SCHISTOSOMIASIS OF THE APPENDIX WITH SPECIAL REFERENCE TO INFESTATION WITH S. HAEMATOBIOUM.

A. W. ROSE.

M.B., Ch.B., D.T.M & H.

m. d. 1936.
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SECTION I.

Introduction.

Bilharzial involvement of the appendix is accorded recognition as a clinical and pathological entity by the majority of authors in well known text books on Tropical Medicine, notably Manson's Tropical Diseases, Stitt's Tropical Diseases, and Madden's Surgery of Egypt. On the whole, however, it may be said that very little information is to be gained on this subject by consulting these authorities. As a rule, only a passing reference is made to the condition, or it may be an example is quoted which has come under the author's personal observation, but rarely does the description run to more than a few lines, and seldom, if ever, are the lesions or the histopathology described in any great detail.

Madden (1), for example, deals in a most painstaking manner and at great length with the general and regional findings in Schistosomiasis from the clinical and pathological stand-points, but the only reference to involvement of the appendix given by him is as follows:-

"Sometimes the appendix with the Meso-appendix is affected and included in one large mass with the caecum, and all the adjoining structures; but it may also be the seat of a severe Bilharzial infection on its own account,
and give rise to symptoms of chronic appendicitis, or even form abscesses, presenting anteriorly or in the loin behind the caecum, if the appendix is retrocaecally placed."

As in the above instance Bilharzial appendicitis, when mentioned, is usually included among the lesions due to S. Mansoni, and in certain instances S. Mansoni is specifically incriminated.

The above remarks appear to apply in some degree also to literature devoted exclusively to recording most able and comprehensive investigations of the clinical, pathological, and experimental aspects of Schistosomiasis in man and animals.

Dew (2) in an exhaustive enquiry into the pathology of human Schistosomiasis in general, emphasises the relative frequency with which ureters, appendix, and pancreas are affected, and gives the fullest account of the condition so far encountered. In his own words, "S. Mansoni not infrequently causes lesions of the Vermiform Appendix. The ova are deposited in the Sub-mucosa, and Subperitoneal zone: fibrosis appearst to be the rule; the whole wall is thickened, and often kinked. Papilloma formation has not been noted, but the mucosa is greatly thickened, and verrucose, the lumen, as a result, being partially or totally occluded, while subperitoneal nodules and fibrosis are common. In one interesting case a sinus in the right Iliac fossa led to a Bilharzial appendix with surrounding granulation tissue."
Barsoum (3) has recently published a communication on the subject of the Bilharzial appendix, in which, after emphasising the frequency with which it harbours ova, he concludes that Bilharzia does not cause, or even predispose to appendicitis, and is merely an accidental concomitant; but it appears that by appendicitis he means what, for lack of a better term, may be defined as bacteriologically infective appendicitis. He also observes that the Bilharzial infection may be diffuse, or it may take the form of small subperitoneal nodules (Bilharziomes); but no histopathological details are included in his article.

Fairley (4), in a comparative study of experimental Bilharziasis in monkeys, contrasted with hitherto described lesions in man, when referring to Bilharzial pericolitis with subserous tubercles, observes that "these characteristic lesions which are so frequent in experimentally infected monkeys, do not appear to have been recorded in man."......"Recently also I have seen a case, with Dr. F. C. Madden, in an appendix removed from a hernial sac. In this case Bilharzial ova were found. The probable reason why this condition has not been more commonly recorded ...... not being a fatal disease at this early stage, very few cases come to autopsy save by accident, or when they do so, their real nature is not appreciated."

To sum up, therefore, it seems quite fair to deduce:—

(a) The term Bilharzial appendicitis is widely
recognised, but as a rule only brief reference is made to it in the literature.

(b) Macroscopic lesions of the appendix due to Bilharzia are reported, but the histopathology of the condition is seldom described or illustrated in detail, and can only be deduced by inference.

(c) In consequence, confusion sometimes arises as to the exact nature of the term Bilharzial appendicitis.

(d) Usually the infecting agent is designated, or assumed to be S. Mansoni, and if S. Haematobium has here-tofore been frequently incriminated, the fact has not received sufficient emphasis.

In the following communication, the macroscopic and microscopic findings in a series of appendices removed at operation are described, discussed, illustrated, and contrasted with a series in which no ova could be detected. In all but one of these thirty-five cases, the patients were found to be excreting terminal spined ova in the urine.

It is with the aforementioned deductions in mind that one ventures to hope that this account may not only serve to confirm our present knowledge, but even to amplify it.
SECTION 2.

Selected details of the Helminthology, and Pathology, of Schistosomiasis as hitherto described.

From time to time, it will be necessary to discuss certain questions that arise in the light of our present day knowledge of Schistosomiasis, and it is well, therefore, at this stage to review briefly in this connection the outstanding views held to-day of the Helminthology, Symptomatology, and Pathology of the subject. In Africa man is the definitive host of two species of Schistosoma, namely S. Haematobium and S. Mansoni. In the extra-corporeal, or intermediate phase of their life histories, they inhabit certain types of snail, notably Bullinus and Planorbis.

The eggs, terminal spined in the case of Haematobium and lateral spined in the case of Mansoni, are passed by man in his excreta, and for further development must rapidly find themselves in water inhabited by a suitable species of snail. The eggs hatch out in water, and the larval, or miracidial form enters the snail.

After a period of development during which multiplication occurs, the fully developed or infective (to man) form emerges in large numbers from the snail. These are the forked tailed cercariae, which swim about actively, and for development to adult state must rapidly penetrate the skin or upper alimentary tract of man. In doing this they shed their tails, and entering the vascular system are carried to the liver where they are carried to the
Portal vessels. On reaching maturity the sexes pair off, and the female is carried in the gynecophoric canal of the male. The female is longer and more slender than the male, and in the case of S. Haematobium her measurements are stated to be $2\frac{1}{2}$ cms. in length and 0.25 mms. in width.

In the case of S. Mansoni the worms do not migrate from the liver until they are completely mature, and the female has commenced to lay her eggs, and as a result lateral spined ova are often found in the liver which are judged to have been laid there by the worm, and not to have been carried in from a distance.

