INFESTATION BY FASCIOLA HEPATICA

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Although *Fasciola hepatica* (liver fluke, *Lewerbot*) is essentially a parasite of herbivorous animals, especially sheep and cattle, in which it causes the disease known as 'liver rot', it has been reported in man as an erratic infestation. The recent recognition of 2 human cases, one presenting with massive haemorrhage from the liver into the intestine, and the other with intermittent obstruction of the common bile-duct, prompted an extensive review of the literature, from which it became apparent that fascioliasis is not so very rare in man, in whom it may produce variable clinical pictures.

It is the purpose of this paper to draw attention to the

pathological effects of infestation by *F. hepatica*, to discuss the clinical features, diagnosis and treatment of fascioliasis (distomiasis), and to report the 2 cases encountered.

Fasciola hepatica (*Distoma hepaticum*), a flat, leaf-shaped worm, pale-grey in colour with dark borders (Fig. 1), belongs to the class Trematoda or flukes. It is related to *Chlonorchis sinensis*, the common liver-fluke of Eastern races, and also to the blood flukes (Schistosoma

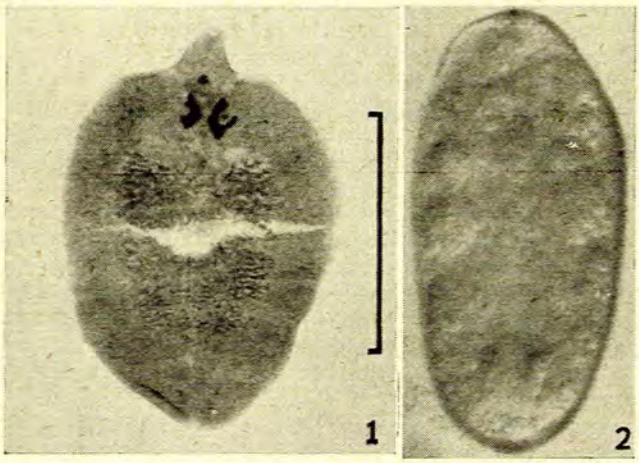

Fig. 1. *Fasciola hepatica.* Adult fluke (the scale represents 1 cm.).

Fig. 2. The ovum of *F. hepatica.* Note the relatively small operculum.

or Bilharzia), common in Africa. The adult is 20-30 mm. long, and 10-15 mm. broad. The conical head-end is surmounted by an oral sucker, behind which is a larger, triangular ventral sucker. The eggs (Fig. 2) measure 130-180 microns by 70-90 microns. They are ovoid, have a yellowish-brown operculated covering or shell, and contain the ovum and yolk-sac.

LIFE CYCLE

The parasite requires two hosts for reproduction (see Fig. 3): The *definitive host*, in which the adult fluke develops, is found chiefly in domestic animals, especially sheep, cattle and goats, and rarely horses and pigs. The fluke also occurs in the other plant-eating animals, e.g. buffalo, hare, rabbit, elephant, hyrax (dassie) and kangaroo, and occasionally in domestic carnivora, e.g. dog and cat.

The *intermediate* hosts are fresh-water snails of the genera Limnaea and Physopsis. In Europe the species is *L. truncatula* in Japan, *L. pervia*; in South Africa, *L. natalensis*, *Physopsis africana* and *Bulinus verreauxii*.

The adult fluke lives in the bile-ducts of the definitive host. Ova are discharged into the bile, and pass down the intestinal canal to be excreted in the faeces. The eggs may thus reach fresh-water ponds, where they can remain viable for 2-3 weeks. The ciliated embryo or miracidium which hatches from the egg cannot survive for more than 8 hours in the water. However, if it finds a snail the life cycle is continued. In the snail the miracidium

