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FASCIOLIASIS IN MAN: AN OUTBREAK IN HAMPSHIRE

BY

R. V. FACEY, B.M.

Senior Pathologist, Bournemouth and East Dorset Group of Hospitals

AND

P. D. MARSDEN, M.B., M.R.C.P., M.R.C.P.Ed., D.T.M.&H., D.A.P.&E.

Formerly Medical Registrar, Hospital for Tropical Diseases, London

During the autumn of 1958, in the Hampshire market town of Ringwood (population 7,000), several patients presented themselves with a mysterious illness characterized by pain in the right hypochondrium and an irregular pyrexia lasting over six weeks. The most striking finding in each case was the presence of a marked eosinophilia. Some form of helminthiasis was naturally suspected, and the symptoms suggested the possibility of infection with the liver fluke *Fasciola hepatica*. This theory was supported by the evidence of a veterinarian that the incidence of the infection among local farm animals was very high. A preliminary notification of this outbreak has been published (Facey, 1959).

Six cases are here reported, in five of which the diagnosis was subsequently confirmed by the finding of ova of *F. hepatica* in the faeces. Several other cases with similar symptoms were seen, but have not been included because the diagnostic evidence was not fully conclusive.

So far as we can discover this is the first occasion that epidemic infection with this helminth has been recorded in Britain. A search of the records back to 1903 has revealed reports of 12 cases, but all were isolated observations and in most of them the parasite was found at operation or necropsy (Ward, 1911; Owen, 1928; Patterson, 1928; Biggart, 1937; Manson-Bahr and Walton, 1941; Shaw and Clyne, 1941; O'Donnell, 1949; Murphy and Pascall, 1950, three isolated cases; Ramage, 1951; Catchpole and Snow, 1952). Ward refers to four earlier cases, bringing the number up to 16 in all. Several hundred cases have occurred abroad, including a number of outbreaks of acute illness due to the invasive stage of the disease. The countries most affected have been Latin America, France, Algeria, and Russia.

In the present communication the world literature is reviewed and our own cases are reported in some detail in the expectation that other outbreaks will come to light in this country from time to time.

The Outbreak

It is probable that three aetiological factors have combined to cause this outbreak. The disease is endemic in the Ringwood district of the Avon Valley, where nearly 100% of the cattle in some herds are infected and sheep cannot be reared; secondly, there are a

number of natural watercress beds near by; and, thirdly, we have the precipitating cause, the wet summer of 1958.

All the patients live in this area and all of them were in the habit of eating watercress frequently.

The first patient, a general practitioner, was treating himself until one of us (R. V. F.), called in as pathologist, took charge of the case. After investigations at home and in hospital the patient was sent to London with a confident diagnosis of fascioliasis. At the Hospital for Tropical Diseases the diagnosis was confirmed by the finding of the ova of *F. hepatica* in the faeces. Throughout nearly all his illness he has been under our close observation.

The other patients were seen in neighbouring hospitals and at the laboratory of the Royal Victoria Hospital, Bournemouth. The two general practitioners principally concerned soon became able to spot likely cases by the liver tenderness, the fever, and asthenia, especially if accompanied by urticaria.

In five of the cases acute symptoms began during November, 1958, to January, 1959.

Case 1

A doctor aged 57 had always been healthy until 1958, when he had transient bouts of haematuria with pain after micturition, occurring in March and again in October. A blood count then showed eosinophils 2% (see Table) and a culture of the urine was sterile. There was a third attack on December 13, and after this he had an evening pyrexia, but he kept at work until December 20, when he had a rigor and his temperature rose to 104° F. (40° C.). A profuse sweat followed. The next morning he was afebrile, looked relaxed, and had no complaints, but from then on he kept to his room.

On examination the liver was enlarged two fingerbreadths below the costal margin; it was smooth and soft, and at this stage was not tender. No other abnormality was found except that a blood count gave eosinophils 19% (874/c.mm.).

The pyrexia and sweats continued during the next few weeks; temperature 98–103° F. (36.6–39.4° C.). He began to complain of slight discomfort over the whole abdomen. The only other symptoms were constipation, impaired powers of concentration, and increasing weakness.

An agglutination test against *Brucella abortus*, two blood cultures, and liver-function tests were all negative, but his condition was steadily deteriorating, and on January 2, 1959, he was admitted to Salisbury Infirmary. While in hospital

he complained for the first time of severe attacks of pain in the right hypochondrium, his liver increased in size and became tender on palpation, and he had an attack of urticaria. A skiagram of the chest was normal. Serological examination for leptospira and examination of faeces gave negative results. Treatment was empirical with antibiotics and antihistamines. There was no response and he discharged himself.