S. Haematobium, however, leaves the liver for its site of election before the female is completely mature, and proceeds to the Vesical and Pelvic plexuses by way of the Mesenteric and Inferior Haemorrhoidal veins. En route, the female may deposit some of her ova in the intestinal veins, and this is a possible explanation of the following facts which are not infrequently noted, namely, that terminal spined ova may be found in the stool before they are present in the urine, and that mucoid diarrhoea is an early symptom of vesical Schistosomiasis in a certain proportion of cases.

The worms are found lying in copula in the veins of their chosen habitat, and may be seen in the larger vessels of the Submucosa and Subserosa in sections of the viscus. When she desires to oviposit the female is stated to leave the male, and to advance as far as she is
able down the narrowing venule against the blood stream. In doing this she stretches the wall of the vessel, and finally blocks the lumen completely, causing cessation of the blood flow through that particular vein. She then lays her eggs in a row within the vessel; they may number up to twenty in the case of Haematobium, and are deposited in the following manner: an egg is ejected from the genital pore which lies just behind the ventral sucker, with the spine pointing in the direction of the blood stream. The worm then retires down the vein a short distance and repeats this manoeuvre, until a line of eggs up to twenty in number are lying within the vessel lumen.

As the worm recedes, the vessel wall stretched a moment before to its utmost limit, contracts down upon the egg which has just been deposited.

The final result can be easily pictured; a line of eggs resembling a string of sausages, with the vessel wall representing the skin of the sausage. In addition, the retirement of the female to a wider part of the vein relieves the obstruction to the venous flow, and the returning blood stream impinging on the blunt extremities of the ova alters their axes, and causes the spines to engage in the wall of the vessel, eventually effecting rupture of the latter, and extrusion of the ova into the surrounding tissues. The eventual journey of the ovum through the tissues to the internal surface of the organ, and to freedom, is said to depend not so much on the
presence of the spine in the shell, as on the mobility common to all foreign bodies in a like situation, and to an ill comprehended principle which orders its course. Surprising as it may seem, there is very little evidence to show that the worm itself causes any damage to the vessel wall which might result in thrombosis.

That the worm produces a toxin, or products of metabolism which can act as toxins seems fairly clear; as evidence of this we may quote firstly, the early general symptoms and signs such as headache, pyrexia, urticaria etc., which are so commonly manifest; secondly, the almost inevitable increase of the polymorphonuclear eosinophil leucocytes in the blood, and a similar increase of these and the eosinophil myelocytes in the bone marrow; thirdly, the Fairley complement deviation test, and intradermal skin test, demonstrating the existence of circulating antibodies specific for this group of helminths.

A detailed account of the general pathology of Bilharziasis would be both tedious and irrelevant, and it is only necessary to consider data which it is felt have a definite bearing on the work in hand.

Attention will therefore be focussed on lesions of the colon, and in this connection the work of Fairley (4) and Dew (2), will be freely quoted, and at some length, to allow of subsequent comparison with one's own findings.

Fairley (4), in contrasting the lesions occurring
in man with those obtained experimentally in monkeys, showed that there were many points of similarity, and that the following main types of lesion of the colon were common to both.

1. Pericolitis with subserous tubercles.
2. Acute Bilharzial dysentery.
3. Pseudopapillomata.

As quoted previously he found, however, that a type of lesion very characteristic of the monkey infection was but rarely recorded in man, namely pericolitis with subserous tubercles. In describing his experimental work on monkeys the lesions associated with the appendix have been mentioned previously, and in addition he makes the following interesting observations:

1. "..... terminal spined ova could be demonstrated earlier in the faeces than in the urine."
2. "Large numbers of S. Haematobium ova were constantly found in the liver, small and large bowel....."
3. "..... a definite relationship exists between the production of macroscopic lesions in the viscera, and the quantitative distribution of ova in these situations."
4. "The chief factor determining focal distribution of ova in any organ is the anatomical distribution of the blood supply, and the calibre and elasticity of its vessels."
5. "In the hollow viscera such as the intestine ..... ova and worms are generally located in the submucous and peritoneal zones, while muscular layers are unaffected."
Occasionally ova may be seen between the circular and longitudinal muscle coats, and then always in the intermuscular fibrous tissue.

6. (Under Pathology of the large intestine) "Plastic peritonitis may occur. Tubercles are scattered on the free surface."

Dew (2) sums up the lesions of the colon in humans under the headings:

1. "Subacute dysenteric condition. The ova have been deposited in the submucosa and have not been aggregated into macroscopic foci."

2. "Pedunculated papillomata."

3. "Sloughing and ulceration."

4. "Large pericolonic inflammatory masses."
The Pseudo-Tubercle.

The Histopathology of this characteristic structure was first described in detail by Fairley (4) when recording his experimental work on monkeys. It is quite clear that he also recognised its existence in human cases. Three years later a similar account was published by Dew (2) in connection with the pathology of human Schistosomiasis under the sub-title "General Pathology". Their respective descriptions and conclusions may be summarised as follows:-

FAIRLEY (4)

It is formed within three months in heavily infected monkeys - size 0.5 to 4 mms. - in the centre one or more ova with terminal or lateral spines and crenated chitinous shells and contained miracidia - giant cell or plasmodial mass tending to develop ova found at this early stage - surrounding them a zone of the eosinophil cells - more peripherally zone of mononuclears - due to crowding and absorption of toxins, degeneration of central eosinophils - central amorphus mass with scattered pyknotic nuclei results - reparative changes with encircling fibroblasts and linear capillaries - eosinophils decrease and disappear leaving mononuclears - changes coincide with the passage of ova containing live miracidia which either escape almost immediately or becoming imprisoned in fibrous tissue, die - the late degenerative changes in the Bilharzial ova were not seen in any of the experimental monkeys, although they occur frequently in human tissues which have
long been the seat of the disease.

**Giant Cells.**

Giant cells are produced in response to mechanical irritation of the ova - probably endothelial in origin - peripherally placed nuclei in active karyokinesis - individual cells may coalesce to form a plasmodial mass which may enclose intact ovum.

**Eosinophils.**

They are produced in response to miracidial toxin - only in the acute stage are such great eosinophil accumulations seen - it is otherwise in chronic human cases where ova are mostly dead and calcified and are encapsulated in fibrous tissue in which eosinophil cells are rare. In human tissues, when collected at operation, he states that he has seen similar eosinophil collections around living ova.

