLE OF OVA

Though both Fairley (1920) and Dew (1923) concluded that the presence of ova was not a prerequisite for the subsequent development of pipe-stem fibrosis, Brumpt & Chevallier (1934); Koppisch, (1943); Makar (1952) and Meleney et al., (1953) amongst others, demonstrated both experimentallly and in human material, the importance of ova in producing the typical lesions.

Meleney et al. (1953) from experimental evidence, concluded that fertile ova (i.e. with a miracidium) were more important than non-viable ova. They believed that this was due to the release of toxic substances by the miracidium. Gonnert (1955), Coelho (1955) and Cameron & Gangulay (1964) confirmed these observations and demonstrated a more severe reaction around viable ova. There were qualitative differences in the lesions produced by dead or immature ova and those produced by mature and viable ova. Makar (1952) quoted work done by Sorour (1928) and Hashem (1947) who had obtained similar results.

Deschamps et al. (1955), Lichtenberg et al., (1955), Hashem (1947), Hamilton et al. (1959) and Polak et al. (1959) from observation on human material were of the opinion that the ova were the prime factor in promoting hepatic fibrosis. Cheever (1961) and Warren (1961 & 1964) supported this view more recently. Warren (1961) stated that "on the basis of the

results/...

results obtained, it is felt that eggs are the prime factor in the development of hepato-splenic schistosomiasis in the mouse - ".

In the present studies, in both biopsy and autopsy material, histology supported the findings of previous authors that the ovum was the agent most often encountered in all stages of hepatic pathology. Moreover it appeared that the mature ovum was essential in initiating the most intense reaction - the early eosinophilic microabscess. Subsequent development of portal fibrosis was apparently dependent on the number of ova present in the liver.

The difference in reaction to the ova of the two species is probably dependent on the viability of the ova. As the ova of S. mansoni are deposited directly in the upper portal tract, they are viable and mature when they reach the liver and consequently produce the severe reaction. On the other hand, the ova of S. haematobium are, as a rule, not laid directly in the portal stream but in the pelvi-vesical plexus. The smaller numbers of ova which subsequently do reach the liver via the portal system have been laid in ectopic sites and are likely to be immature or non-viable. Such ova produce a much milder, usually foreign-body type of reaction.

ROLE OF WORMS

Gillman (1957) in experimental animals demonstrated the typical reaction around ova but also reported severe peri-pylephlebitis provoked by the embolization of dead adult worms.

He/...

He noted that this might in fact play a bigger role than ova in the pathogenesis of portal fibrosis and suggested that in man treatment might precipitate such a situation. Meleney et al. (1953) from animal experiments observed that: "Living worms in terminal vessels do not apparently stimulate a tissue reaction, but dead worms stimulate thrombosis of the vessel and an intense perivascular reaction which leads to disappearance of the worm, scar formation and often recanalisation of the vessel". He emphasised, however, that "Dead worms are found more frequently in unsuitable hosts". Koppisch (1943) had also observed that dead worms were important in producing pathology in experimental animals but not in man.

Dimmette (1955) found worms in 7.3% of 189 liver biopsies but suggested that these may have been adolescent. Hamilton et al. (1959) observed that in addition to the reactions produced by ova, 7 out of 73 liver biopsies also revealed intense reactions around dead worms. They suggested that waves of dead worm emboli in the liver portal circulation could result in a pattern not unlike that of portal fibrosis. Polak et al. (1959) found granulomatous lesions associated mainly with ova but the one case on whom an autopsy was performed also revealed hepatic lesions around vessels occluded by dead worms. Although in their own studies Andrade et al. (1959) found egg reactions only, they suggested the possibility that dead worms might result in focal fibrotic reactions. Cheever (1961) and Cameron & Gangulay (1964) found no significant pathology produced by dead worms.

Some authors suggest that the hepatic shift of worms due to treatment might result in severe lesions (Gillman, 1957;

Hamilton/...

Hamilton et al., 1959) and the experimental observations of Warren (1961) seem to confirm this view. Warren (1961) however, reported that the lesions following treatment subsequently disappeared and considered that "dead worms alone appear to play no significant role in the development of hepato-splenic schistosomiasis in mice". Menenzes (1963) on the other hand, demonstrated the apparent rapidity with which Symmers' type of hepatic fibrosis occurs in experimental animals following embolization of the portal system with dead worms. He stressed the importance of this in the pathogenesis. However, the susceptibility of unsuitable hosts, superinfection and artificial conditions raises doubts whether similar conditions hold in the human host (Coelho, 1951-1952; Cheever, 1961 and Warren 1962 & 1964).

In the present study, no lesions caused by adult worms were demonstrated in either the liver biopsy or autopsy series. In earlier autopsy studies however, 2 cases were encountered with worm lesions - one in the late stage of pipe-stem cirrhosis (Bhagwandeen, 1964) (Fig. 115) and the other a child who died of acute bilharzial dysentery. In the latter case, two dead and one live, worm were found. While the viable worm produced no reaction (Fig. 112) there was an intense periphlebitis around the dead worms (Figs. 113 & 114). The present study does not indicate that adult worms play any significant part in the pathogenesis of bilharzial portal fibrosis.

HEPATIC VASCULAR LESIONS

Shaw & Ghareeb (1938) demonstrated the severe vascular

lesions/...

lesions produced by ova in the lungs and several authors have described similar lesions in the liver. Hamilton et al. (1959) demonstrated that the primary hepatic lesion was a chronic peri-pylephlebitis associated with both ova and worms. Similar observations were made by Lichtenberg (1955), Bogliolo (1957), Rodriquez et al. (1955), Gillman (1957) and Cameron & Gangulay (1964).

Coelho (1955) observed that lesions produced by ova are primarily endovascular and both Bogliolo (1957) in human material, and Cheever (1961) from experimental animals, demonstrated the gross vascular lesions and subsequent anatomic disarrangement. Cheever (1961) believed that "obstruction of the small veins by granulomata appeared sufficient cause for portal hypertension". Several authors (Salomon et al., 1963; Cheever, 1961; Bogliolo, 1957; Aufses et al., 1959 and Rodriquez, 1955, amongst others) showed that the obstructive lesion due to bilharziasis was pre-sinusoidal in contrast to the post-sinusoidal lesions of true cirrhosis.

In the present study the only definite endovascular lesions observed were in the larger portal vessels. Either worms or ova were responsible. As stated earlier, past autopsy material revealed 2 cases with severe peri-pylephlebitis evoked by dead worms. One case (autopsy series) demonstrated granulomatous lesions around eggs on the endothelial surface of a large portal radicle (Figs. 120 & 121). However, this was the only such lesion encountered and it is believed that such lesions are rare.

In 2 biopsy cases, medium sized portal veins demonstrated an intense vasculitis (Figs. 118 & 119), one clearly

related/...

related to an embolic ovum (Fig. 118). A much more constant pattern was observed in the liver portal radicles. The pseudo-tuberculoid reaction had completely distorted the affected portal tract and it was impossible to identify the portal radicles in the smaller triads (Figs. 101 & 102). Whether the granuloma arose directly from an embolised vessel or immediately adjacent to it following escape of the egg, was not apparent. One feature which was conspicuous was the constant relationship of the granulomata to the portal radicles (Figs. 95, 98, 101 & 102). Contrary to the reports of Gelfand (1950) and Carter & Shaldon (1959) no ova or granulomata were demonstrable in the liver parenchyma or in relation to the central vein. Although from a random section a granuloma might appear to be situated in the parenchyma, serial sections always demonstrated their true relationship to the portal tracts. The proximity of these lesions to the portal radicles and the apparent inability to identify the fine portal radicles suggests that the granulomata, if not endovascular, are nevertheless sufficiently intimately related to them to produce the periphlebitic and subsequent perivascular fibrotic lesions.