When seen again at home he was very weak and still had an irregular pyrexia. His pulse, previously unaffected, had increased to 120 a minute. Normally rotund and rubicund, he had lost 2 st. (12.7 kg.) in weight, his eyes and temples were sunken, and his skin had an extraordinary earthy colour. The bouts of pain were becoming more severe. The pain was "like toothache," always in the same spot, deep to the right lower ribs anteriorly. There was also referred pain at the tip of the right shoulder. The bouts came on suddenly, lasted a few hours, and then quickly passed off, leaving a feeling of discomfort, which persisted until the next bout. He was never jaundiced at any time.

When the case was reviewed at the end of January the most significant abnormality was thought to be the eosinophil count, particularly since two other patients (Cases 2 and 3) showing the same abnormality were then under investigation. The liver fluke was suspected, and inquiries confirmed the high incidence among farm animals in the district. All three patients declared that they were habitual consumers of watercress, and as they were all febrile with "liver pain" and two had enlarged tender livers it was thought that a presumptive diagnosis had been established.

In view of the weakened condition of our patient (Case 1) it was decided to send him to the Hospital for Tropical Diseases for treatment, though examination of the faeces had, so far, been negative.

On admission on February 5 the liver was enlarged four fingerbreadths below the costal margin, firm, regular, and tender. No other physical signs were noted. Examination of faeces revealed scanty operculated ova of *F. hepatica*. The complement-fixation test for fasciola was strongly positive; the total leucocyte count was 7,600/c.mm., of which 47% were eosinophils.

Treatment was started on February 10 with chloroquine 300 mg. eight-hourly. After a week he complained of dizziness and developed a marked tremor. The dose was cut to 150 mg. six-hourly and he tolerated this quite well. The pains soon stopped, and on February 22 he returned home.

While in London he had lost more weight, making a total of 3 st. (19 kg.), but the acute symptoms had subsided and on return home his liver was only two fingerbreadths below the costal margin. His colour was still earthy and had a greenish sheen. He completed the treatment by March 23—total chloroquine 33 g.—and started work in April. In March and again in July electrophoresis of his serum showed a considerable increase in gamma-globulin.

By December, 1959, he was almost free from symptoms and had regained some weight, but his liver was still slightly enlarged. His blood count was normal, eosinophils 5%, erythrocyte sedimentation rate 10 mm. in one hour, and the electrophoretic pattern of the serum had returned to normal. Live ova of *F. hepatica* were still present in the faeces.

(It is possible that the initial attacks of haematuria were due to ectopic flukes, but the normal count in October, 1958, suggests that at that time the larvae had not entered the liver.)

Case 2

A factory worker aged 48 who had always been healthy began to feel tired in November, 1958. On December 17 he started to have an irregular pyrexia, temperature 98.4–101° F. (36.9–38.3° C.), with some abdominal discomfort. Early in January, 1959, he got an aching pain in the right hypochondrium and right shoulder. He was a muscular man and neither liver nor spleen was palpable. He had lost 1 st. (6.4 kg.) in weight.

Investigations showed leucocytes 7,400/c.mm., eosinophils 47%. Agglutination tests against *Br. abortus* were negative.

Two examinations of faeces were negative, but on February 17 scanty operculated ova of *F. hepatica* were found in them.

Treatment was then started with hydroxychloroquine sulphate 600 mg. daily, and in spite of some side-effects the treatment was continued for six weeks. At the end of this period he was ambulant, afebrile, and free from pain, but viable ova were still present in the stools. Early in May the pain and fever returned, the eosinophil count was 28%, and ova were still present in the faeces.

He was given two courses, each of 18 injections, of emetine hydrochloride $\frac{1}{2}$ gr. (32 mg.) subcutaneously. After these he remained afebrile and free from symptoms. He put on weight and returned to work. From the middle of the first course of emetine onwards the faeces were free from ova. Six tests have been made, the last in January, 1960, when the eosinophil count was also normal (4%). It is hoped he is cured.

Case 3

A housewife aged 45 had a history of malaria in the Sudan in 1944. She returned to England in 1945, and in 1957 she had a cholecystectomy for gall-stones. Early in November, 1958, she complained of abdominal discomfort in the right upper quadrant and pains "all over her." A pain in the right shoulder was aggravated by coughing. In December she began to have sudden attacks of dull pain in the epigastrium and right hypochondrium, "nearly passing out" with them. The liver was just palpable, but the spleen could not be felt. There was a slight irregular pyrexia.