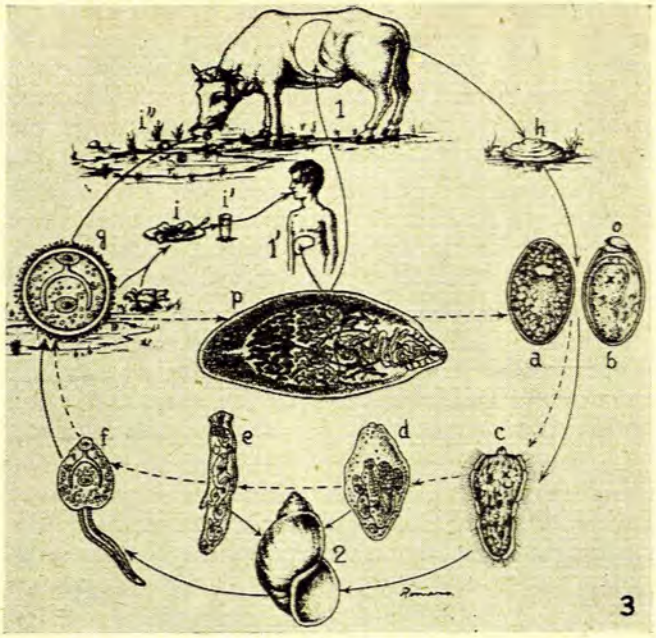

Fig. 3. *Fasciola hepatica.* Life cycle. The adult parasite (p) lives in the bile ducts of the definitive host (cattle, 1; man, 1′). The eggs (a) are passed in the faeces (h). After reaching the water they become embryonated (b), the miracidium (c) hatches through the operculum (o), and swims freely in the water until finding the intermediate host (2) (*Lymnea cubensis* and *Physa cubensis* in Cuba), where the sporocysts (d), rediae (e) and cercariae (f) develop. The cercaria (f) leaves the snail and becomes encysted in the water either freely or attached to water plants, developing into the metacercaria (g), which is the infective stage for the definitive host (1, 1′). When the definitive host ingests the metacercaria with water or vegetables (i, i′, i″) it reaches the intestine, the cystic cover dissolves and frees a young fluke; this bores through the intestinal wall and reaches the liver surface through the peritoneum; when boring through the fibrous capsule and the liver parenchyma, the parasite produces necrosis; in the bile it becomes an adult hermaphroditic parasite and lays eggs which are passed in the faeces (h), beginning a new cycle. (*After Drs. Kouri and Basnuevo.*)

develops into a sporocyst which liberates up to 20 rediae. Each of these produces about 20 cercariae which escape from the snail and swim about freely in the water.

After about 8 hours the cercariae lose their tails, and encyst on blades of grass or aquatic plants (watercress), which are eaten by the mammalian hosts. The encysted cercariae may survive for long periods, e.g. several weeks in dry hay, the whole winter in water, and for a year or more in damp hay.

After the cercaria has been ingested by the definitive host, its outer covering is dissolved in the alimentary canal of the animal, and a young fluke emerges. These young flukes are attracted to the host's liver by positive chemotaxis, and they reach it by a variety of routes. Most commonly the flukes burrow through the intestinal wall and migrate transperitoneally (compare the similar migration by *Paragonimus*). Less commonly they reach the liver via the portal blood-stream or lymphatics (compare the migration of Schistosoma) or very rarely they pass up the common bile-duct (compare the passage

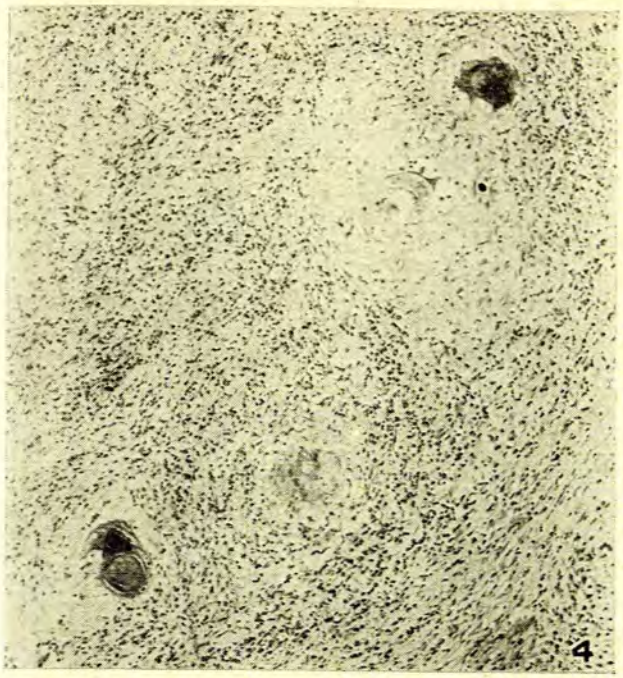

Fig. 4. Microphotograph showing distorted ova of *F. hepatica* surrounded by localized foci of pseudo-tubercles in the connective tissue surrounding the cystic duct.

of *C. sinensis* and *Ascaris*.) Occasionally the flukes are deflected from the liver and settle in neighbouring tissues, e.g. abdominal wall, spleen, stomach, appendix, etc., or they may pass through the liver to reach the systemic circulation and lodge in distant organs, e.g. cerebrum, kidney, peripheral veins, or even the foetus of pregnant animals.

The transperitoneal migration of the young flukes may be questioned, but the following observations appear to support this method of spread:

1. Small haemorrhagic foci are often found on the peritoneal surfaces of the intestine and liver along the path of migration of the flukes.

2. Ectopic foci of infestation are usually in the neighbourhood of the liver, particularly in the subcutaneous tissues of the right hypochondrium.

3. In our first case ova were found in the connective tissue *outside* the cystic duct and not in the lumen or wall of the duct (Fig. 4).

The young flukes wander about in the liver parenchyma until maturity is reached in 6-12 weeks. The adult eventually reaches the larger bile-ducts where it feeds on blood, liver tissue and bile. In animals the parasite usually survives for 9 months, but it may live for 5 years and longer. It is possible that *F. hepatica* may exist in man for even longer periods (*C. sinensis* has a life-span of 12 years, and schistosomes may survive for 30 years.)

DISTRIBUTION

Infestation of animals has been reported from all parts of the world, but particularly from sheep- and cattle-raising countries with marshy areas. The disease is particularly common in the West Indies, Central America and Central Africa. In the Far East it is much less common than clonorchiasis. In some parts of the British Isles 20-25% of sheep and cattle are infested, 90% of them coming from marshlands.