ROLE OF TOXINS

Fairley (1920) from experimental evidence, and Dew (1923) from human studies, rejected the hypothesis that eggs were solely responsible for the severe pathology. They postulated that toxins liberated by adult worms were the most important factor.

Meleney *et al.* (1953) and Koppisch (1943) considered

that/...

that a toxic or allergic response to the presence of adult worms was not unlikely in the early stages of the infection. They were of the opinion, however, that it did not contribute significantly towards the late fibrosis. Similarly, Bogliolo (1957) and Warren (1961), although conceding that the possible role of a bilharzial toxin could not be excluded, stated that it was unimportant in the pathogenesis of hepatic fibrosis. Cameron & Ganguley (1964) demonstrated a tissue reaction evoked by subcutaneous injection of schistosome antigen but concluded that mature ova were the more important agents in the pathogenesis of hepatic fibrosis.

Damage to individual parenchymal cell has been described in the present liver biopsy studies. This was manifest as cloudy and feathery appearance of the cytoplasm, variation in size of nuclei, vacuolation of the nuclei and parenchymal cellular mitotic activity (Figs. 116 & 117). There was a constant relationship with the stage of hepatic disease, the changes being most prominent in the early acute stage. Only Gönnert (1955) from his experimental studies had described similar cellular changes.

As these cellular changes bore no relationship to the granulomatous lesions or the ova, they may have resulted from a bilharzial toxin. The role of such a toxin in promoting hepatic fibrosis, however, is doubtful.

Recently, Andrade et al. (1962), suggested that either a schistosomal toxin or an antigen-antibody reaction may be responsible for the progression of hepatic lesions after elimination of the active infection by treatment. To them the "piece-meal" focal necrosis described in hepatic bilharziasis,

also/...

also common in other types of cirrhosis, suggested an additional factor specific for bilharziasis. This specific factor, they believed, might be related directly to liver-cell breakdown probably due either to an antigen-antibody reaction in response to circulating antibodies or to a cell-bound immunity related to a delayed hypersensitivity as suggested by Burnet (1961).

In an earlier publication, Andrade et al. (1961) ploying the fluorescent-antibody test demonstrated schistosomal tibody in the reticulo-endothelial cells of the l ver and spleen. o explain the focal post-necrotic form of cirrhosis and active chronic hepatitis encountered in hepatic bilharziasis, they postulated that there may be an immunologic basis for the self-perpetuating hepatic lesions in schistosomiasis similar to that suggested in post-necrotic cirrhosis of unknown etiology.

Filho & Coutino-Abath (1961) also explained the progressive hepatic lesions and the splenomegaly on the basis of a greater immunologic response resulting in a marked mesenchymal activation. They considered that the splenomegaly was a result of a combination of reticulo-endothelial hyperplasia and secondary congestion. Pucci & Carvalhal (1958) considered that the pathogenesis was partly related to schistosomiasis and subsequent progressive changes depended on the same factors operative in other forms of cirrhosis.

Stirewalt (1963) has recently exhaustively reviewed the subject of immunity in schistosomiasis and demonstrated the wide possibilities in individual reactions to an identical stimulus.

ROLE/...

ROLE OF BILHARZIAL PIGMENT

Many investigators have commented on the presence of a specific pigment in hepatic bilharziasis. Fairley (1920) whose findings were confirmed by Koppisch (1943); Meleney et al. (1953); Johnson et al. (1954) and Hamilton et al. (1959), after special study, concluded that it could not be differentiated from malarial pigment.

The pigment is an excretory product of the worm and is believed to be a haematin compound. Early in the infection the pigment is found in Kupffer cells but later is present in the portal tracts both within cells and free in the tissue (Fairley, 1920). Meleney et al. (1953) observed that it did not appear to stimulate fibrosis or a cellular reaction.

Warren (1961) considered it insignificant in the production of hepatic fibrosis. Cameron & Gangulay (1964), by subcutaneous injection of acid haematin, demonstrated "a diffuse non-granulomatous cellular reaction, quite unlike that produced by adult parasites or ova".

Pigment was present in variable amounts in 88% of the liver biopsy series in the present study. It was less conspicuous in the autopsy studies especially in pure S. haematobium infections, but very prominent in the more severely infected group of S. mansoni (Fig. 109). From both studies it became apparent that the amount of pigment was related to the severity of the lesions and the presence of active infections. In common with the findings of other observers, it was quite obvious that the pigment itself stimulated no reaction. The presence of the pigment is useful in diagnosis if ova cannot be found in healing

granulomatous/...

granulomatous lesions. As Durban is now free of malaria, confusion with malarial pigment is unlikely.

ROLE OF DIET

Gelfand (1950) and Symmers (1951) believed that diet and not bilharziasis, was responsible for the cirrhosis. Ragheb (1956) reported that a high proportion of his cases suffered from hypoproteinaemia. Jaffe (1941) and Menendez (1958) also considered undernutrition an important factor in the pathogenesis. Popper & Schaffner (1957) emphasised the severe fatty changes accompanying some cases of hepatic bilharziasis.

Carter & Shaldon (1959) and Hamilton et al. (1959) demonstrated all grades of hepatic involvement in the absence of undernutrition, whilst Warren (1964) from experimental evidence, demonstrated that diet was unimportant for the subsequent development of fibrosis in hepatic bilharziasis.

In the present study, none of the clinical group had gross evidence of undernutrition. Neither the liver biopsies nor the autopsy sections showed fatty degeneration. If diet plays any part in the genesis of the late lesions, it would appear to be insignificant and indirect.

SUMMARY/...

SUMMARY.

(1) The problem of hepatic bilharziasis was investigated in 2 groups of cases:

i) Liver biopsy studies on 25 clinical cases;
ii) Autopsy studies of liver sections from 50 autopsy cases.

(2) The clinical, histopathological and morbid anatomical features have been presented and examined critically in the light of reports from other endemic areas of bilharziasis.

(3) The genesis of the pseudo-tubercle and the progressive stages of hepatic involvement culminating in pipe-stem portal fibrosis have been demonstrated. A simplified classification of the hepatic changes has been presented and it has been shown that the basic pathology is unaltered in apparently different froms described by previous authors.

(4) While it is probable that a single agent in itself may not produce the entire pathology, a combination of all or some of the factors must undoubtedly be operative. This study has revealed, however, that S. mansoni is a more potent agent than S. haematobium in promoting hepatic pathology. A probable reason has been postulated.

(5) Individual liver parenchymal cellular damage, not previously described in human schistosomiasis, was a constant feature in biopsy studies. It is postulated that this is indicative of a circulating bilharzial toxin.