The eosinophil count was 18%, later rising to 40%. The Westergren sedimentation rate was 40 mm. A liver biopsy was carried out in Southampton Hospital, and Dr. R. A. Goodbody reported: "The portal tracts are infiltrated by polymorphs, histiocytes, and quite large numbers of eosinophil leucocytes" (Fig. 1).

FIG. 1.—Case 3. Liver biopsy. Fascioliasis ($\times 450$). By courtesy of Dr. R. A. Goodbody. (Photomicrograph by Mr. J. Wilson.)

After two negative examinations a specimen of faeces examined on February 18 showed scanty ova of *F. hepatica*.

Treatment was started with chloroquine sulphate 800 mg. daily, but was not well tolerated. The dose was reduced and by the end of three months 30 g. had been given. She has since had repeated bouts of abdominal discomfort, but so far has refused further treatment. Ova of *F. hepatica* were still present in the faeces in January, 1960, though her eosinophil count was only 2%.

Case 4

A housewife aged 56 was in Kenya from 1930 to 1951. While there she had amoebic dysentery and malaria. She had suffered from migraine for some years, and in August, 1958, began to lose weight. In September she complained of weakness, cough, tightness across the upper part of her

chest, and slight pain at the left base on inspiration. There were signs of bronchitis but no fever, and a chest x-ray film was negative. Antibiotics brought no improvement. From January to March, 1959, she had an irregular pyrexia with a temperature of 98 to 101° F. (36.7–38.3° C.). By March 7 she had lost 2 st. (12.7 kg.) in weight, had been bedridden for eight weeks, and was deteriorating. She was admitted to hospital in Bournemouth. On examination the tip of the spleen was just palpable but there were no other physical signs. The liver was not enlarged. A routine blood count showed eosinophils 44%, and an examination of faeces next morning showed ova of *F. hepatica*.

On March 13 treatment was started with chloroquine sulphate 900 mg. daily, but she soon developed tremors, marked visual incoordination, nightmares, and dryness of the skin. The dose was reduced to 600 mg. and eventually to 150 mg. daily. A total of 35 g. was given.

It was soon impossible to feel the spleen, and after the treatment she regained some of her lost weight. Her general health improved. In October, 1959, a blood examination showed leucocytes 7,500/c.mm., eosinophils 10%, E.S.R. 16 mm. in one hour. The faeces still contained a few ova of *F. hepatica*.

Case 5

A housewife aged 59 had a history of a perforated gastric ulcer in 1938 but no other significant illnesses. She moved to Ringwood and started to eat watercress on November 1, 1958 (she was able to fix this date precisely). The symptoms started suddenly on December 8 with severe epigastric pain which did not radiate. There was a transient urticarial rash. The pain eased and she was fairly well until May 30, 1959, when she had a sudden attack of pain in the right iliac fossa, moderate pyrexia, and another attack of urticaria. She vomited, and on June 4 the pain became worse. She was admitted to Salisbury Infirmary as a case of "acute abdomen." On examination the temperature was 99° F. (37.2° C.), the pulse was 96, and the tongue was clean. There was a hard and acutely tender mass in the right side of the abdomen. Though on palpation this mass was apparently continuous with the liver it did not move on respiration. It was dull on percussion. The chest was clear.

Investigations.—I.V.P. and barium enema showed no abnormalities. June 4: leucocytes 7,000/c.mm., eosinophils 32%, E.S.R. 46 mm. in one hour; plasma proteins normal; examination of faeces revealed the ova of *F. hepatica*; the urine was normal.

Treatment was started on June 19 with chloroquine sulphate 250 mg. t.d.s., and after two weeks the dose was increased to 200 mg. q.i.d. After 12 weeks she had taken 66 g. and was suffering from visual incoordination, giddiness, and anorexia. By this time, the middle of September, she had lost nearly 2 st. (12.7 kg.) in weight, but the mass

had disappeared and the liver was not palpable. When seen again in March, 1960, she was well except for occasional niggling pains in the right hypochondrium. She was gaining weight. A blood examination showed 8% eosinophils. Liver-function tests were normal. The faeces contained a few ova of *F. hepatica*.