**Small Round Cells.**

These occur commonly in recent Bilharzial lesions derived from diapedesis and partly by proliferation of connective tissues.

**DEW (2).**

Earliest stage ovum surrounded by leucocytes - eosinophils predominating - around this reaction of tissue cells, large and small mononuclears - almost an abscess - thus ova escape to lumen - ovum held up in tissues may be engulfed by phagocytic cells or giant cells may form around it up to 120 in diameter.
aggregation of the eosinophils, lymphocytes, tissue cells around central giant cells gives rise to Bilharzial tubercle - phagocytosis may go on until replaced by fibrous tissue and finally fibrous nodule.
SECTION 3.

Description of the material used and Pathological Technique.

All the appendices examined in this series were removed at operation from adult Nigerian natives who were found to be excreting S. Haematobium ova in their urine. These men were inhabitants of the Sokoto Emirate of North Western Nigeria, a district where Schistosomiasis is endemic in both its forms, but S. Haematobium infections predominate.

The majority of the men gave a history of recurrent abdominal trouble extending over a considerable period, and mucoid diarrhoea was very frequently a prominent symptom. In a few of the cases, notably those in which gross macroscopic lesions were shown to exist, there was a definite history of attacks of appendicular colic sufficiently severe to necessitate operation. The appendices numbering thirty five in all were examined in the course of routine work at a central clinical laboratory.

They were received in 10% formol-saline accompanied by the clinical notes of each case and the microscopical findings in the urine and stool. After examination a pathological report was rendered to the surgeon.

The specimens were each dealt with as follows:-

**Macroscopic.**

Measurements were taken using a caliper gauge graduated to a sixteenth part of an inch as well as to a millimeter. The total length was measured as accurately

*I am deeply indebted to my colleague Dr. A.C.Lovett-Campbell for permission to refer to his clinical notes and the data concerning the urines and stools of the patients.*
as possible and recorded in inches. A point was chosen where it was judged that the diameter was of average (for that specimen) magnitude. The diameter, and subsequently the thickness of the appendicular wall were measured at this point, and the readings recorded in centimeters. Particular attention was also paid to the following points:

Abnormalities of Conformation such as kinking, nodules, or callosities etc. The presence of adhesions and congestion of the surface vessels; the latter, and also the vessels of the meso-appendix were searched for adult schistosomes. The Appendix was subsequently opened down its length and the presence or absence of concretions, foreign bodies, adult helminths, blood, and mucus recorded. The mucous membrane was examined for evidence of hyperplasia, congestion, oedema, polypoid growths, and ulceration. The state of configuration and patency of the lumen was noted.

Microscopic.

The organs were examined microscopically as follows:

1. Scrapings taken from the mucous and submucous coats together with a portion of the contents of the lumen triturated in normal saline.

2. The centrifuged deposit from portions of the complete circumference of the appendicular wall at the level of the base, centre, and tip, finely divided and digested in 4% caustic potash. at 56° C.
(3) Paraffin sections of the whole circumference of the appendicular wall at the level of the base, centre, and tip. No serial section method was employed. Haematoxylin with eosin was the routine stain employed supplemented by Van Gieson’s stain in certain cases.

Any obvious macroscopic lesion was dealt with in a similar manner. In addition, in those cases failing to reveal ova of Bilhartzia by the above methods, the entire remains of the appendix were digested, and the deposits re-examined. By these means twenty out of a possible thirty five specimens revealed the presence of indisputable S. Haematobium ova, including four cases in which gross macroscopical lesions were present, and the number of ova in each case was found to vary considerably. The number was on the whole greatest in those cases showing macroscopic lesions, and it was found as one would expect, that when scanty the ova could be detected by digestive methods more readily than by examining paraffin sections or scrapings.

No S. Mansoni ova were ever encountered.

The accompanying table summarises the results.

<table>
<thead>
<tr>
<th>Method of Examination</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrapings, section and digestion</td>
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<td>65%</td>
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<tr>
<td>Section and digestion only</td>
<td>4</td>
<td>20%</td>
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<tr>
<td>Digestion only</td>
<td>3</td>
<td>15%</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
<td><strong>Cases</strong></td>
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</table>

Positive by different methods of examination.
It will be seen that the specimens are now divisible into groups.

Group I.

Twenty cases revealing the presence of S. Haematobium ova of which four cases showing gross macroscopic lesions (which will be shown later to be directly due to Bilharzia) are dealt with separately, thus leaving sixteen cases for analysis.

Group II.

Fifteen cases showing no evidence of the presence of Bilharzia ova.

In view of the fact that only one completely normal appendix was encountered, it would be as well to contrast in tabular form and to discuss the findings in these two groups before embarking on a detailed description of the gross pathology of the above mentioned four cases.

For purposes of comparison the findings in these four cases are also separately included in the table as a third group.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Abnormalities of Configuration</th>
<th>Congestion</th>
<th>Adhesions</th>
<th>Helminths</th>
<th>Concretions</th>
<th>Eosinophilia</th>
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### Table I (Contd.)

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<th>Case No.</th>
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<th>Adhesions</th>
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<td>E</td>
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</table>

Table I represents the findings in the total number of cases investigated.

Cases in which *Bilharzia* Haematobium ova were found in the appendix are typed in red, cases negative for ova are typed in black.

Those cases which show gross pathology due to *Bilharzia* are marked with an asterisk.

_E_ refers to adult *Entero.table Vermicularis.*
<table>
<thead>
<tr>
<th></th>
<th>GROUP I</th>
<th></th>
<th>GROUP II</th>
<th></th>
<th>GROUP III</th>
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<td>L.</td>
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<td>Abnormalities of</td>
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<td>Configuration</td>
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<tr>
<td>Congestion</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>4</td>
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<tr>
<td>Adhesions</td>
<td>6</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Enterobius Vermicularies</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Concretions</td>
<td>4</td>
<td>12</td>
<td>1</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>16</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Catarrh</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>4</td>
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</tbody>
</table>

**Group I** = 16 Bilharzia Positive cases with no macroscopic lesions.

**Group II** = 15 Bilharzia Negative cases.

**Group III** = 4 Bilharzia Positive cases with macroscopic lesions.
Allowing for the very small difference in their totals, it is at once apparent that there is a close resemblance between the figures in Groups I and II. The averaged measurements show a slight tendency to increase in girth and thickness of the wall in those cases harbouring ova, particularly so in the small group which shows macroscopic lesions.