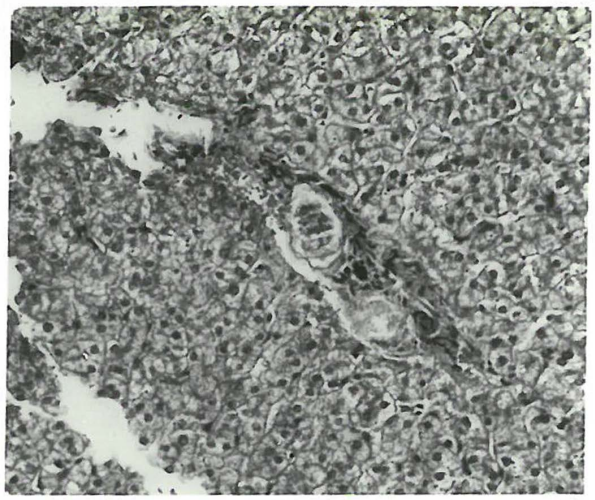
(6)/...

(6) It has been demonstrated that the extent of eosinophilia and evidence of parenchymal cellular damage may be employed as an index of the age of the lesions.

(7) The pathogenesis of Hepatic Bilharzial Fibrosis has been critically examined in the light of the present study.

(8) The present study has revealed the hitherto unrecognized fact that in South Africa the severity of the hepatic pathology due to S. mansoni is such as may well lead to pipe-stem portal fibrosis.

CHAPTER VIII/...



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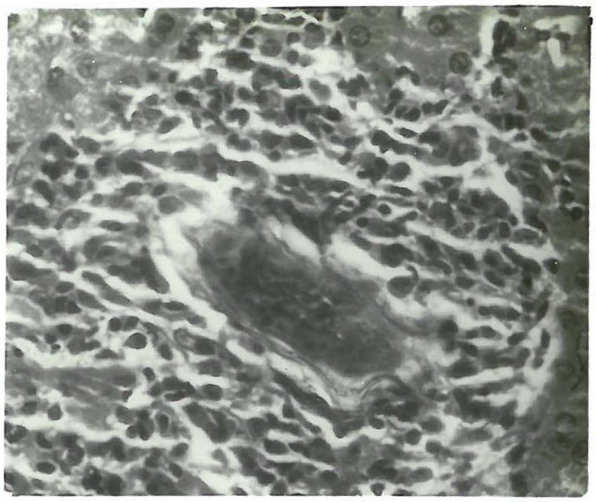

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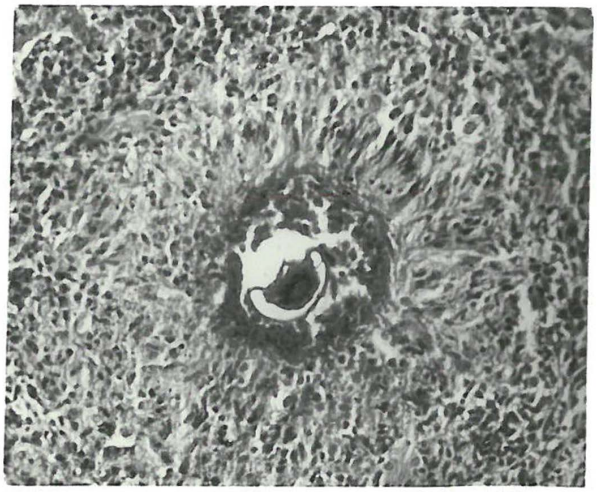

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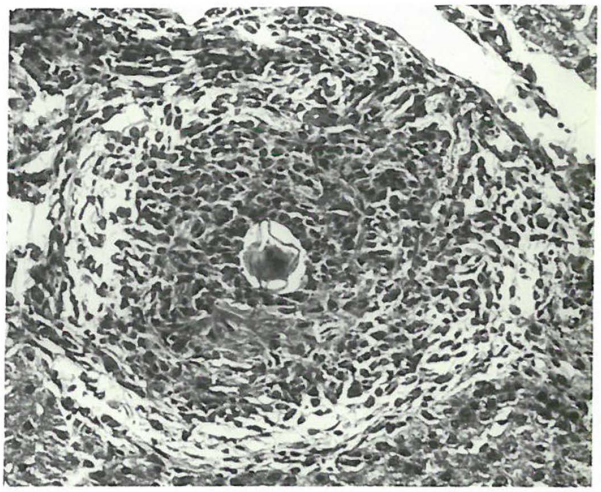

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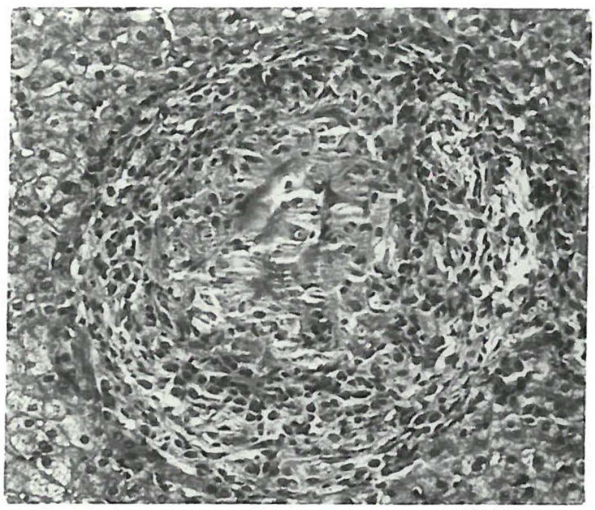

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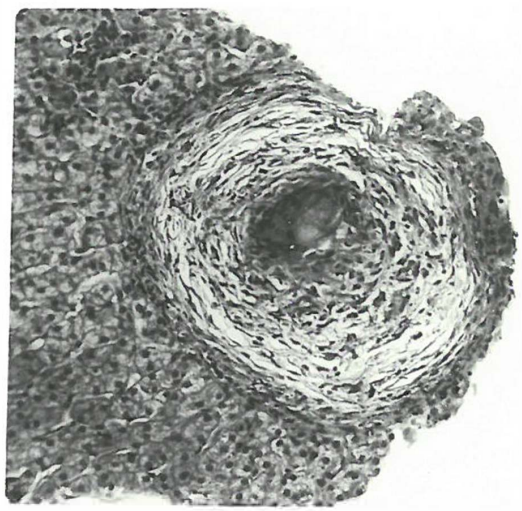

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PLATE XVIII

Fig. 98 The late stage of the pseudotubercle with a giant cell engulfing the egg remnants and prominent fibroblastic response with mature collagen being laid down and merging with the portal tract (left upper).
Liver biopsy : HE x 125

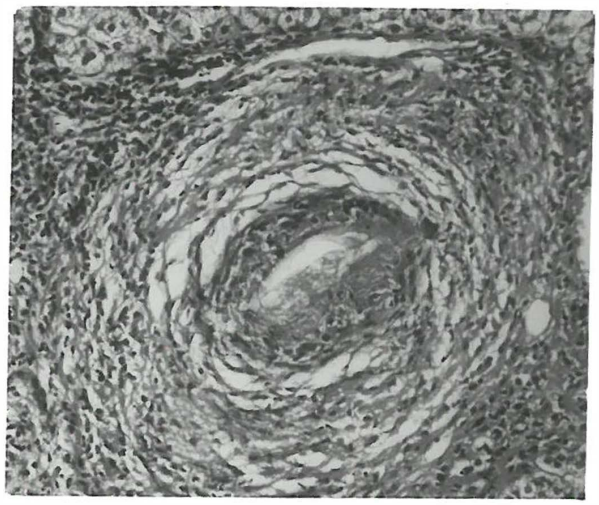
Fig. 99 Reveals the final stages in the evolution of the pseudotubercle - a late fibrotic pseudotubercle (right middle) with concentric layers of fibroblasts and complete absence of inflammatory infiltrate; and a healed hyalinised pseudotubercle (upper left) with no inflammatory response. The relation of the pseudotubercles to the portal tract is evident. Liver biopsy : HE x 125

Fig. 100 Reveals the earliest stage of portal tract involvement (Stage I) with widening due to preominant cellular infiltrate. Liver biopsy : HE x 125.