Case 6

A housewife aged 30 had a history of a short attack of pain in the right hypochondrium in 1957 but no other illness. In January, 1959, she had a violent attack of epigastric pain and a brief urticarial episode. In March she had a pain "like a stitch" under the right costal margin and referred pain in the right shoulder. There was an irregular pyrexia, the temperature reaching 103° F. (39.4° C.). The liver was just palpable and tender. By the end of April she had no symptoms except weakness and dyspepsia and there were no physical signs. The haemoglobin was 75%, leucocytes 14,000/c.mm., eosinophils 28%, E.S.R. 43 mm. in one hour. Examination of the faeces failed to show any ova, but the complement-fixation test for fasciola was strongly positive.

She was given a course of chloroquine sulphate, total 20 g. The eosinophils fell to 11%, and when seen in August she was free from symptoms and the faeces still contained no ova.

Comment

All the more important characteristics of the invasive phase were illustrated in the illness of the first patient, and with less severity in those of four of the others. With one exception they were all examples of the hepatic syndrome, with hepatomegaly in four cases. One patient (Case 4) showed the respiratory syndrome, probably due to ectopic flukes, and she alone had splenomegaly. Another (Case 5) probably had an ectopic fluke in the right iliac fossa which may have been due to a second infection.

It seems probable that the actual infection of at least two of the patients (Cases 1 and 5) took place in October or November, 1958. The ova were found in the faeces of the first three patients in February, 1959. If they were all infected at about the same time this allows a period of three to four months for the parasites to attain sexual maturity, the minimum possible.

Five patients were treated with chloroquine sulphate and one with hydroxychloroquine sulphate. Three of them took 30 g. or more in six weeks; in the others the dose had to be reduced. All complained of troublesome side-effects, especially tremors and visual disturbances. (Possibly the liver damage impaired their tolerance.)

Details of Cases

	Case 1				Case 2			Case 3		Case 4		Case 5		Case 6	
Date of onset of acute symptoms:	20.12.58				17.12.58			3.11.58		1.8.58		8.12.58		30.1.59	
	1958		1959		1959			1959		1959		1959		1959	
	Oct.	Dec.	Jan.	Mar.	Jan.	Feb.	May	Feb.	Apr.	Mar.	May	June	Sept.	Apr.	July
Haemoglobin (%)	104	100	80	78	94	108	88	87	—	75	83	95	86	75	88
.. (g./100 ml.)	15.2	14.6	11.7	11.4	13.7	15.8	12.8	12.7	—	11.0	12.1	13.9	12.5	11.0	12.9
Leucocytes c.mm.	5,900	4,600	—	5,200	7,400	9,030	6,100	9,100	—	9,500	6,500	7,000	3,710	14,000	6,700
Eosinophils (%)	2	19	29	45	47	32	28	24*	—	41	9	32	9	8	11
.. c.mm.	118	874	—	2,340	3,478	2,880	1,708	2,184	—	4,180	585	2,240	333	4,000	737
E.S.R. (Wintrobe) mm. hour	3	29	47	49	15	21	43	15	—	38	14	46	16	43	10
Thymol units	—	—	6	5	—	—	1	4	—	—	—	—	—	—	1
Alkaline phosphatase units	—	—	18	19	—	—	31	9	—	—	—	—	—	—	6
Bilirubin (mg./100 ml.)	—	1.0	0.8	0.5	—	—	1.2	0.5	—	—	—	—	—	—	0.8
C.F.T.	—	—	—	+++	—	+++	—	+++	—	+++	—	+	—	—	+++
<i>F. hepatica</i> ova in faeces	—	—	Neg.	+	Neg.	+	+	+	+	+	+	+	+	Neg.	Neg.

* When this patient was in the Southampton Hospital in January the eosinophil count was 40%.

Chloroquine quickly relieved the symptoms in every case but it completely failed to kill the flukes, for all the patients continued to pass ova with the exception of the last, in whose faeces they have never been found. All refused further treatment except one (Case 2) who had a relapse and was given two courses of emetine, after which the ova disappeared from his faeces.

Though all the patients were free from acute symptoms several still complained of occasional abdominal discomfort and at least four were still infected.