If it were not for the figures in Group III one might be tempted to believe that the presence of concretions is associated with Bilharzial infestation. They were usually of small size, multiple, and being almost transparent were quartz like in appearance; probably derived from inspissated mucus.

The inference to be drawn from this analysis is that it is well nigh impossible, where marked and typical macroscopic lesions are absent, to tell a Bilharzial infected appendix from a non-infected one except by the microscopic discovery of the ova.

One can only point to the high incidence of infestation with Enterobius as a possible explanation of the abnormalities encountered in Group II. At the same time, one cannot ignore their possible significance also in the case of Group I.
* Particulars of the average age of the patients; presence of Bilharzial ova in the stool and urine; alleged average duration of urinary symptoms.

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>26 years</td>
<td>23 years</td>
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<tr>
<td>(16-50 yrs)</td>
<td>(13-40 yrs.)</td>
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<tr>
<td>Stool</td>
<td></td>
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<tr>
<td>Haematobium ova present</td>
<td></td>
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<tr>
<td>0 cases.</td>
<td>1 cases</td>
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<tr>
<td>(Mansonii ova present 1 case.</td>
<td>0 &quot;</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Haematobium ova present</td>
<td></td>
</tr>
<tr>
<td>19 cases.</td>
<td>15 &quot;</td>
</tr>
<tr>
<td>(Mansonii ova present 0 cases.</td>
<td>0 &quot;</td>
</tr>
</tbody>
</table>

Alleged average duration of symptoms: 17 years (4-40 yrs.) 8 years (2-17 years)

* I am indebted to Dr. A. C. Lovett-Campbell for permission to use these data.
Clinical and pathological reports of four cases showing gross pathology.

The following four cases numbered in the series, 9, 23, 26, and 31, are those showing gross macroscopic pathology, and it is from these that most of the photomicrographic illustrations are taken.

The case histories and pathological notes detailed below were made at the time of examination and are quoted in full.

CASE NO. 9.

Clinical History.

Abdominal symptoms commenced nine years ago; he had four severe attacks of pain during this period. During an attack he was forced to lie face downwards. Each attack was preceded by vomiting. The attacks would commence gradually, attain great severity, and subside at the end of two days. All four attacks were so severe "that they nearly killed him". Last attack occurred about nine months ago. The pain was always most severe over the appendix region, and the patient added that in this area the abdomen "became like a stick". He has never had attacks of diarrhoea or looseness of the bowels. He tended rather to be constipated.

Pathological Notes.

The appendix is distorted and kinked $\frac{3}{4}\"$ from the
tip by a fibrous tumour 1.4 x 1 cm in size which occupies and forms half of the circumference of the appendicular wall on the side remote from the mesenteric attachment. The mucous membrane is not invaded but is pressed upon and pushed inward thus distorting the lumen and rendering it crescentic in shape with the concavity towards the tumour.

The mucosa is intact but shows congestion and catarrh and the lumen contains a plug of amorphous matter coated with a layer of inspissated mucus, degenerated epithelial cells, and red blood cells; this plug is adherent to the mucous membrane in places. The mucosa also shows intense infiltration with round cells and eosinophil cells most marked in the region of the tumour.

The tumour is composed of chronic inflammatory reaction surrounding very numerous ova of S. Haematobia which have been deposited in the submucosa at a point furthest away from the mesenteric attachment. The tumour has ruptured through the circular muscle coat, and the ruptured ends are distinctly visible. Three quarters of the tumour lies peripheral to the muscle. The serous coat is seen stretched out over the tumour for a short distance and then it merges into it.

The structure of the tumour varies in different parts; broadly speaking there tends to be more cellular reaction within the muscle layer, and more fibrous reaction outside. If the tumour is arising in the submucosa, the inference is that it is the original inflammatory mass which has pushed its way through the muscular coat.
The cellular reaction mentioned is mainly composed of wandering and eosinophil cells.

The general structure is best described as made up of whorls of chronic inflammatory reaction surrounding single, or more commonly, groups of ova of S. Haematobium. Often these whorls are very reminiscent of Miliary Tubercles. These whorls differ from each other in their construction only in detail. It is believed that these differences probably depend on their age. The types that are seen will now be described, but first of all it should be made clear that the whorls which are definitely formed as a result of the ova, themselves lie in a matrix of cellular and moderately vascular fibrous tissue abundantly infiltrated with wandering and eosinophil cells. The whorls, on the other hand, like tubercles, appear to be avascular.

Types of Whorl.

1. The ovum or ova are usually central and is/are surrounded by a dense concentration of wandering and eosinophil cells nearest the ova, and outside them a layer of cells resembling fibroblasts, but with pale vesicular nuclei very similar, if not identical with, the "Endothelioid Cell" of the tubercle.

2. Similar to 1, but there is now a layer of granular eosinophilic debris surrounding the ovum, with the remains of the nuclei of the eosinophil cells which have apparently gone to form it still visible. The ovum is sometimes degenerate and takes on the eosin
instead of the haematoxylin stain. At the periphery of this zone there are seen to be acidophilic fibres and processes which connect the granular zone to an outer zone of spindle shaped cells often arranged at this point in a radial manner around the central mass like the spokes of a wheel; these cells form a loose reticulum. Outside this again is a more compact layer of fibroblastic cells arranged concentrically, appearing to wall in the central contents, and the whole is limited by a concentration of the wandering and eosinophil cells which go to form the matrix of the tumour.

3. The granular debris is absent or has been absorbed, and foreign body giant cells have made their appearance, extremely similar to the multinucleated giant cells of the true tubercle; these are almost always in close proximity to the ova, and can often be seen engulfing the ova or egg shells. The giant cells connect up by protoplasmic processes with the radially arranged zone of spindle cells, and outside this the structure is as described as under 2.

4. The central ovum is possibly no longer apparent, and the multinucleated giant cell is now the central feature, with the zones of spindle cells and cellular reaction as described above surrounding it. The appearance is now almost identical with a true miliary tubercle.

5. Only a concentric scar of relatively acellular hard fibrous tissue remains.
CASE No. 23.

Clinical History.