In South Africa animal infestation is fairly general in the summer-rainfall areas. Up to 75% of sheep and cattle have been infested with *F. hepatica* and *F. gigantica* in certain parts of the Bethlehem and Utrecht districts of the Free State, in portions of the Carolina, Volksrust and Ermelo districts of the Transvaal, and in various inland areas of Natal. In the winter-rainfall areas (Cape Western Province) infestation is much less common, and only occasional cases are seen, although isolated epidemics localized to particular farms have been reported. In the dry areas such as Namaqualand and South West Africa, infestation is very rare. The percentage infestation at various abattoirs in the Union is given in Table I. This naturally depends on the areas from which slaughter animals are drawn. Thus Pretoria, which draws its animals mainly from the Eastern Transvaal, where infestation is common, has a high incidence, while Johannesburg, which draws animals from all parts of the Union, has a comparitively low incidence.

TABLE I. PERCENTAGE INFESTATION AT MUNICIPAL ABATTOIRS

	Sheep	*Cattle*
Cape Town ..	0·06%	0·4%
Port Elizabeth ..	0·28%	3·42%
East London ..	3·5—5%	8·7%
Durban	2·7%	7·6%
Pietermaritzburg ..	'Seen almost daily'	'Seen almost daily'
Pretoria	10% *F. hepatica* and *F. gigantica*	10% *F. hepatica* and *F. gigantica*
Johannesburg ..	0·23%	1·47%
Kimberley	Nil	0·02%
Windhoek	Cattle and Sheep 0·47%	

Cases of human infestation have been noted in Cuba, Venezuela, Argentine, France, Germany, Hungary, Salonika, the Dardanelles, Belgian Congo, Moçambique, and the Far East. No South African cases have hitherto been reported. Human infestation appears to be particularly common in Cuba, whence two large epidemics have recently been reported. In the epidemic of 1944 a single doctor attended to over 40 affected patients, all of whom had eaten watercress. In the 1947 epidemic, which occurred in the same province, 52 patients were seriously affected. Apart from these there have been sporadic outbreaks where several members of a family were affected.

PATHOLOGICAL EFFECTS

When the definitive host is first infected the parasite or its waste products may be responsible for anaphylactic reactions (compare the swimmers' itch of schistosomiasis, and reactions to hydatid disease and ascariasis).

The major effects are due to destruction of the liver and irritation of the bile-ducts by the flukes. The young flukes destroy the hepatic parenchyma as they move about, leaving haemorrhagic tracts in their wake. As they grow the amount of destruction increases, resulting in multiple areas of focal necrosis and considerable loss

of blood with consequent anaemia. Heavy infestation, which is common in sheep but rare in man, causes great enlargement and congestion of the liver, with numerous small dark-red areas of necrosis containing the young flukes. Blood and parasites pass into the larger bile-ducts, and then into the intestines. Massive infestation may result in rupture of the liver capsule, with intra-peritoneal haemorrhage or frank bleeding into the intestine *via* the bile-ducts. This is the usual cause of the sudden deaths which occasionally occur in animals and, although it has not been reported in man before, was a major feature of our first case. In most of the human cases that have come to operation or autopsy the liver has been enlarged, with multiple small 'abscesses' containing necrotic material and a well-marked peri-hepatitis. This was well demonstrated in our first case, where the liver was studded with numerous necrotic abscesses, the largest of which were about 5 cm. in diameter. These were lined by vascular granulation-tissue, surrounded by epithelioid cells and giant cells and a peripheral zone with eosinophilic infiltration. (Others have noted the presence of Charcot-Leyden crystals in this zone.) In both animals and man these necrotic areas are liable to secondary infection. In sheep infection by *Cl. oedematiens* causes the condition referred to in Australia as 'black death'. In man pyogenic infection results in a septic cholangitis (Case 1).

As the disease becomes more chronic the effects of irritation of the mucosa of the bile-ducts by the adult flukes become manifest. A chronic cholangitis is produced (Fig. 5), with gross thickening (up to $\frac{1}{2}$ cm.) of the walls of the ducts, which become visible through the capsule of the liver as small yellowish streaks (in man) or thick white cords (particularly in cattle—Fig. 6).

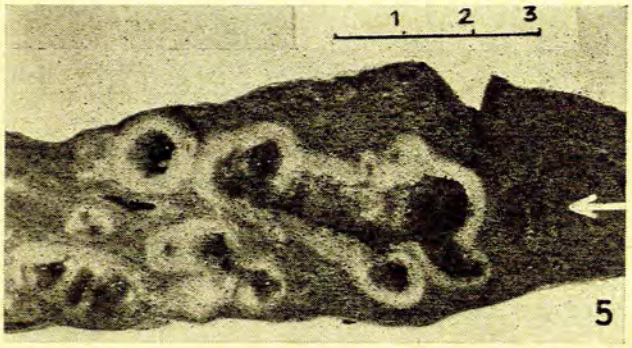

Fig. 5. Photograph of cut surface of ox liver showing grossly thickened and dilated hepatic ducts with calcified walls. The arrow points to an adult fluke. The scale shows 3 cm.