Blood Changes.—Every patient had a high eosinophilia, the average initial count being 34%. In only one case was there a leucocytosis. Anaemia was not a prominent feature, but a chance observation in one patient (Case 1) whose haemoglobin fell nearly 3 g. in a month may be of some significance. In December, 1958, films prepared from defibrinated and incubated blood showed marked spherocytosis and avid erythrophagocytosis, an abnormality not seen in straight films of his whole blood. The reticulocyte count was 1.8%, the Coombs test was positive, optimum A.H.G. dilution 1/16, but cold agglutinins were not detected at 4° C. or 20° C. The bilirubin was 1 mg./100 ml. These results are thought to suggest sensitization of the red cells to a circulating antibody. A high red-cell sedimentation rate was found in all cases, and it was sustained for some time after the acute symptoms subsided.

Liver-function tests were generally not very helpful, but electrophoretic studies showed an increase in serum gamma-globulin in four cases. The shape of the curve suggested that this was due to antibody formation. The complement-fixation test for fasciola was positive in all six cases. A liver biopsy (Case 3) showed a marked infiltration of eosinophils.

Faeces were examined for ova by a modified formal-ether method (Ridley and Hawgood, 1956), which proved very reliable. Ordinary flotation methods were not satisfactory. Care was taken in each case to ensure that the patient had eaten no offal for at least eight days before the test.

Review of the Literature

Valuable studies have been made by Burgi (1936), in Germany, who collected 186 cases from the literature; by Kourí (1948), in Cuba, with experience of 100 cases; by Rodriguez (1952), in Argentina, with 20 cases; by Rial *et al.* (1951), in Uruguay; and by Lavier and Marchal (1942), in France. It seems worth while to give a general description of the disease based on these publications and others, since the literature on the subject in English is somewhat scanty.

Aetiology and Natural History.—*F. hepatica* is normally a parasite of herbivora, particularly sheep. The mature flukes live in the bile-ducts of the host, their eggs being passed in the faeces. In wet and muddy conditions the eggs hatch, giving rise to motile forms, the miracidia which enter snails (Figs. 2 and 3), where they multiply and whence they emerge as tadpole-like cercariae, soon losing their tails to encyst on water-side vegetation as just-visible snow-white cysts (Brumpt, 1949). Three wet summer months are necessary to permit the development of the snail, *Limnaea truncatula*, and the fluke. Outbreaks may occur in animals or humans in the following autumn or spring (Ollerenshaw, 1958). In all countries where human fascioliasis has been reported watercress

has been found to be the usual vehicle. When the infected herb is ingested the parasite excysts in the duodenum of the host, penetrates the gut wall, passes

FIG. 2.—Ovum of *Fasciola hepatica* (×400). (Photograph by Mr. R. H. Hunt.)

through the peritoneal cavity, and enters the dome of the liver through Glisson's capsule. The larvae plough through the liver substance to enter the bile-ducts, where they grow to maturity and start to lay eggs. From the time of ingestion of the infected vegetation this process takes three or four months (Krull and Jackson, 1943). The site of the parasite and its stage of development determine the "phase" of the disease, a distinction of prognostic and therapeutic importance.

FIG. 3.—Adult *Fasciola hepatica* and its intermediate host, the snail *Limnaea truncatula*. (Photograph by Mr. R. H. Hunt.)

Phases of the Disease

The acute illness of the *invasive phase* is due to allergic, immune, and toxic local and general reaction to the presence of *larvae in the tissues* (Craig and Faust, 1951). Liver biopsies* have shown the paths of the larvae, leaving tracks of necrosis with infiltration of histiocytes, of polymorphs, and notably of eosinophils. There are vascular thromboses and associated areas of necrosis (Claisse and Hartmann, 1954).

The *symptoms* of this phase have been well described in a report on 52 Cuban cases by Arenas *et al.* (1948). Similar observations have been recorded in European and Algerian cases by Martin *et al.* (1944), Sédallian *et al.* (1949), Brouet *et al.* (1951), Meriel *et al.* (1954), Bickel and Secretan (1954), Lemoine (1954), Jacquemin and Rool (1957), and Michon *et al.* (1957). Levina (1950), recording 20 cases in the Moscow district, gave almost identical descriptions.

After a short period of dyspepsia and, perhaps, of slight fever, the onset is usually abrupt, with high fever and abdominal pain.

*A good description of the lesions due to the similar fluke, *F. gigantica*, is given by Stemmermann (1953), who ascribes the toxic effects to digestive enzymes liberated by the larvae.

The *pain*, which can be excruciating, is likened to toothache or cramp, coming on in waves, dragging, less often stabbing or a "stitch"; it is often aggravated by coughing or movement. It lasts some hours, and on passing leaves a feeling of weight which persists until the next attack. The pain may be general over the whole abdomen, but it soon becomes localized in the right hypochondrium or sometimes in the epigastrium. Radiation to the tip of the right shoulder is common.