Abdominal trouble commenced six years ago. There was colicky pain and mucoid diarrhoea. Mild attacks occurred at intervals of four months - gradual onset - would last one day. No vomiting occurred. No hematuria was noticed.

Operation 10.8.35. Appendix kinked, bound down in the mid length by its mesentery.

Pathological Notes.

At about the junction of the proximal and middle thirds, 2 cms. from the base of the appendix, there is an irregular tumour 2 cms. X 1 cm. in size, formed by a localised increase in the thickness of the appendicular wall. The peritoneum is stretched over it and appears to be intact and glistening. Minute greyish nodules can be seen on the surface of the tumour resembling Miliary Tubercles. The tip of the appendix is irregular and is distorted into a solid beak-like projection pointing towards the mesenteric attachment; this also shows the presence of tubercle like nodules. A much smaller pedunculated tumour is found at the junction of the middle and distal thirds resembling a smooth wart.

A section through the large tumour shows that the lumen is filled with a plug of mucus and catarrhal epithelial cells. The mucosa is abundently infiltrated with round cells and a few eosinophil cells. The
germinal centres of the lymph nodes are prominent. The submucosa is thickened and fibrous and contains S. Haematobium ova surrounded by typical pseudo-tuberculous reaction. Phagocytosis of ova by giant cells is seen. The circular muscle coat is intact except in one place where it is split into two bands by an area of giant cell and spindle cell reaction. The longitudinal muscle and serous coats are widely invaded and replaced by granulation tissue consisting of a fibrous stroma heavily infiltrated with eosinophil cells. Numerous capillaries course through it. Here and there are collections of ova or single ova surrounded by pseudo-tubercles, and externally a concentration of the eosinophil cells. The whole band of reaction is as broad as the rest of the appendicular wall.

CASE No. 26.

Clinical History.

Abdominal trouble commenced three years ago with colic. Attacks occurred every three months and were severe with a gradual onset. Vomiting always occurred and preceded the attacks. Mucoid diarrhoea was present. Pain commenced in the epigastrium spreading towards the right Iliac Fossa. Pain was relieved by applying pressure over this area. Haematuria has been present since childhood, recurring every three months.

Pathological Notes.

Apart from slight general thickening the conformation of the appendix proper is fairly normal. At the
distal extremity, however, there is a dense band of adhesion 2 cms. long, uniting the apparent tip of the appendix to a tumour which is solid and 1½ cms. X 1 cm. in size. The adhesions are very vascular. The tumour appears to be completely covered with peritoneum, and might have been formed by the natural amputation of part of the appendicular wall. The adhesions are twisted on themselves. The surface of the tumour is smooth and glistening, but nodular owing to the presence of minute grayish elevations very similar in size and appearance to Miliary Tubercles. On section the tumour is firm and elastic and possesses a mottled surface.

(a) The appendix proper. The lumen contains red blood cells and catarrhal epithelial cells. The mucosa is congested and abundantly infiltrated with eosinophil cells, and contains a few S. Haematobium ova. The lymph nodes are prominent with active germinal centres. The submucosa is not markedly thickened, but contains numerous clumps of S. Haematobium ova varying in number from 1 to 10, situated on the side of the wall remote from the mesenteric attachment. The muscular coats are normal, but the serous coat is thickened and infiltrated with S. Haematobium ova.

(b) The Tumour. Appears to be covered with a thin layer of peritoneum, and may well have taken origin from this coat. It is composed of masses of S. Haematobium ova, countless in number, and of the pseudo-tuberculous reaction to which they have given rise. The vessels
which course through the tumour are "cuffed" with lymphocytes. The pseudo-tubercles are avascular.

(c) The Adhesions. Are very similar in structure to the solid tumour, and contain very numerous ova and pseudo-tubercles, but are exceedingly vascular. No sign of the adult worm if seen.

CASE No. 31. Male aged 37.

Clinical History.

Abdominal trouble first started five years ago. It commenced with mid-abdominal colic. There were attacks of pain alternating with periods of freedom from symptoms. He has had four attacks in five years. The early attacks were mild, but the last attack occurring five months ago was the most severe of all. An attack continues for about three days. The pain commences above the middle of the right Inguinal Ligament, and radiates upwards. He is forced to lie still during an attack. There is no vomiting but diarrhoea accompanies the attack, and sometimes slight blood and mucus is passed. Has a history of haematuria since childhood.

Operation 14.9.35. Appendix difficult to locate, with the caecum fixed and immobile. Appendix lying retrocaecally, buried in adhesions, enlarged and tortuous. Serous coat much injected.

Pathological Notes.

There is a catarrhal plug in the lumen. The mucous membrane is slightly thickened with marked cellular
infiltration. The submucosa is also slightly thickened in parts, and infiltrated with round cells, eosinophil cells, and fibroblasts. S. Haematobium ova are scattered throughout it, lying singly and in pairs. The muscular coat appears to be thickened. The serous coat is definitely thickened in places and is very vascular. Fairly numerous ova are found in it. The smaller blood vessels are often "cuffed" with lymphocytes. The serous coat is thickened at one point to form an adhesion binding down the tip to the main body of the appendix.

* The clinical histories are included by kind permission of Dr. A.C. Lovett-Campbell.
SECTION 5.

General Pathology and the pathological process with special reference to the formation of the Pseudo-tubercle.

The site of the ova.

The ova were found in the following situation:

- Submucosa . . . . . . . . . 5 cases.
- Submucosa and subserosa . 1 case.
- Submucosa and mucosa . . . 7 cases.
- All coats including the muscular . . . 4 cases.
- Unknown . . . . . . . . . 3 cases

Total 20 cases.

It will be seen that the ova are more commonly met with in the submucosa than elsewhere, but no coat is exempt. In view of Fairley's (4) findings with regard to the rarity with which the muscular coat was found to be involved in monkeys, it is interesting to note that ova and specific tissue reaction are occasionally demonstrated in our cases actually separating the muscle fibres. On the whole, however, there is a tendency for this coat to escape.

In all cases showing macroscopic pathology ova are demonstrable in the serous coat, and in only one case where this coat is involved are macroscopic lesions absent. The ova are found singly or in clumps up to as many as twenty or thirty in number, and are usually situated in the wall of the appendix at some point remote from the mesocolic attachment. They are almost invariably found in the tissues and not in the blood.
vessles. Occasionally the majority of them appear to be healthy and the miracidia can be seen within the shells, but more often some of them, or all of them, are degenerate or even calcified.