Fig. 101 Stage II : Widening of the portal tract (left) due to inflammatory cellular infiltrate, pigment and fibroblastic reaction, and an associated bilharzial granuloma (right). Liver biopsy : HE x 125

Fig. 102 Stage II : Distortion and widening of a portal tract with a subacute granuloma merging with the fibroblastic proliferation in the tract. Liver biopsy : HE x 125

Fig. 103 Stage III, grade (i) : Established portal fibrosis with deposition of mature collagen. A healing pseudotubercle is evident (upper left). Liver biopsy : HE x 50



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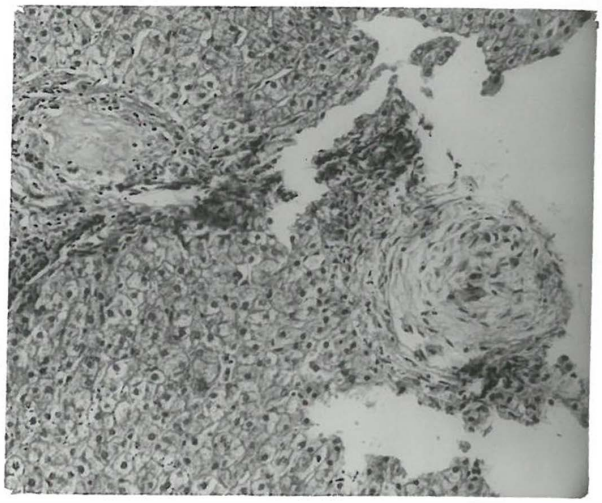

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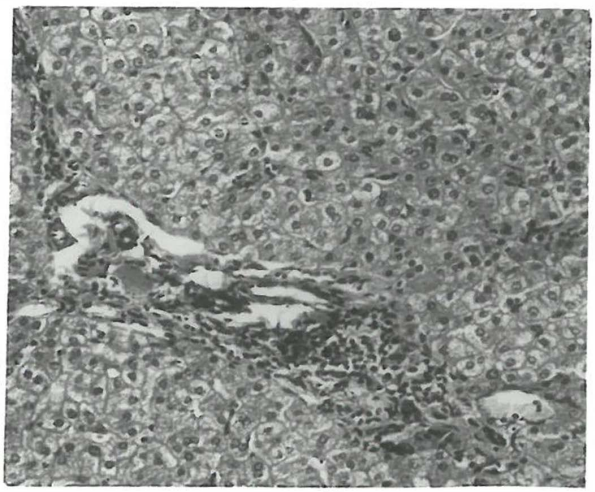

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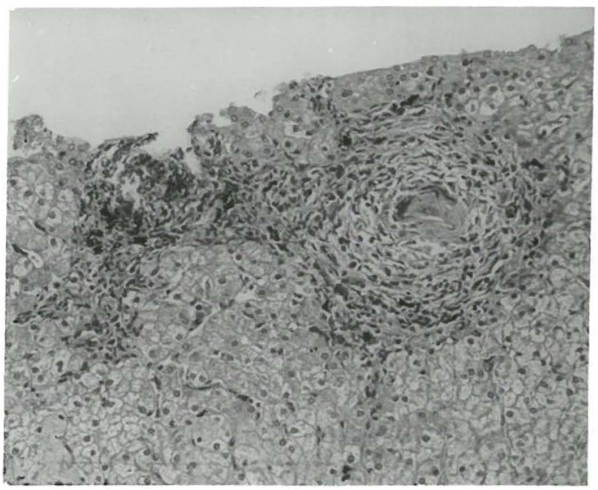

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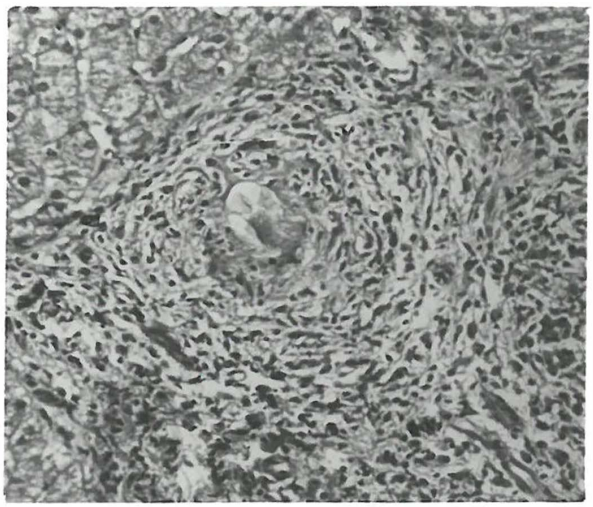

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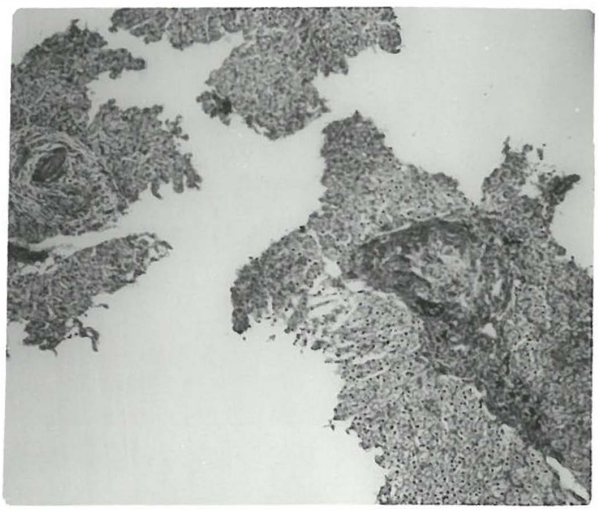

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PLATE XIX

Fig. 104 Stage III, grade (i) : Established portal fibrosis. There is marked distortion of the portal tracts by bilharzial granulation tissue. Liver biopsy : HE x 50

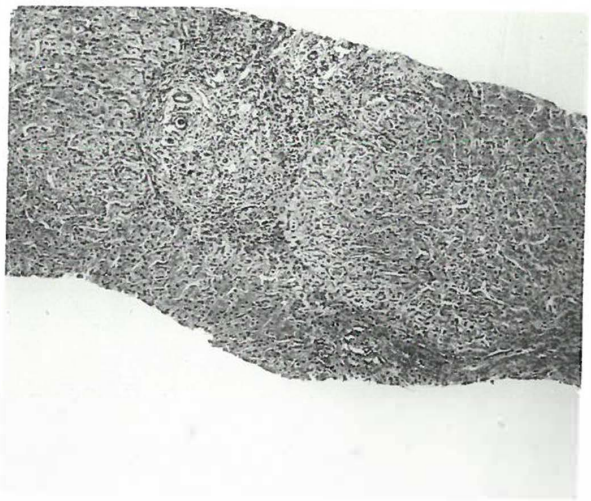
Fig. 105 Same case as Fig. 104, with a reticulum stain to demonstrate the distortion of the portal tracts. Liver biopsy : Retic x 50