The *liver* is often much enlarged, sometimes reaching down to the right iliac fossa. Arenas *et al.* found some enlargement in 73% of their cases. The hepatomegaly may follow some time after the pain, or it may precede it.

The *fever* completes the triad which, with the eosinophilia, is almost diagnostic of the condition. The sudden rise of temperature at the onset may reach 104° F. (40° C.). Sometimes it is persistent at a somewhat lower level for a week or two, but characteristically it oscillates, with a rise to 102–103° F. (38.9–39.5° C.) at the end of the day. It may last for eight weeks or more. According to Arenas *et al.* fever is invariably present. An occasional rigor is not uncommon, and sweats, often severe enough to suggest brucellosis, are the rule.

Asthenia, which may be extreme, occurs in most cases. The limbs feel heavy.

Wasting can be very great in severe cases. Anorexia, capricious appetite, flatulence, vomiting, diarrhoea, and constipation are frequently reported.

Urticaria is often an early episode, though it sometimes occurs at the height of the attack. It is a useful diagnostic pointer. An earthy coloured skin is a striking abnormality which, when present, is of diagnostic importance. It may lead to a false diagnosis of Addison's disease.

Splenomegaly occurs in 25% of cases.

Respiratory symptoms, especially cough, are common. There may be crepitations at the right base with a pleural rub and sometimes haemoptysis. Polyadenopathies have been reported, especially in children (Rial *et al.*, 1951). Other patients may have headache, insomnia, nightmares, muscle and joint pains, transitory hemiplegia, dermatographia, abdominal rigidity, meteorism, melaena, or epistaxis. In spite of this imposing list there is seldom much malaise.

Recovery may occur by the parasites being evacuated through the intestine or they may become shut off and calcified (visible radiographically). If live adult flukes are retained in the bile passages the disease passes into the next stage.

The Latent Period.—The symptoms now subside suddenly and for months or years the patient may suffer nothing worse than indigestion, though there are sometimes one or more relapses with return of the acute symptoms.

The *obstructive phase* of the disease has been described in English reports already quoted and by d'Allaines *et al.* (1942), Nañagas *et al.* (1954), Derom *et al.* (1956), and many others. Since the treatment of this disease depends upon the use of protoplasmic poisons the question of prognosis becomes very important; but unfortunately the percentage of cases which pass into the obstructive phase has not been ascertained, as so few observers have followed up their cases long enough.

A good account of the *pathology* has been given by Biggart (1937). Adult flukes in the bile-ducts irritate the biliary epithelium, causing adenomatous thickening and dilatation of the ducts. Malignant changes have occurred in animals and in clonorchis infections of man (Hoepli, 1933), but no human cases have been ascribed to fascioliasis according to Bürgi (1936).

If many flukes are present, atrophy and fibrosis may lead to biliary cirrhosis (Manson-Bahr and Walton, 1941). Sometimes the flukes eat their way back into the liver and seed it with their eggs (Craig and Faust, 1951). But the commonest sequel is obstruction of the bile-ducts by the flukes or by calculi which often accompany them. Secondary bacterial infection may cause acute inflammatory lesions of the biliary tree.

Detailed description of the obstructive phase is beyond the scope of this article except for the differential diagnosis from the invasive phase. Here the eosinophil count is the significant factor. It is seldom much raised in the obstructive phase. A high count is a contra-indication to operation according to Faiguenbaum *et al.* (1958).

Ectopic Fascioliasis.—One of the strangest manifestations of fasciola infections of man is the occasional appearance of immature flukes in sites other than the liver, most commonly in the abdominal wall. The parasites never grow to maturity in such positions and they may later continue their migration to the liver; they may become calcified or, more characteristically, become incorporated in a granuloma which has sometimes been observed itself to migrate subcutaneously towards the liver (Catchpole and Snow, 1952). Sometimes the young flukes enter the blood-stream and pass to distant parts of the body (Ortiz, 1934–5; Shaw and Clyne, 1951; Neghme and Ossandon, 1943).

Halzoun.—In the Levant there occurs a form of pharyngeal fascioliasis known by this name. This is a direct infection derived from the ingestion of raw liver of animals in sacrificial rites.