In nearly all the cases in this series the ova can be demonstrated in varying numbers throughout the length of the organ, and this applies even to the cases in which macroscopic lesions are found. In this case ova are more numerous, however, in the region of the obvious lesions. They have no orderly arrangement so that on section they may be cut in any plane. In the mucosa they are always seen lying between the glandular crypts, and in this site the spine is sometimes pointing towards the lumen.

The number of the ova.

The number of ova present appear to vary with each case. Unfortunately no attempt at an accurate egg count was made, and the number was judged only very roughly in two ways.

(1) The number of eggs which could be recovered by digestion of pieces of tissue of approximately the same size.

(2) The ease and frequency with which ova could be found in the stained sections.

As a result, four admittedly inexact gradations were evolved, varying from a case in which only one to two ova could be found and marked scanty, to a case in which almost a hundred ova might be seen in one microscopic field and
marked very numerous.

In this way 3 cases show very numerous ova (more than 10 per field)
7 " " numerous ova (more than 1 per field)
5 " " fairly numerous ova (1 per field or less)
5 " " scanty ova (only 1 or 2 present).

It is fully realised that a method such as the above may be grossly misleading, and it is to be deplored that the full significance of the practical utility of an accurate count did not strike one forcibly at the time. One is not entirely satisfied that the presence of macroscopic lesions is solely dependent on the number of ova present, although doubtless this and the manner in which they are concentrated are factors of supreme importance.

In two of our cases the reaction present appeared to be out of all proportion to the actual number of ova, whereas a most puzzling and not infrequent phenomenon is the presence of comparatively large numbers of ova in the tissues, not necessarily in a state of degeneracy, provoking apparently no tissue reaction whatever.

**Tissue Reaction.**

The specific reaction of the tissues to the ova has been demonstrated in four cases. In two other cases it occurred but was not obvious except in microscopic sections. In seven other cases there was seen to be some excess
fibrosis, or young fibroblastic reaction, of a non-specific character (by non-specific is meant the absence of pseudo-tubercles). Finally, in the remaining seven cases there appeared to be no reaction whatever to the presence of the ova.

The result may be summarised as follows:

- Specific Pseudo-tuberculous reaction present, 6 cases
- Non-specific fibrosis or young fibroblastic reaction present, 7 cases
- No reaction present, 7 cases

Total 20 cases

From a careful study of the cases showing typical reaction it is believed that two of these cases present early lesions, and that in the others, all stages, or only late stages, are seen. It has been possible, collectively, to build up what is believed to be the pathological process involved, and to confirm in every detail the previous observations of Fairley (4) and later, of Dew (2).

In view of this close conformity, differing only in detail, it seems of particular interest to emphasise the fact that at the time when these beliefs were formulated, and illustrated by photomicrographs, one was in complete ignorance of the text of the publications of Fairley (4) and Dew (2). In this respect only, can any claim to originality be made for the description of the histopathology, with the addition perhaps of the fact that these lesions do not appear to have been described in detail before in the appendix.
The pathological process referred to above is illustrated step by step in the photomicrographs. The earliest changes were studied mainly in the subserous coat, for in this coat the reaction was most intense. In response to the deposition of ova a characteristic type of granulation tissue is laid down, and the response may appear to be out of proportion to the number of ova present. It is possible, however, that appearances are misleading in this respect, and that the ova originally concentrated in a mass have been separated from each other by the intense inflammatory reaction which they evoke. As a result the subserosa becomes enormously thickened and may equal in breadth the remainder of the appendicular wall. The new granulation tissue is extremely vascular and very abundently infiltrated with eosinophil polymorph leucocytes. There is a marked concentration of these eosinophil cells in the region of the ova, which at this stage are either healthy or only slightly degenerate. A few lymphocytes and mononuclear cells may be present in the neighbourhood of the ova. The smaller vessels may show lymphocytic "cuffing", and there may be hyperplasia of the endothelium of their walls. In places, the reaction may have advanced to the formation of pseudo-tubercles.

The macroscopic appearances at this stage probably consist of localised thickening and bulging of the appendicular wall, and possibly also dense fleshy adhesions.
may be present. The serous coat, however, may be smooth except for the presence in its substance of minute greyish nodules, slightly raised above the surface, 1 to 2 mms. in size, and resembling closely Miliary Tubercles.

The inflammatory process may involve and may have actually spread from the submucosa. The mucosa is apparently not seriously involved as a rule, and polypoid tumours and ulcerations were never observed in this series. The mucosa may be pressed upon by an inflammatory mass in the submucosa with resulting distortion of the lumen, and epithelial catarrh is frequently evident.

Extensive pseudo-tuberculous reaction, extending throughout the wall of the appendix, gives rise to a distinct localised tumour, which may project as much as half an inch beyond the normal limits of the appendicular wall and be larger in size than a cherry stone; in this case it is stony hard to the touch and the surface is studded with tubercles.

The Pseudo-tubercle.

The pseudo-tubercle is formed round an ovum, or a group of ova, in the substance of the aforementioned granulation tissue.

Firstly, the eosinophil cells, which are concentrated immediately around the ova, commence to degenerate. Very soon mononuclear cells, wandering cells, and fibroblasts arrange themselves radially around the degenerate mass, and a circular wall of hard fibrous tissue is formed at
the extreme periphery. By this time the central eosinophil cells have become entirely degenerate, and converted into a granular mass with only a few pyknotic remains of the nuclei to indicate its origin. At this stage, spindle cells are observed ranging themselves around the central mass of debris like the spokes of a wheel. They are seen to give off protoplasmic processes which connect them with the central granular mass and with each other, thus forming a loose reticulum. It is probable that they are in reality young fibroblasts, but they do to some extent resemble the endothelioid cells of the true tubercle, and it is possible that, at any rate, some of them take origin from the proliferated endothelium already mentioned. At any rate, sections stained by Van Gieson's stain show very little deposition of collagen fibrils in this zone, although very intense fibroblastic activity is evident at the extreme periphery. The resemblance to the true tubercle is very striking at this stage. It is from these cells, one believes, that the multinucleated giant cells are formed so commonly seen in the later phases. These spindle cells are occasionally aggregated into a mass in which the individual outlines of the cells are lost, and the appearance somewhat suggests a step in the formation of a giant cell. At the same time, the nuclei of a giant cell were never seen in an active state of karyokinesis as recorded by Fairley (4).