Fig. 106 Another example of a Stage III, grade (i) with pronounced widening of the portal tracts by granulation tissue. Liver biopsy : HE x 50

Fig. 107 Reveals late fibrosis (Stage III, grade (i)) with septation and pseudolobulation. Fibrous tissue predominates in the portal tracts. Liver biopsy : EVG x 50

Fig. 108 Acute miliary hepatic bilharziasis with numerous pseudotubercles and linkage of the portal tracts producing a pattern of pseudo-septation. Autopsy specimen : HE x 20

Fig. 109 A later stage (Stage III, grade (i)) with widening of portal tracts due to fibrosis. Healing pseudotubercles and prominent bilharzial pigment can be seen. Autopsy specimen : HE x 20



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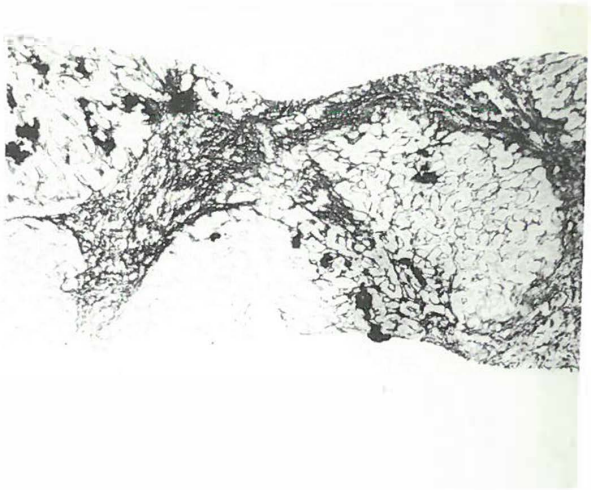

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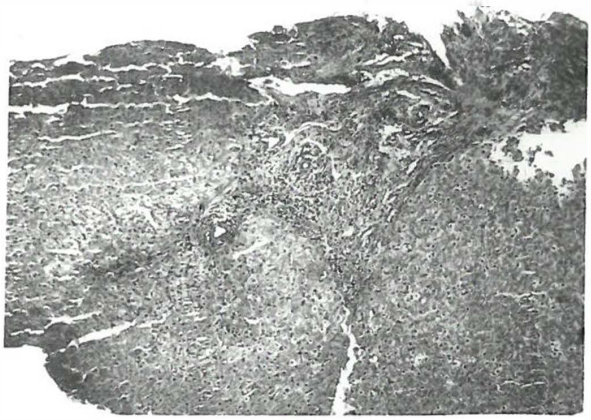

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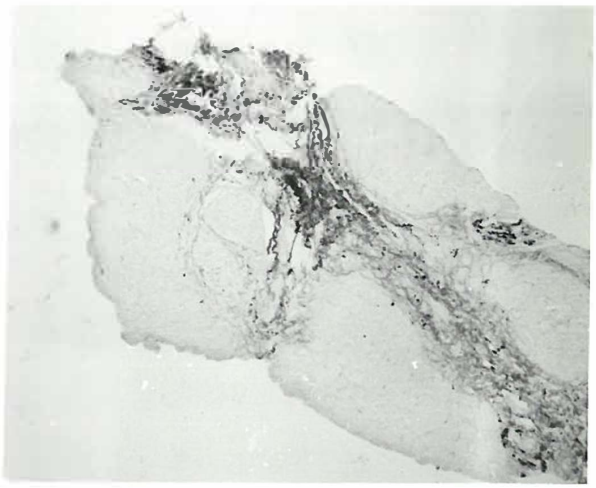

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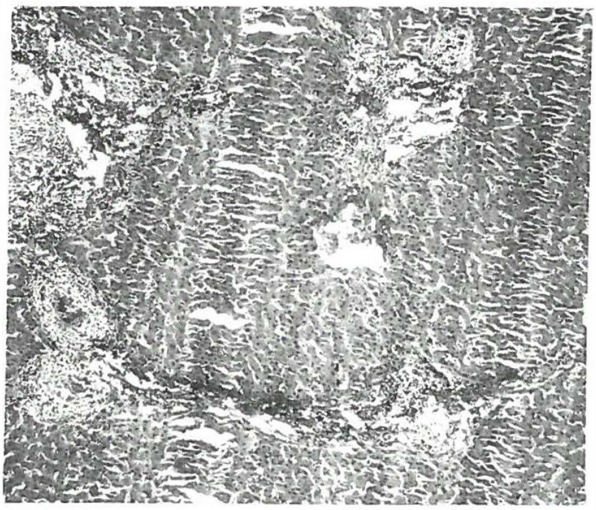

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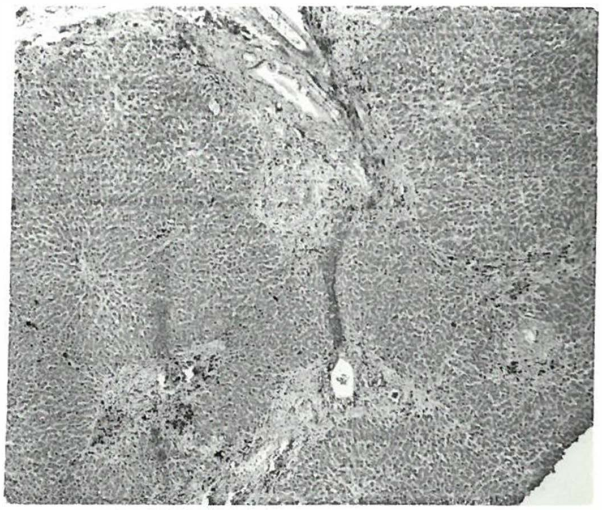

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PLATE XX

Fig 110 Stage III; grade (ii) : Pipe-stem fibrosis with marked widening of portal tracts due to collagen deposition. There is minimal inflammatory response. An active pseudotubercle is evident in the upper middle field.
Autopsy specimen : HE x 20

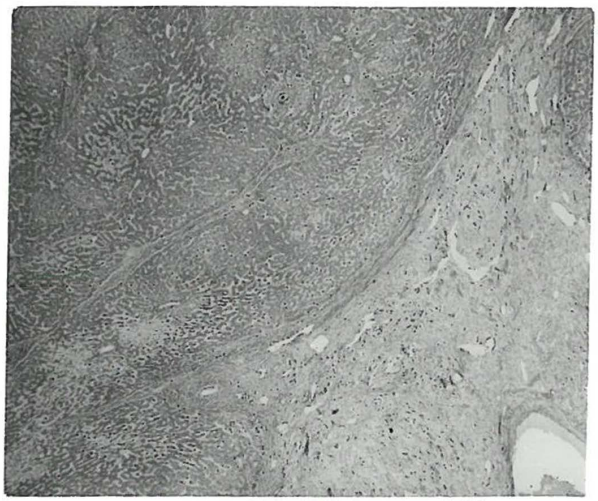
Fig. 111 An example of late pipe-stem cirrhosis, Stage III, grade (iii). (Reported earlier - Bhagwadeen, 1964).