These cords are best seen on the inferior surface of the left lobe of the liver, which is usually mostly affected. In long-standing infestations the ducts become converted into inert, convuluted tubes, expanding in places into cavities or diverticula as large as a hen's egg, and lined by bile-stained fibrous tissue and calcareous material (Fig. 5). They contain numerous parasites and ova, epithelial debris, sandy concretions and muco-pus. The epithelial lining becomes markedly hyperplastic, and may undergo malignant changes (compare bilharziasis).

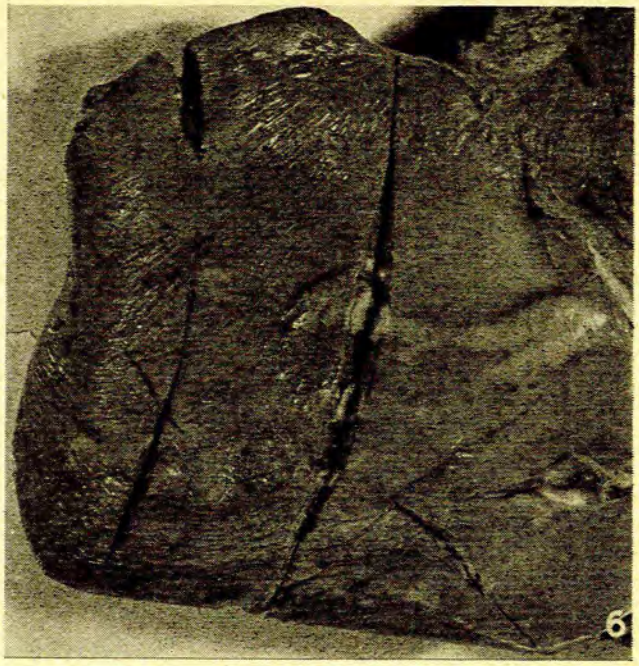

Fig. 6. Photograph of the under-surface of ox liver. The grossly thickened bile-ducts are visible through the capsule of the liver.

Anaemia is a common accompaniment, and is due mainly to loss of blood from the liver and to a lesser extent to a haemolytic toxin produced by the parasite or bleeding from oesophageal varices.

The adult flukes also tend to irritate and block the extra-hepatic bile-ducts, and give rise to jaundice (case 2). A striking feature is an intense inflammatory reaction in the walls of the ducts and peri-ductal connective tissue, which was well illustrated in our second case. Biliary stasis and the presence of foreign material in the ducts predispose to the formation of primary common-duct stones in both animals and man, and also to ascending septic cholangitis.

The gall-bladder is often normal although distended (both our cases), but it may show evidence of chronic inflammation with or without stones, or even an empyema. It is exceptional to find flukes in the gall-bladder (only 1 human case reported). Our first case was of interest in that there was an intense inflammatory reaction in the connective tissue surrounding the cystic duct, with diffuse infiltration of plasma cells, macrophages and eosinophiles and, in addition, localized foci of pseudo-tubercles surrounding recognizable ova (Fig. 4).

From the above it should be clear that *jaundice* may be due to a variety of causes, viz. multiple intra-hepatic 'abscesses' with or without cirrhosis, septic cholangitis, and obstruction of the common bile-duct by adult flukes (case 2), gall stones, or even blood clot (case 1). However, jaundice is not a constant feature and does not necessarily accompany hepatomegaly.

In ectopic sites, e.g. subcutaneous tissues, appendix, spleen, brain etc., similar granulomatous 'abscesses' are

produced. In addition, multiple haemorrhagic foci have been described in the lungs and a fibrinous peritonitis may occur expecially in cattle. Catarrhal changes in the intestinal mucosa are common, and may be due to irritation by the flukes or their waste products.

In the late stages of the disease there is gross wasting and oedema with hydrothorax and ascites. Terminal pulmonary lesions occur in animals and man.

SYMPTOMATOLOGY IN ANIMALS

In rare *acute cases* the animal dies suddenly with blood-stained froth appearing at the nostrils and the passage of blood *per anum*.

In *ordinary cases* the disease is insidious in onset, and the first symptoms occur when the young flukes have reached a fair size.

Sheep. At first the sheep shows a tendency to fatten. (In certain areas use is made of this fact by driving the sheep into marshy infected parts before they are sold!) Soon the animal becomes weak and 'off colour' from fever, loses its appetite, and becomes anaemic. As the pallor increases, the skin becomes dry and scaly, and the wool, becoming brittle, falls out in patches. Later oedema develops, especially in the intermandibular space—hence the name 'bottle jaw'. Death may occur at this stage or earlier, and there may be blood-stained diarrhoea or constipation.

Cattle. The most characteristic symptoms are digestive disturbances. There may be marked constipation, with passage of hard and brittle faeces, or severe diarrhoea. The animal becomes dull and weak, and in chronic cases there is marked cachexia with gross anaemia. Severe prostration is especially common in calves.

Other Animals. Weakness, anaemia and emaciation are the most prominent symptoms.