Fairley (4) and Dew (2) emphasise the presence of giant cells in early lesions, but this is not our...
experience. Giant cells, although very numerous, were never seen in the tubercles until after the absorption of the granular debris. By the time the eosinophilic mass has completely disappeared, the ova are found in most instances to be quite degenerate and often partially calcified. It is now that the giant cell plays its part as a scavenger, and it may frequently be seen lying in close proximity to, or appearing to engulf, the calcified remains of an ovum. It seems logical to regard this characteristic cell as an essential part of the reparative process which is a later phase of the reaction.

Fibrosis proceeds apace and all that eventually remains to indicate the site of the pseudo-tubercle is a concentric hard fibrous scar.

Between the individual pseudo-tubercles fibrous granulation tissue is found infiltrated with mononuclear, fibroblastic, plasma, and eosinophil cells, together with occasional ova. Capillary blood vessels course through it but do not appear to enter the substance of the tubercles, and this fact together with a toxin emanating from the ova may explain the central degeneration.

As has already been mentioned the mucosa is hyperplastic; the nuclei of the epithelial cells are frequently in a state of mitosis. The mucus cells are active as are also the germinal centres of the lymph nodes.

- - - - -
SECTION 6.

Discussion.

Certain questions arise when we attempt to reconcile some of the findings in the investigation with accepted modern theories.

How are the ova distributed so widely throughout the appendix, and if it is agreed that specific tissue reaction is dependent on the number and concentration of ova present, how can we account for the apparently paradoxical facts that numerous ova may be peacefully tolerated, whereas presumably scanty ova can cause undeniably inflammatory reaction?

Barsoum (3) recognises a diffuse and a focal distribution of ova, and admits that both may be found together. He explains this on the basis that in the focal distribution the worm reaches the appendix, but that in the wider distribution the eggs have been carried in by the blood stream from a distance. He does not attempt to elaborate this conjecture.

Believing, as we do, this suggestion to be the correct one, it is necessary to explain how it is that ova are able to proceed against the blood stream. Concentration methods using saturated solutions are seldom effective for Bilharzia ova, a fact which demonstrates their unusual weight. Is it not possible that the eggs are able to sink by gravity even against the blood current? The centre of gravity being nearer to the blunt end than to the spine would account for the
fact that the eggs are found lying in the vessels with the spines pointing in the direction of the blood stream. Assuming this to be the case, a point would be reached when the vessel becomes too narrow to accommodate the egg; the latter now entirely fills the lumen. As successive ova pile up on each other from behind, the vessel becomes completely occluded; possibly as a result of the cessation of the blood stream, and the consequent negative pressure exerted by the collateral circulation, and partly owing to irritation of the vessel walls, the latter contract down upon the ova, causing the "string-of-sausages" effect. The ova leave the vein owing to pressure necrosis of the vessel wall or to muscular (peristaltic) movements.

Thus it is possible to picture the worm shedding its ova at some point in the venous system, it may be proximal to the termination of the Ileocolic vein. Ova are continually reaching all parts of the appendix in conjunction with other portions of the bowel. These ova are not sufficiently numerous to cause a specific reaction, but rapidly make their way to the mucous surface where they set up a catarrhal condition of the bowel wall resulting in mucoid diarrhoea. A few of the eggs are trapped in the fibrous tissue of the submucosa, where they subsequently become calcified, and are joined by others from time to time.

In a few instances the worm actually descends to the region of the appendix itself, and there is now such a marked local concentration of helminthic toxin, that a
specific reaction is set up, not entirely dependent on the site and number of ova deposited. Once mobilised, and following the retirement of the worm, the reactionary cells concentrate on the nearest toxic foci, namely the ova. In this manner is born the pseudo-tubercle.

This hypothesis may seem absurd for many reasons, not the least that there is no shred of experimental evidence to support it; but are we to believe that the adult female worm patiently makes her way down almost every vein in the appendix from base to tip, to deposit her ova in the accepted manner?

Even then it is difficult to believe that such minute vessels as those of the appendicular submucosa could accommodate her: they are naturally much smaller than similar vessels supplying other parts of the bowel in which the worms have been actually observed.

Further, one would expect to have encountered the adult worm in at least one of the thirty five specimens examined. It is, therefore, suggested that there is room for further experimental work on this aspect of the subject.

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In cases where there is gross pathology present, approximately how long have the lesions been present?

It has been suggested, and this is confirmed by Fairley (4), that massive concentration of eosinophil polymorphonuclear cells bespeaks an early lesion. If this be true we must regard at least two, or possibly
three of the cases described in detail as showing evidence of recent inflammation.

Fairley (4) has shown that the length of time which elapses between infection and the appearance of symptoms and lesions in monkeys and men is closely similar, namely, two to three months. He has also shown that all but the later phases in the formation of pseudo-tubercles can be demonstrated in that time.

Making all due allowance, it is hard to believe that the histories given by the patients in this series of the duration of their symptoms and signs, can have any bearing on the age of the lesions found in the appendices unless we emphasise the probability of re-infection of them from time to time. On this basis only are we able to explain the periodicity of the attacks.

Is the softening of the central zone of the tubercle an attempt at extrusion of the ovum, and is it likely that an ovum will escape once it is held up in the tissues?

Except in the immediate vicinity of the mucosa, it is hard to believe that ova held up in the tissues ever escape through lysis of the surrounding cells. In most cases before this occurs a confining wall of fibrous tissue has formed, and it is not unlikely that the softening of the central group of cells results partly from the restriction locally of a toxin derived from the degenerating miracidium.

Probably most of the ova which penetrate to the lumen
are those which are lucky enough to escape detention.
SECTION 7.

Summary and Conclusions.

(1) The literature of Bilharziasis of the appendix is reviewed, and shown to lack histopathological detail; it is pointed out that no reference is made to S. Haematobium infections.

(2) A selective extract is given of accepted modern views on the helminthology, and the natural and experimental pathology of the colon in Schistosomiasis.