Fig. 112 A viable worm (? immature) in the central vein with no inflammatory reaction. Autopsy specimen : HE x 50

Fig. 113 A recently dead worm surrounded by polymorphs and eosinophils and producing an endophlebitis.
Autopsy specimen : HE x 75

Fig. 114 A later stage of a worm lesion with severe thrombo-periphlebitis. The surrounding hepatocellular damage is apparent. Autopsy specimen : HE x 50

Fig. 115 The late stage with eosinophil necrosis involving the portal vein and spreading in the portal tract. The pronounced fibroblastic reaction in the portal tract is evident. Autopsy specimen : HE x 50



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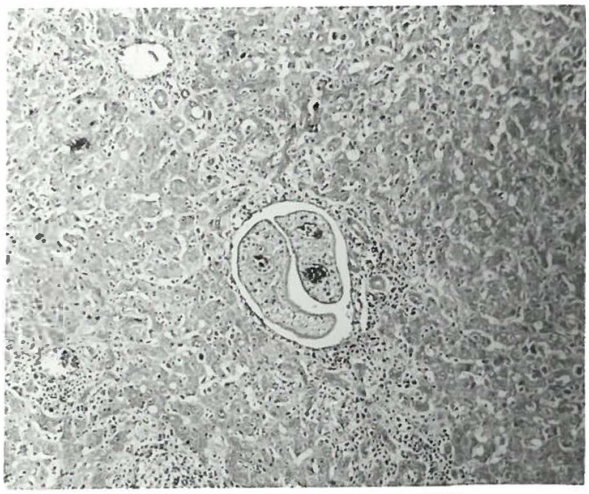

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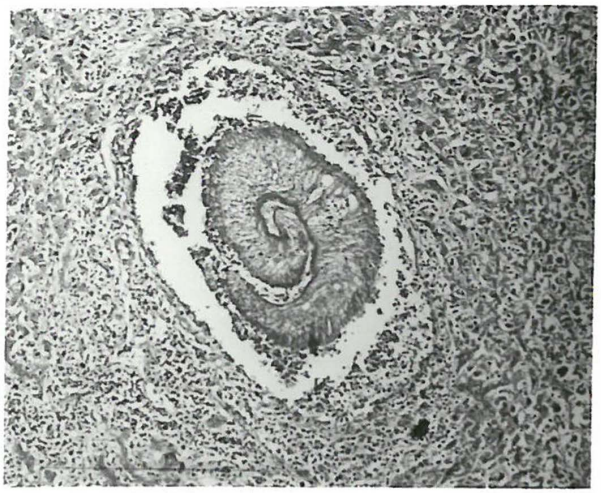

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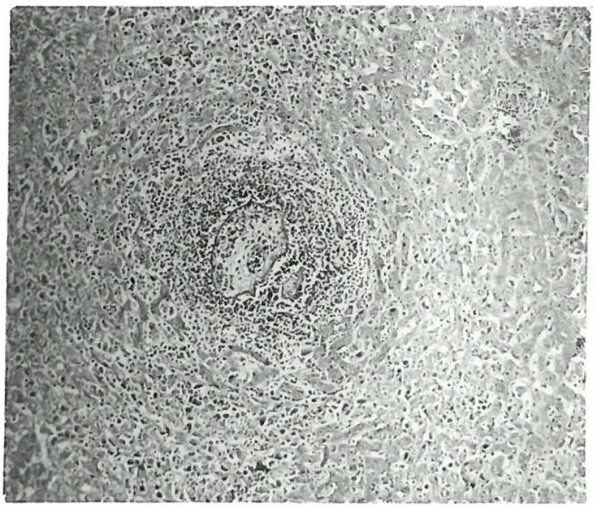

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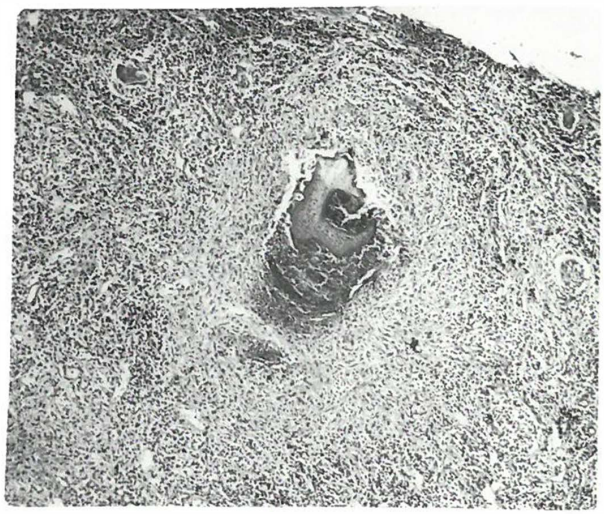

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PLATE XXI

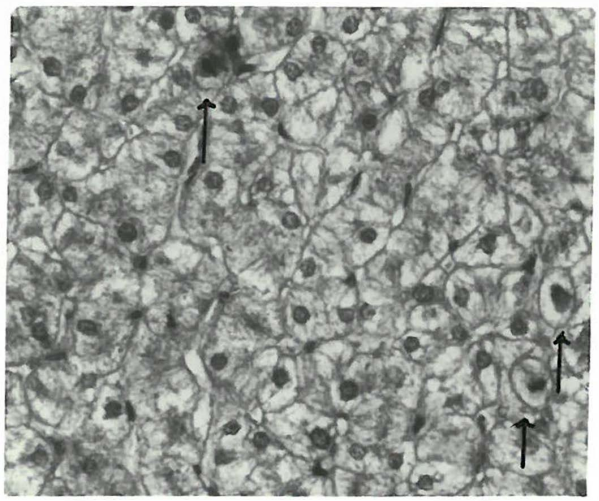
Fig. 116 117 Liver parenchymal cellular damage with hepatic bilharziasis. Vacuolation and variation of nucleii is evident in fig. 117. Both figures show evidence of mitotic activity (arrows) and the feathery nature of the cells is evident. Liver biopsies : HE x 50

Fig. 118 Medium sized portal vein demonstrates vasculitis associated with an ovum imbedded in the endothelium. The normal anatomical relationships of the wall have been completely destroyed. Liver biopsy : HE x 50

Fig. 119 Another medium sized portal vessel showing destruction of the normal relationships and severe narrowing of the lumen. The perivascular inflammatory reaction is evident. Liver biopsy : HE x 125

Fig. 120 Reveals several endovascular granulomata in a large portal radicle. An ovum in the centre of one of the granulomata can be clearly seen.
Autopsy specimen : HE x 50

Fig. 121 A high power view of the same case to show the endovascular granuloma and its relationship with the endothelium. The narrowing of the vessel lumen is evident. HE x 125