CLINICAL FEATURES IN MAN

In general the disease runs a protracted course, with chronic ill-health and a long history of gastro-intestinal and hepato-biliary symptoms, which fail to respond to the usual methods of treatment. Frequently, however, there are no symptoms, or else very mild digestive disorders, and infestation is 'accidentally' diagnosed by the discovery of ova in the stools. In some cases, acute obstruction of the common bile-duct may be the first clinical manifestation of the disease (case 2). Fulminating cases with severe haemorrhage from the liver (case 1) have not been reported before. In most of the reported cases the disease presents two phases, viz. the stage of invasion, and later the stage of established infestation.

THE STAGE OF INVASION

In this stage symptoms are produced by the young flukes as they pass through the liver to the bile ducts. The symptoms, viz. abdominal pain and anaphylactic reactions, appear during the incubation period of 2-3 months, and disappear when the flukes reach maturity.

Abdominal pain, which may be extremely acute or only mild, is usually present and associated with a slightly enlarged, tender liver. It is accompanied by slight fever and toxaemic symptoms, e.g. anorexia, listlessness or simply being 'off colour'.

Anaphylactic reactions may occur during this stage. Pruritus and urticaria are common. Pulmonary symptoms are not infrequent, including a dry, non-productive spasmodic cough, asthma and pleural effusion. Pains in the joints and muscles occur occasionally. *Eosinophilia* is a constant and important finding, and often presents at a high level throughout the illness. Counts of 40% are frequent, and occasionally they reach 80%. Sometimes no eosinophilia occurs, or the count may gradually fall as the general condition deteriorates (this was noticed in our first case). On treatment with emetine the eosinophilia gradually diminshes, but may not reach a normal figure until 4 months later.

THE ESTABLISHED DISEASE

Various clinical pictures are found, the commonest being gastro-intestinal and hepato-biliary. These will be discussed under separate headings, but it must be remembered that a mixed clinical picture is not uncommon.

1. *Gastro-intestinal Manifestations*

Pain is almost invariably present at some stage of the disease. It is situated in the epigastrium and right hypochondrium. Often it is mild and described as indigestion, or it may simulate the pain of peptic ulceration. Occasionally it is very severe. (Biliary pain will be referred to below.)

Anorexia is common. *Nausea* and *vomiting* may occur, especially during attacks of severe pain. Although *constipation* may occur, *diarrhoea* is commoner. Occult blood is often present in the stools, and accounts for the anaemia, which is a common finding. Only one case of frank melaena has been reported, but it was not severe. Our first case was thus unique in that he had several massive gastro-intestinal haemorrhages requiring virtually exchange transfusions. Occasionally there is alternating constipation and diarrhoea.

2. *Hepato-biliary Symptoms*

A painful and tender diffuse enlargement of the liver is common in the early stages and may be associated with jaundice. Later the organ may become firm and irregular, with a nodular surface. The liver function tests in our first case gave grossly abnormal results.

Attacks of biliary colic, usually associated with jaundice, are common, and are mostly due to obstruction of the common bile-duct by the adult flukes themselves (case 2). These attacks are usually associated with distention of the gall-bladder, which may become palpable. Eight previous cases of operative removal of flukes from the common bile-duct have been reported, and in 4 of them stones were present in the gall-bladder, but not in the ducts.

Enlargement of the gall-bladder is usually due to obstruction of the common duct by flukes, but in our first case it probably resulted from the massive haemorrhage into the biliary system. Very rarely it may be due to acute cholecystitis with empyema.

Although *jaundice* may be absent, even in very ill patients, it is commonly present. It may last from a few

days only to a week and be accompanied by biliary colic, which is caused by mechanical obstruction of the common bile-duct or, if lasting over a prolonged period, by septic cholangitis. In the latter event it is often associated with rigors, high fever, and a leucocytosis, while eosinophilia is often present.

Splenomegaly associated with the hepatomegaly has been recorded on a few occasions (case 1). It may be due to infestation of the spleen or may be secondary to portal hypertension.

In the late stages the *abdomen becomes distended*, with dilated subcutaneous veins, ascites and other evidence of cirrhosis.

3. *General Symptoms*

Pyrexia is usually present in the stage of invasion, and later when there is septic cholangitis. A low grade fever with malaise, headache and anorexia may be the only manifestation of the disease. This may continue for a prolonged period. Later oedema appears and gradually the patient becomes increasingly cachectic and dies after the passage of several years.

Anaemia is a very common finding, and is due mainly to loss of blood into the bile-duct and bowel. *Leucocytosis*, with an *eosinophilia* of 20 to 40%, is a characteristic feature of the disease.

Various *other symptoms* which are less frequent, include cough and dyspnoea, headaches, insomnia and other nervous manifestations and allergic phenomena.

4. *Ectopic Sites*

Catchpole and Snow (1952) reported a case that presented with a granulomatous nodule in the abdominal wall overlying the right iliac fossa. This apparently 'migrated' to the right subcostal area within a week, and when it was excised it was found to contain an immature liver-fluke. They collected from the literature 24 other cases of ectopic siting, 14 in the subcutaneous tissues (9 in the right hypochondriac area), 2 in the peripheral veins, 2 in the appendix, and one each in the cerebrum, urine, portal vein, stomach, and peritonium. In one case the site was not mentioned.