(3) A detailed account is given of the pathological technique employed in the examination of a series of thirty five appendices removed at operation from adult natives of Nigeria, thirty of whom were found to be excreting S. Haematobium ova in the urine. Digestion of the tissues is proved to be the most accurate method of detecting and diagnosing the type of ova present.

(4) In this series it is shown that twenty (57%) of the specimens are found to harbour S. Haematobium ova, and that in four (20% of the infected or 11.4% of the total specimens) gross pathology is evident.

(5) The pathological findings in sixteen cases in which ova, but no gross pathology, were demonstrated are contrasted in detail with fifteen cases in which no ova were found; the conclusion is reached that except for the presence of the ova on microscopic examination, it
is impossible to discriminate between them, and that ova can be present in comparatively large numbers without provoking tissue reaction.

(6) The symptoms and pathological reports of four Bilharzial infected cases showing gross pathology are given in detail; it is shown that the latter is directly attributable to the Bilharzial infection, and that a specific type of tissue reaction is present.

(7) The pathological process is described in detail, and theories advanced to explain the formation of the pseudo-tubercle, and the origin and function of the cells which go to form it.

(8) It is shown that certain facts observed in this investigation are believed to be incompatible with modern theories, especially in regard to the manner in which the ova are deposited; an hypothesis is elaborated which appears to answer all the known facts. It is suggested that there is room for further experimental work on this subject. While admitting the probable importance of the number and concentration of ova and the site where they are deposited,(the serous coat having been shown to be unduly sensitive), as factors in determining the presence of macroscopic lesions, it is believed that toxin from the adult worm may also play a part in the production of typical pseudo-tuberculous reaction, together with the effect of irritation and a toxin
produced by the ova; and that macroscopic lesions are probably the result of repeated deposits of ova at intervals.

(9) It is believed that as a rule ova held up in the tissues seldom escape.

(10) In a proportion of cases under certain conditions Bilharzial infection of the appendix is capable of causing a chronic type of appendicitis, but more often it probably forms part of a general infection of the colon giving rise to symptoms of mucoid diarrhoea.
ILLUSTRATIONS.

Figs. 1 to 4.
Figs. 1 to 4 illustrate the macroscopic pathology of cases Nos. 9, 23, 26, and 31 in the series; note the tumour formation in Figs. 1, 2, and 3, and in Fig. 4 the dense fleshy adhesions binding down the tip to the main body of the appendix.

Fig. 5.
Deposit from a digested portion of an infected appendix; note several terminal spined ova of S. Haematobium, also the presence of T. Saginata and Enterobius Vermicularis ova.

Fig. 6.
Calcified ova in the Submucosa and Mucosa.

Fig. 7.
A large clump of calcified ova in the Submucosa and Mucosa.

Fig. 8.
Calcified ova in the Submucosa; one ovum is seen in the Mucosa between the glandular crypts. Note the absence of any specific reaction.

Fig. 9.
A calcified ovum is seen in the substance of the circular muscle coat.

Fig. 10.
A low power magnification of pseudo-tuberculous reaction;
note the whorls of fibrosis around the calcified ova, and a capillary blood vessel in the stroma.

Fig. 11.
Pseudo-tubercles; note calcified ova, whorls of fibrous tissue, and several multinucleated giant cells.

Fig. 12.
Advanced stage of pseudo-tuberculous reaction; very numerous calcified ova are present and dense fibrosis.

Fig. 13.
Numerous ova and whorls of fibrous tissue in a late stage. The ova show degenerative changes.

Fig. 14.
A pseudo-tubercle showing the outline of a terminal spined ovum, and central degenerative change; note the radial arrangement of the central zone.

Fig. 15.
Pseudo-tuberculose granulation tissue. A degenerate ovum is seen at the top of the picture, and a mass of granular softening in the lower part.

The Stages in the Formation of a Pseudo-Tubercle.

Fig. 16.
1st Stage. Dense concentration of eosinophil polymorphonuclear leucocytes around an ovum.

Fig. 17.
2nd Stage. Early degenerative changes in the eosinophil
cells next to the ovum.

Fig. 18.
3rd Stage. Complete degeneration of the eosinophil cells which are now converted into a granular mass; note the well marked zone of spindle cells arranged round the ovum like the spokes of a wheel, and the concentric fibrosis at the periphery. At this stage the resemblance to a true Tubercle is striking.

Fig. 19.
4th Stage. The multinucleated giant cell.

Fig. 20.
5th Stage. A giant cell is seen enveloping an ovum which is completely calcified.

Fig. 21.
6th Stage. The final concentric fibrous scar.

Fig. 22.
A healthy ovum is seen at the top right hand corner of the picture. The miracidium can be plainly seen within the egg shell. In contrast at the lower left hand corner a calcified fragmented ovum is encircled by a multinucleated plasmodial mass, (giant cell).

Fig. 23.
Two ova undergoing early degenerative changes. Note the hyaline bodies within the shells.
Fig. 24.
Hyperplasia of the endothelium of a small blood vessel.

Fig. 25.
Two capillary blood vessels are seen; the upper shows endothelial hyperplasia, the lower diapedesis and lymphocytic "cuffing".
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ACKNOWLEDGEMENT.

To my colleague, Dr. A. C. Lovett-Campbell, I am deeply grateful for permission to use the clinical and other data acknowledged throughout the text.

It is a pleasure also to acknowledge a debt of gratitude to Mr. Knight of the Medical Research Institute, Lagos, for unstinted pains taken with the preparation of ten of the illustrations, namely, Figs., 5, 10, 11, 12, 14, 16, 18, 19, 20, and 21. The remaining fifteen illustrations are by the author; the photographs in every case were taken of the author's original preparations.
Fig. No. 1.
Case No. 9
Base
Tip
Tumour

Fig. No. 2.
Case No. 23
Tip
Tumour
Base

Fig. No. 3.
Case No. 26
Adhesions
Tumour
Tip
Base

Fig. No. 4.
Case No. 31
Base
Fleshy Adhes
Tip
Fig. No. 10
Case No. 9
60 x

Fig. No. 11
Case No. 9
60 x

Fig. No. 12
Case No. 26
45 x

Fig. No. 13
Case No. 26
93 x

Fig. No. 14
Case No. 9
120 x

Fig. No. 15
Case No. 9
93 x