Differential Diagnosis

In the *differential diagnosis* acute fevers such as brucellosis and typhoid must be excluded. Other parasitic diseases, ascariasis, trichinosis, schistosomiasis, filariasis, and in young children, visceral larva migrans (Beaver *et al.*, 1952) have to be considered. Some cases may simulate Loeffler's syndrome, tropical eosinophilia, the reticuloses, or eosinophilic leukaemia.

Treatment

We have found no reports of fully controlled clinical trials. Kourí and Arenas (1932) introduced the emetine treatment, advising a course of 5 mg./kg. of body weight given in a daily dose of 40 mg. of emetine hydrochloride subcutaneously or intramuscularly. This procedure has been widely adopted (Martin *et al.*, 1944; Minning, 1952). Antimony compounds, extract of male fern, and other toxic anthelmintics have often been given, but the weight of evidence favours emetine as the drug of choice.

Prophylaxis

Ideally watercress should be grown under artificial conditions and the inoculum should be healthy (Friess, 1946). In practice it is often cut from natural beds fed by streams running through pastures (Brumpton and Lavie, 1939).

Discussion

A few hundred cases of human fascioliasis have been reported from various parts of the world. Rare in England, cases in the U.S.A. seem to be rarer still. Adams (1934), reporting a case, could find no other records there. This is surprising, as Olsen (1948) found that a third of the jack-rabbits of Texas were infected, forming a "vast reservoir of infection." The incidence among farm animals in England, already high, increased very much during the wet summer of 1958. The number of human cases in France has risen greatly in the last few years, so it is reasonable to expect outbreaks here.

According to Belding (1952) only 5% of cases are diagnosed in the invasive phase. This must be due to unfamiliarity with the disease. The acute symptoms call for a blood count, which will often reveal an eosinophilia higher than is found in most other diseases in temperate climates. The history of having eaten watercress is significant, especially in endemic areas. Confirmation may be sought in the complement-fixation test (Fairley and Williams, 1923; Mohr *et al.*, 1951) or the intradermal test (Lavie and Stefanopoulou, 1944), though there has been little experience of these reactions in this country so far.

Ova will not be found during the first three to four months after infection, since the parasites have not attained sexual maturity. They are said to be first detected in bile from a duodenal tube (Coudert, 1952). A method devised by Kourf has been described (Gradwohl, 1943). A week or two later they are to be seen in the faeces, soon becoming quite numerous, though their demonstration by ordinary flotation techniques is unreliable. A modified formol-ether method has given good results. In the later stages of the disease the ova become very scanty and often cannot be found at all, while the eosinophil count may be normal. Careful history-taking is then the only hope for a "medical" diagnosis of the underlying parasitic aetiology.

Many observers have stressed the importance of starting emetine treatment while the parasite is still in the larval form and said to be most susceptible. This course has not found favour with orthodox opinion in this country as it means using an unproved remedy for an unproved disease. We ourselves have found it a hard decision to take, but future experience may well show that early treatment with emetine offers the best hope of cure.

In view of the successful use of chloroquine in clonorchis infections (Chu, 1957) it had to be tried in fascioliasis. The effect on the symptoms in our cases was dramatic, but unfortunately it did not cure.

Anaemia occurs comparatively rarely in the invasive stage. It is usually described as "toxic" in origin, but our accidental findings in one case suggest that it is due to a red-cell-sensitizing antibody. It is interesting to note that Mello (1910) produced spherocytosis with an extract of dried flukes and that Flury and Leeb (1926) found that the excretions of flukes had haemolytic properties. The occurrence of a red-cell-sensitizing antibody in patients with other parasitic infections is reported by Zoutendyk and Gear (1950, 1959).

In an attempt to trace the course of the Ringwood outbreak watercress from a local bed in a cow pasture was fed daily to four newly weaned rabbits from June to October, 1959. The absence of any evidence of infection when the animals were killed in January, 1960,

may well have been due to the exceptionally dry summer of 1959. The fact remains that many watercress beds in this country are wide open to infection. There is a need for some measure of control in endemic areas, especially after wet summers.

Summary

Though 16 isolated cases of fascioliasis have previously been recorded in this country this is the first outbreak to be reported.

At least six patients were affected, in five of whom the diagnosis was confirmed by finding the ova in the faeces.

All the patients were in the habit of eating watercress grown in natural beds.

Prolonged fever, pain in the right hypochondrium sometimes associated with hepatomegaly, asthenia, and often urticaria were the main symptoms, with, most significantly, a very high eosinophilia in every case.

The ova do not appear until three to four months after infection. They are best demonstrated by the formol-ether method. Ordinary flotation procedures are not satisfactory.