5. *Halzoun*

In the Lebanon an infection known as Halzoun (because of suffocation) occurs after the ingestion of raw infected liver from sheep and goats. The parasites attach themselves to the mucosa of the mouth and pharynx, causing irritation, congestion and oedema, with respiratory embarrassment and sometimes associated anaphylactic symptoms.

DIAGNOSIS

Infestation by *F. hepatica* should be considered in all cases of obscure hepatic disease, particularly in areas where animal infestation is known to occur. Intermittent pyrexia, evidence of septic cholangitis and gastro-intestinal symptoms are features which should suggest the possibility of fascioliasis, particularly if these symptoms occur in epidemics.

DIFFERENTAL DIAGNOSIS

The main conditions which have to be considered in the differential diagnosis are:

1. *Gastro-intestinal diseases*, e.g. peptic ulceration, enterocolitis, and even carcinoma of the colon.
2. *Hepato-biliary diseases*, particularly cholelithiasis and also other causes of jaundice and hepatic enlargement.
3. *Other parasitic diseases:*

Amoebiasis, which is a common cause of diarrhoea and painful hepatomegaly in tropical and subtropical countries may present a very similar clinical picture. Since both amoebiasis and fascioliasis respond to emetine therapy, response to the drug cannot be taken as evidence in favour of either disease. It is possible that cases of fascioliasis have been mistaken for amoebiasis for this very reason.

Clonorchiasis produces a clinical picture which is indistinguishable from that of fascioliasis, but is almost entirely confined to the Far East, where up to 50% of the inhabitants in some districts are affected.

Fasciola gigantica, which is related to *F. hepatica* but larger (up to 75 mm. in length) and without a cephalic cone, is found chiefly in Africa and the Far East, where it may give rise to difficulties in diagnosis. Human infestation is very rare, but at least one case has been reported.

Schistosomiasis may affect mainly the liver and intestinal tract, and produce gross hepato-splenomegaly, but jaundice is uncommon. This disease also responds to emetine which, therefore, cannot be used as a therapeutic test.

Hydatid Disease of the liver is a fairly common cause of hepatomegaly in sheep-raising countries and, if the hydatids rupture into the larger intra-hepatic bile-ducts, the clinical picture may resemble that of *fascioliasis* very closely. Daughter cysts, like *F. hepatica*, may cause intermittent obstruction of the common bile-duct, with biliary colic, jaundice and a palpable gall-bladder, or rupture may be followed by secondary infection and a septic cholangitis.

Ascariasis may be responsible for mild toxaemic and digestive symptoms. Occasionally the parasite may enter the common bile-duct and cause biliary colic and jaundice associated with a palpable gall-bladder (we have encountered several such cases).

INVESTIGATIONS

1. *Eosinophilia* is an important finding in fascioliasis, and, in obscure cases, would suggest the possibility of a parasite infestation. It is usually more marked in fascioliasis than in other parasitic diseases.

2. *Ova in duodenal aspirate.* When the flukes are mature and passing eggs into the bile, the most reliable method of establishing the diagnosis is to find the ova in bile obtained by duodenal aspiration. In characteristic cases the bile contains brownish yellow floccules in which the ova are to be found. Possible sources of error are the unfertilized ova of *Ascaris lumbricoides* (which seldom inhabits the duodenum), and the ova of *Fasciolopsis buskii* (which is encountered in the Far East only.) This method of diagnosis was attempted in our first case but failed.

3. *Ova in the stools.* Ova may be recovered from the faeces in both human and animal cases. The faeces are

mixed with 50% glycerine and centrifuged. Other parasitic eggs float to the surface, but the heavy ova of *F. hepatica* sink to the bottom. The diagnosis in our first case was established by finding ova in the faeces and later in the connective tissue around the cystic duct. False positives may be obtained in subjects who have eaten infected livers that have not been adequately cooked.

4. *Intradermal and complement-fixation tests*

In the stage of invasion and while the flukes are maturing, which may take up to 3 months, the intradermal and complement-fixation tests may be of value. Although there appears to be some doubt about the reliability of these tests, Lavier and Stefanopoulo (1944) are quite emphatic about their value. Admittedly, their series was very small, but they had no false positives and no false negatives; 5 patients with fascioliasis were tested with intradermal and complement fixation tests, and all gave positive results for both tests. Four of the patients had had symptoms from 4 months to 10 years, and a 5th had had the disease for 10 years but had been cured by emetine treatment 6 months before the tests were made. The controls were 3 patients with Loa Loa infection, 1 with *Taenia saginata*, 1 with hydatid disease, 2 with serologically positive tests for syphilis, and 3 without fascioliasis who showed respectively an eosinophilia of 50%, a 'moderate' eosinophilia and a normal eosinophile count. All the controls gave negative intradermal and complement fixation tests to *Fasciola hepatica* antigen and all the patients with fascioliasis gave negative tests to antigens prepared from the other parasites. No antigen from Bilharzia was used in the tests; this may give false positive results, since *Fasciola hepatica* and schistosomes are closely related. The antigen was prepared by Farley's method as follows:

For the *intradermal test* fasciola obtained from the slaughterhouse were dried and powdered and 1 g. of the powder was kept in 100 c.c. of physiological saline for one day at 37° C and the supernatant fluid filtered through a Seitz filter. For use it was diluted 1 : 4 or 1 : 5 or more. The antigen gave an immediate intradermal reaction; after 3-5 minutes a wheal with pseudopodia appeared, which reached 3 cm. in diameter, erythema appearing later. In 1-2 hours both erythema and wheal had disappeared, but infiltration of the skin and tissues round the reacting area persisted for 4-6 hours. After 24 hours the reaction had disappeared completely. Delayed reactions were not observed but some patients who gave strongly positive reactions showed delayed phenomena such as generalized urticaria or pain and swelling of neighbouring joints and 2 showed nausea, profuse diarrhoea lasting several hours, and shock. Subjects sensitive to foreign proteins may show false positive reactions, but these reactions are usually surrounded by a small erythematous halo not more than 1 cm. in width, which disappears very quickly.

For the *complement-fixation test* 1 g. of dried and powdered *Fasciola hepatica* was dissolved in 100 c.c. of absolute alcohol, and kept at 37° C for 24 hours, filtered and evaporated until, when it was evaporated to $\frac{1}{3}$rd of its volume, it (usually) became cloudy. Absolute alcohol was added to make up the initial volume and the precipitate disappeared. This final solution formed the antigen. It was usually effective at a dilution of 1/20.

TREATMENT

Prophylaxis

1. Eradication of the intermediate host. The snails may be destroyed by burning the vleis and marshes in the dry season. This is simple and cheap but not entirely successful. A better but more laborious and expensive method is to add some chemical such as copper sulphate to the water. The details of this method can be found in any standard veterinary text-book.

2. Infection can be avoided by not eating watercress etc., and by boiling or filtering all drinking water that might be contaminated.

Curative Treatment

Animals. Pure carbon tetrachloride was formerly used for sheep, but was too toxic for cattle; now hexachlorethane is used for both sheep and cattle. It is recommended that sheep recently removed from pastures should have a second course of treatment after 4-6 weeks, on the supposition that the young flukes in migration may not be destroyed.

Man. The fluke normally lives for 9 months (though it may live up to 5 years), and mild infestations with minimal symptoms may be self-limiting, provided that re-infestation does not occur.

Emetine is specific and should be given as soon as the diagnosis is made. Gradwohl and Kourí advise consecutive daily subcutaneous injections of 4 cg. till a total equivalent to 0·5 cg. per kg. of body-weight has been reached. A second course of treatment has not been recommended in man, but our first patient failed to respond to a single course of emetine, and yet made a dramatic recovery after the second course, which was given 4 months later.

Surgical treatment is not necessary, provided the diagnosis can be made without operation. If, however, diagnosis is only made at operation during exploration of the common bile-duct, the flukes should be removed and the duct drained by a T tube. This should be left *in situ* for varying periods depending on the degree of inflammation and fibrosis of the duct. The gall-bladder in these cases should be opened, for it may contain flukes occasionally, but it need not be removed unless it contains stones or is inflamed.

Operative intervention for haemorrhage is of no avail, as illustrated by our first case.

CASE REPORTS

Case 1

J.C L., a European boy aged 3 years and 4 months, was admitted to the Groote Schuur Hospital, Cape Town, on 7 March 1953. He had been resident in the Belgian Congo for 15 months, and became ill 9 months before admission. During these 9 months the following were the main clinical features:

1. Recurrent febrile episodes (100-102° F), with upper abdominal pain, vomiting and diarrhoea.
2. Progressive anaemia and listlessness and increasing pallor but weight stationary at 30 lb.
3. White blood cells varying (in 5 counts) between 12,600 and 18,900 per c.mm., with eosinophiles varying between 17% and 32%.

4. Hepatomegaly, first detected 4 months before admission.
5. Two episodes of malaena—on each occasion a blood transfusion of 300 ml. had to be given.

The salient features on admission were as follows:

1. Gross pallor (haemoglobin 5·5 g.%).
2. Pyrexia of 100-104°F.
3. Gross hepatomegaly, with 3 nodules on the surface of the right lobe of the liver.
4. Gall-bladder palpable.
5. Tip of spleen palpable.
6. Signs in the lungs suggestive of pneumonia.
7. White-cell count 16,700 per c.mm., with 24% eosinophiles.
8. Blood in the stools.
9. Grossly abnormal liver function tests (thymol turbidity 5, thymol flocculation 4, colloidal gold 4).

Stools were sent for microscopical examination and culture, and on two occasions ova of *F. hepatica* were isolated.

Progress in hospital was briefly as follows:

1. A blood transfusion (500 ml.) was given immediately and the boy was put on emetine, gr. 1/5 daily for 10 days, and antibiotics. No dramatic improvement followed, but the malaena ceased, and the gall-bladder became impalpable. Ova of *F. hepatica* disappeared from the stools after 1 week and were never found again.