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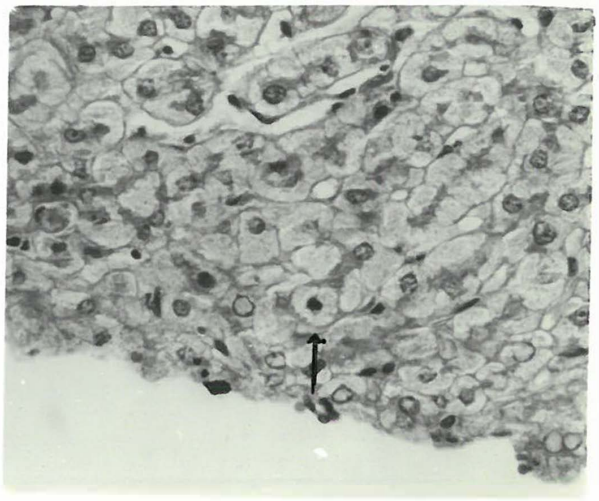

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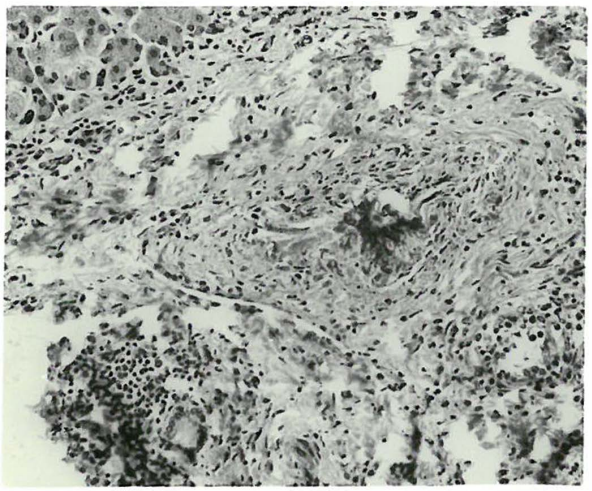

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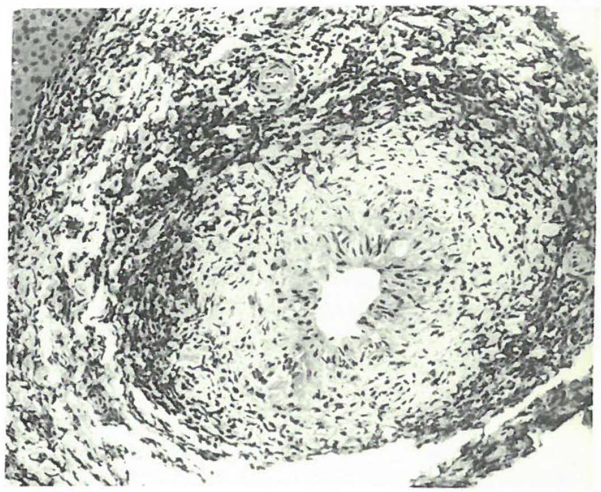

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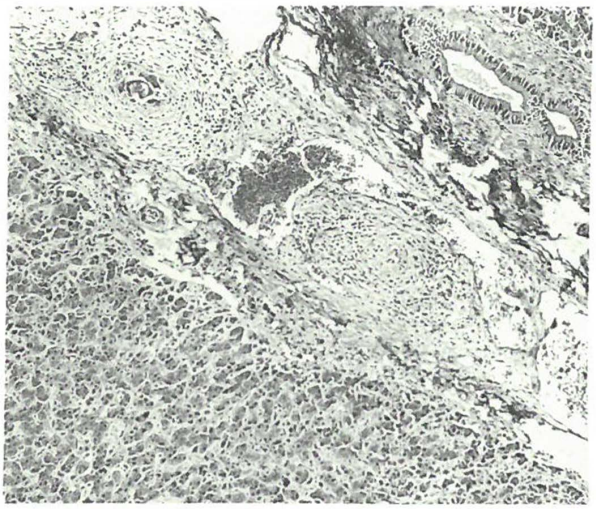

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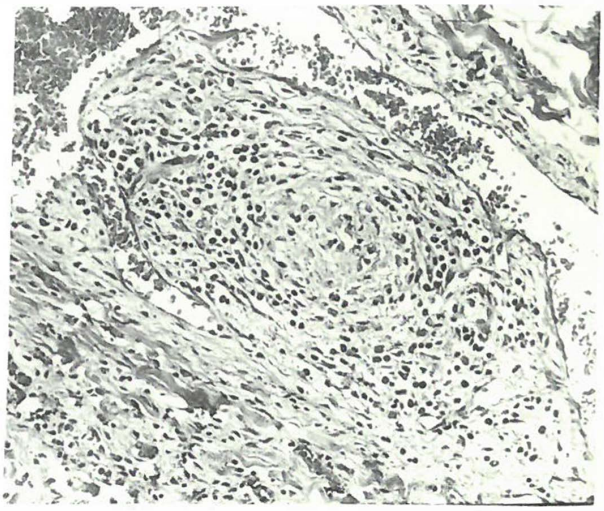

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CHAPTER VIII

R E S U M E

The aims of the author were set out in the introduction to this thesis. These were firstly, to demonstrate the clinico-pathological manifestations of Bilharziasis in the Durban Indian and African and secondly, to examine the validity of the, not infrequently contrasting, opinions expressed by previous workers both at home and in other endemic areas.

Durban, as has been confirmed in this study, is an endemic area of both S. haematobium and S. mansoni. Previous workers have reported conflicting incidences for S. haematobium in this area (Dormer, 1948 - 10%; Freedman & Elsdon-Dew, 1958 - 50% and Elsdon-Dew, 1962 - approximately 100%). However, most of these reports were based on inadequate sampling and no systemic survey has been previously conducted to assess the prevalence of Bilharziasis.

Employing various techniques in autopsy and clinical material to demonstrate ova (the only absolute criterion for diagnosis), the incidence of S. haematobium in the present study was found to be of the order of 30% in both African and Indian.

Similarly, in contrast to previous reports (Bates & Alberto, 1952 - 1-3% and Schneider, 1958 - 11-15%), the present study revealed that the incidence of S. mansoni in both races was approximately 10%.

Whereas/...

Whereas Pitchford (1959b) reported a high incidence of human infection with the cattle schistosome S. mattheei in focal areas of the Transvaal, this study revealed that though present in the Durban Indian and Africa, this zoonosis is insignificant.

Although the protean manifestations of Bilharziasis soon became evident, in this thesis attention was focused on the primary site of bilharzial involvement of each species - ureterovesical for S. haematobium and intestinal for S. mansoni. Furthermore, for each species, one of the most dreaded and perhaps the most controversial late complication was investigated. For S. haematobium this was vesical carcinoma, and for S. mansoni hepatic portal fibrosis.

By determining the load of infection in autopsy material and from the clinical presentation it became apparent that, unlike the reports from Egypt and Mozambique (both hyperendemic areas of S. haematobium), vesical bilharziasis in the Durban African and Indian is generally mild or only moderately severe. Although the Katayama syndrome has been described in European patients (Lurie, 1953; Walt, 1954) it was not encountered in this study. The majority of patients presented with terminal haematuria.