The anaemia found in one case appeared to be due to a red-cell sensitizing antibody.

Chloroquine was used probably for the first time in fascioliasis. This treatment relieved the symptoms dramatically but failed to cure.

Control of watercress beds in endemic areas is advised.

In the review of the world literature a general account of the disease is given.

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THE PITUITARY AND ADRENAL CORTEX IN GENERAL MEDICINE*

BY

J. D. N. NABARRO, M.D., F.R.C.P.

Assistant Physician, Middlesex Hospital, London

The Anterior Pituitary Gland

The hormones of the anterior pituitary gland include corticotrophin, thyrotrophin, gonadotrophin, prolactin, and growth hormone. They are polypeptides, and in some cases the amino-acid composition and sequence have been ascertained. Growth hormone shows a considerable degree of species specificity (Knobil and Greep, 1956) associated with differences in amino-acid sequence (Li and Papkoff, 1956). The anterior pituitary hormones are not easy to purify, and their estimation in body fluids and tissues is still in a very primitive stage.

Corticotrophin regulates the production of hydrocortisone and sex hormones by the adrenal cortex, and in its absence the adrenal stops secreting hydrocortisone although aldosterone production continues. Animal experiments have suggested that there may be two pituitary hormones acting on adrenal cortex—one affecting

adrenal weight and the other concerned with metabolic activity (Liddle *et al.*, 1954). In addition to its effect on the adrenal cortex, corticotrophin has a direct effect on metabolism of fatty tissue with liberation of unesterified fatty acids (White and Engel, 1958); this effect is not seen with injections of corticotrophin and measurement of plasma unesterified fatty acids (Raben and Hollenberg, 1959). Corticotrophin also has a skin-pigmenting effect, independent of but similar to melanocyte-stimulating hormone (*British Medical Journal*, 1957). Bioassay methods for corticotrophin measurement are available, and increased plasma levels have been detected in Addison's disease and occasional cases of Cushing's syndrome secondary to a corticotrophin-producing pituitary adenoma or carcinoma (Clayton, 1958; Lipscomb and Nelson, 1959).

In the case of thyrotrophin, clinical evidence suggests that there is an exophthalmos-producing substance independent of the thyroid-stimulating hormone. This has been demonstrated experimentally in animals (Dobyns and Steelman, 1953). Although thyrotrophin plays an important part in the regulation of thyroid activity the gland can accumulate iodine and secrete thyroxine in the absence of the pituitary and presumably of any thyrotrophin. This has only been demonstrated in patients with thyrotoxicosis or thyroid adenomata (Becker, 1959; Gurling *et al.*, 1959).

Studies with growth hormone have been limited on account of its species specificity and because there is no simple method for its estimation in body fluids. It has been shown that as much growth hormone can be extracted from the pituitaries of adult humans as from those of growing children (Gershberg, 1957), but its role in adult metabolism and physiology has not yet been defined. Metabolic studies have been performed, using human and monkey growth hormone, and have shown nitrogen and calcium retention more marked in patients with deficiency of growth hormone than in normal subjects (Beck *et al.*, 1957). Increased urinary calcium excretion has been noted in several studies (Ikkos *et al.*, 1959; M.R.C. Clinical Endocrinology Committee, 1959). Growth hormone has an *in vivo* effect on fat-metabolism with elevation of the plasma unesterified fatty acids (Raben and Hollenberg, 1958). The possible role of growth hormone in complicated juvenile diabetes and in certain types of cancer is discussed later.

A fat-mobilizing substance has been found in plasma and in urine. Chalmers *et al.* (1958) have isolated it from urine, and found that it is increased on fasting and disappears after hypophysectomy. Whether it is identical with one of the known pituitary hormones has not yet been determined. It is a polypeptide, but does not have the same properties as corticotrophin or growth hormone (Chalmers, 1960, personal communication). Originally isolated in studies on obesity, its relationship to this and other human diseases is at present only a matter of speculation.

Total hypophysectomy by the transfrontal, trans-septal-sphenoid (Heck *et al.*, 1957), and trans-antrosphenoidal (Hamberger *et al.*, 1959) routes has been undertaken for a number of conditions, including juvenile diabetes with complications, disseminated cancer, especially of the breast or prostate, and malignant exophthalmos. The operation is a considerable undertaking in any of these conditions, and other methods of reducing pituitary function have been investigated. External irradiation by conventional and supervoltage techniques has been disappointing and may be hazardous, though

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