2. For 6 weeks he had recurrent episodes of high fever, accompanied by severe malaena, jaundice and enlargement of the gall-bladder. These lasted for 3-4 days, during which time he had to be transfused (300 to 1,500 ml. per transfusion). The episodes were succeeded by remissions of 1-2 weeks.

3. Six weeks after admission *laparotomy* was performed (J.H.L.) to look for flukes in the common bile-duct and a possible source of bleeding (e.g. Meckel's diverticulum) in the small bowel. The liver was found to be grossly enlarged, with marked peri-hepatitis and studded with numerous small necrotic 'abscesses' (material from these contained necrotic tissue and foreign-body giant-cells, but no flukes or ova). The common bile-duct was thickened and slightly distended but on exploration no flukes or calculi were found. The gall-bladder was distended and, although not obviously diseased, was removed. (On histological examination by Dr. Golda Selzer this revealed an extensive intense inflammatory reaction in the connective tissue surrounding the cystic duct. There was a diffuse infiltration of plasma cells, macrophages and eosinophils and, in addition, localized foci of pseudo-tubercles around large ova of *F. hepatica*—Fig. 4. The gall-bladder showed a thickened serosa and a limited inflammatory-cell infiltration of its wall.)

The patient seemed to improve after the operation, but within a week the episodes of fever with jaundice and melaena recurred and now blood also poured from the T-tube that had been inserted in the common bile-duct. Further transfusions were required on several occasions.

A cholangiogram done about 6 weeks after the operation, during an unusually prolonged remission, revealed no abnormality of the biliary tree, and the T-tube was removed. Soon afterwards there was a severe relapse, which was followed by several more during the next few weeks.

4. Nine weeks after the cholecystectomy it was decided to perform another laparotomy in a desperate attempt to get to the source of bleeding, which had become practically uncontrollable. At this operation (J.H.L.) several large necrotic areas in the liver were explored, but the exact source of the bleeding could not be found. The liver was riddled with 'abscesses', some of which projected from its surface.

The child was now *in extremis*. Cortisone was given with no effect and he required many more blood transfusions. By this time he had had 15 transfusions amounting to approximately 6 litres; in one period of 3 weeks no less than 3 litres were given. His blood volume was only 1,500 ml. and on one occasion a single transfusion of 1,500 ml. was required.

5. When he had been in hospital for 4 months, and the condition appeared to be hopeless, he was given another course of emetine, which was followed by immediate and dramatic improvement, cessation of all bleeding and rapid recovery.

6. He was discharged in a fit condition 1 month later, the only abnormality being an enlarged, firm, irregular liver. When last seen in July 1956 (3 years later) he was quite well.

Comment. This case is unique because of his young age, the severe haemorrhage, and the fact that a second course of emetine was required to effect a cure.

Case 2

E.Q.G., a European male aged 45, was referred by Dr. G. J. Budow, of Goodwood, with a history of an attack of severe biliary colic in January 1955, followed by jaundice with pale stools and dark urine for 14 days. In March he again had severe biliary colic followed by jaundice lasting 3 days. There had been no febrile illness or urticaria before the first attack. He was a commercial traveller, but had not been outside the Cape Peninsula for several years and had never drunk water from any stream or pond, but admitted to being very fond of lettuce and watercress.

A clinical diagnosis of stone in the common bile-duct was made and operation advised. Cholecystogram and barium meal were normal.

At operation (W.W.) the liver was normal, but the gall-bladder was distended to about twice the normal size. It contained no calculi and was not thickened or inflamed. The common bile-duct was white, thickened and obviously inflamed when it was explored. Four flat leaf-like structures were removed, which Dr. Selzer identified as liver flukes (*F. hepatica*). There were no stones and a probe passed easily into the duodenum. The gall-bladder was opened, but it contained no flukes or calculi. The gall-bladder and common bile-duct were drained, the latter by a T tube, which was removed after 3 months.

Emetine hydrochloride, gr. 1, was given daily by subcutaneous injection for 10 days. On the 8th day a solitary ovum (Fig. 2) was recovered from the bile, and so a second course of emetine was given after an interval of 10 days. No further ova were recovered.

The patient made an uneventful recovery and has had no further symptoms.

Comment. This is the 9th reported case of operative removal of *F. hepatica* from the common bile duct.

SUMMARY

The distribution, clinical features, diagnosis and treatment of infestation of animals and man by *Fasciola hepatica* are described, and 2 cases of human infestation recently encountered are reported.

It is pointed out that animal infestation is common in certain summer-rainfall areas of South Africa, and it is suggested that human infestation may be less rare than is generally believed.

In endemic areas the condition should be suspected in all persons who present with obscure hepato-biliary disease, especially if associated with anaemia, eosinophilia or bleeding from the intestinal tract.

The diagnosis can be established by recovery of ova from the duodenal aspirate or stools of the patient. Complement-fixation and intradermal tests are available, and may be of some value.

Treatment with emetine is specific, and usually highly successful, but 2 courses at an interval of 1-2 months may be necessary in recently infected cases. Surgical treatment should rarely be necessary, but may be required for obstruction of the common bile-duct.

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