Haematological investigations in active urinary and intestinal bilharziasis revealed a constant eosinophilia. Urinary examination revealed that secondary bacterial cystitis in acute and even in chronic cases, is rare. Differential cell counts of the urinary sediment confirmed the observations of Fairley (1919) and Hutchison (1928) that eosinophils make up the bulk of the "pus cells". This fact has not, generally, been appreciated. Patients with active Bilharziasis were shown

to/...

to have a raised serum gamma-globulin and a corresponding decrease in the serum albumin. Although Egyptian workers have reported similar changes in hepatic bilharziasis and some workers have made similar observations in experimental animal infections, previous literature from South African workers on this aspect of clinical investigation was not available. The present findings demonstrate the need for further investigations of serum protein derangement in Bilharziasis and its probable relationship to the immune response.

A simplified classification of the bladder lesions has been advocated and the nature of the vesical lesions, by correlation of the cystoscopic, cystogram, morbid pathological and histopathological appearances, has been described. It has been shown that active proliferative granulomata are the earliest stage of manifestation of severe vesical Bilharziasis. It has also been shown that these lesions may be revealed on cystogram as filling defects. The sandy patch, composed of myriads of calcified ova, has been shown to be the end stage of a burnt-out bilharzial lesion and is evident on scout x-ray film as linear calcification of the bladder. The incidence of bladder calcification was found to be higher in the African than the Indian and it has been postulated that in the African this reflects either the more prolonged exposure to S. haematobium infection or their later presentation in hospital.

In contrast to the reports from Egypt, the late complications of fibrotic contracted bladder, chronic penetrating bladder ulceration and bladder-neck obstruction were never encountered in the present study.

This study has demonstrated that the ureters are both

more/...

more commonly and more severely affected in all stages of Bilharziasis than hitherto believed. I.V.P. studies in acute vesical bilharziasis revealed the astonishing finding that no less than 40% have detectable ureteric abnormalities while autopsy studies have shown that approximately 70% of cases with vesical bilharziasis have ureteric involvement. Though most authors generally regard ureteric pathology as a late complication of vesical bilharziasis, this study has revealed that even in the earliest stages, it is an integral part of vesical bilharziasis. Histopathology has revealed that, due to the delicate structure of the ureter, bilharzial involvement produces permanent pathological alterations. In contrast with the experience of Kark (1960) and Chapman (1964) no racial difference in ureteric pathology was demonstrable.

It must be emphasised that this study was based on patients with active, acute symptoms of bilharziasis and the apparently less severe lesions do not necessaily hold true for the late, chronic stage of the disease. Both Kark (1960) and Chapman (1964) have emphasised the late manifestations of ureteric bilharzial disease. What was surprising in this study, was the high incidence of severe ureteric lesions in apparently recent S. haematobium infections. The pathogenesis of the ureteric manifestations has been discussed and its significance in management of cases emphasised.

The present study revealed that the incidence of carcinoma of the bladder in the Durban African and Indian was probably no higher than that of non-bilharzial areas. However, there was a significant difference in the pattern of pathology in bilharzial and non-bilharzial areas. The Durban African

pattern/...

pattern conforms with that reported from Egypt in that a younger age group is affected; the incidence of concomitant bilharzial infection is high and squamous carcinoma is the predominant histological type. The pattern in the Indian is less definite, occupying a midposition between the African and European.

The pathogenesis of bladder cancer in relation to Bilharziasis has been examined and the aetiological importance of Bilharziasis discussed. It has been suggested that though no definite causal link has been proven, bilharziasis may, by initiating stasis and secondary infection with the resultant release of urinary carcinogens, act as a promoting agent.

In contrast to reports from Egypt and South America, the clinical manifestations of intestinal bilharziasis in Durban are generally mild. Occasionally, as was illustrated in this work, severe dysenteriform manifestations may become evident and terminate fatally. The role of S. haematobium in producing bowel pathology was found to be negligible.

Histopathology revealed the probable mechanism of escape of the ova into the bowel lumen. It has been postulated that only those ova laid directly in the mucosal epithelium subsequently escape while ova deposited in the submucosa and muscle layers become trapped and evoke the typical pseudo-tuberculoid reaction.

This study revealed that the incidence of severe intestinal pathology in the form of bilharzial polyposis, pericolitis, pericolonic abscesses and fistulae, apparently common in Egypt and South America, was insignificant in Durban African and Indian. However, liver biopsy and autopsy liver

studies/...

studies revealed that the apparent mildness of asymptomatic S. mansoni infections did not preclude visceral involvement.

Surprisingly, liver pathology, from biopsy and autopsy studies, was found to be both common and severe. It became obvious from this study that just as ureteric involvement is an integral part of vesical bilharziasis (S. haematobium), so liver involvement is a primary manifestation of intestinal bilharziasis (S. mansoni).

The genesis and progression of the hepatic lesions have been described sequentially from the earliest stage of Miliary Hepatic Bilharziasis to the late stage of Symmers' pipe-stem fibrosis. A simplified classification of Hepatic Bilharziasis has been advocated and it has been suggested that the term Miliary Hepatic Bilharziasis be used to indicate the early stage of granulomatous lesions in the liver. In the liver biopsy series, an interesting observation previously only reported by Gonnert (1955) in experimental hepatic bilharziasis but never described in human hepatic lesions, was the evidence of damage to individual parenchymal cells, occurring predominantly at the stage of Miliary Hepatic Bilharziasis. This, together with the degree of eosinophil cellular infiltrate, may be employed as an index of the age of the lesions. On the evidence of parenchymal cellular damage, a circulating humoral bilharzial toxin has been postulated. This toxin may produce hepatic dysfunction, but its role in the eventual portal fibrosis is uncertain and probably minor.

In comparison with reports from Egypt and South America, the incidence of Symmers' pipe-stem portal fibrosis in

the/...

the Durban Indian and African is uncommon. Although occasional cases have been encountered previously (Bhagwandeen, 1964), the syndrome of "Egyptian splenomegaly" was not encountered in the present study. It has been shown that the incidence of S. mansoni is comparatively low (10%) and the infections usually mild. The apparent discrepancy in the Egyptian and Durban liver pathology is, therefore, not surprising. It is to be feared, however, that with the lack of awareness of the severe visceral pathology and the laissez faire attitude towards public health measures, especially with the introduction of vast water conservation schemes, S. mansoni may become more prevalent and repeated heavy infections more frequent. Under these circumstances the pattern of pathology must inexorably progress towards the grosser forms as reported in Egypt and South America.

Hepatic Bilharziasis as a clinical entity, has not previously received serious consideration in Durban, or for that matter, in South Africa generally. This study demonstrates the need for further investigations of hepatic bilharziasis in other endemic areas of S. mansoni in South Africa.

From time to time different observers (Pijper, 1934; Adams, 1957; and Elsdon-Dew, 1958 and 1962) have commented on the apparent benignity of bilharziasis in South African and particularly in Durban. From this study has emerged the startling fact that both urinary and intestinal bilharziasis have a high morbidity and that ureteric (S. haematobium) and hepatic (S. mansoni) damage is not only common but is often severe.

This study has demonstrated the need for a new appraisal of bilharziasis and its long term sequelae in the individual and the community, in Durban and in South Africa.

It/...

It has demonstrated the necessity for investigating aspects of human tolerance, immunity, both acquired and induced, and the whole concept of host-parasite relationships. To reiterate the words of Jackson (1958):

> "An attitude of laissez-faire or tolerance of the disease and its effects, on the evidence available, is a dangerous policy to adopt".

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