

Keillar for help in taking blood samples. We should also like to thank the Medical Research Council, the Northcott Devon Medical Foundation, and the South Western Regional Hospital Board for financial support.

REFERENCES

- Atherden, L. M. (1958). *Biochemical Journal*, **69**, 75.
 Baron, J. H., Nabarro, J. D. N., Slater, J. D. H., and Tuffley, R. (1969). *British Medical Journal*, **2**, 793.
 Borst, J. G. G., de Vries, L. A., ten Holt, S. P., and Molhuysen, J. A. (1953). *Lancet*, **1**, 657.
 Doll, R., Hill, I. D., and Hutton, C. F. (1965). *Gut*, **6**, 19.
 Doll, R., Hill, I. D., Hutton, C. F., and Underwood, D. J. (1962). *Lancet*, **2**, 793.
 Elmadjian, F., Hope, J. M., and Pincus, G. (1956). *Journal of Clinical Endocrinology and Metabolism*, **16**, 338.
 Forshaw, J. (1969). *British Medical Journal*, **2**, 674.
 Hausmann, W., and Tarnoky, A. L. (1966). *British Journal of Pharmacology and Chemotherapy*, **26**, 412.
 Horwich, L., and Galloway, R. (1965). *British Medical Journal*, **2**, 1274.
 Khan, M. H., and Sullivan, F. M. (1968). In *Symposium on Carbenoxolone Sodium*, ed. J. M. Robson and F. M. Sullivan, p. 5. London, Butterworths.
 Mattingly, D. (1962). *Journal of Clinical Pathology*, **15**, 374.
 Mohamed, S. D., Chapman, R. S., and Crooks, J. (1966). *British Medical Journal*, **1**, 1581.
 Turpie, A. G. G., and Thomson, T. J. (1965). *Gut*, **6**, 591.

Human Fascioliasis in Shropshire

W. L. G. ASHTON,* B.V.Sc., M.R.C.V.S.; P. L. BOARDMAN,† M.D., M.R.C.P.; C. J. D'SA,‡§ M.R.C.P.
 P. H. EVERALL,§ F.I.M.L.T.; A. W. J. HOUGHTON,|| M.R.C.P.

British Medical Journal, 1970, **3**, 500-502

Summary: Five patients with fascioliasis presented with malaise, pruritus, and pain in the right hypochondrium. Eosinophilia, increase in serum gamma globulin, and pyrexia were other features. Four patients treated with oral bithionol recovered completely and it is suggested that this is an effective form of therapy. The double diffusion precipitin test, being speedy and simple, was used as a screening procedure for diagnosis. The source of infection was wild watercress growing in a farm ditch.

Introduction

The aim of this paper is to describe an outbreak of fascioliasis in humans during which we assessed the response to bithionol (Actamer) and used the double diffusion precipitin reaction as a screening test.

The Outbreak

Clinical Description

Case 1.—A housewife aged 22 years was admitted to hospital on 20 December 1968. She complained of attacks of severe pain in the right hypochondrium for three months, loss of appetite, rigors, and weight loss. She had a fever of 39.4°C. and an enlarged tender liver. Her haemoglobin was 11.6 g./100 ml. and the total leucocyte count was 12,000/cu.mm., of which 6,480 were eosinophils. The erythrocyte sedimentation rate was 33 mm. in the first hour (Wintrobe), the serum aspartate transaminase was 28 units, and the serum alkaline phosphatase was 28 King-Armstrong units/100 ml. The serum albumin was 3.4 g./100 ml. and the globulin 4.5 g./100 ml.; paper electrophoresis revealed an increase of alpha-2 globulin and a diffuse increase of gammaglobulin. The Wassermann cardioliipin reaction was positive, but the *Trepomena pallidum* immobilization test and Reiter protein complement fixation test were negative. A needle liver biopsy demonstrated focal granulomata with small areas of necrosis

heavily infiltrated by eosinophils. Ova of *Fasciola hepatica* were found in the stools. The fasciola complement fixation test was positive 1/80. The double diffusion precipitin test was also positive. The hydatid complement fixation test and Casoni skin test were negative.

This patient was a member of an isolated farming community. The other members of the community were examined; there was neither clinical nor laboratory evidence of infection in 10 of these. The remaining four are described below.

Cases 2-5 consisted of two men aged 58 and 49 and two females aged 45 and 14 years. All had pain in the right hypochondrium, malaise, and pruritus, and in three the liver was enlarged and tender. Eosinophilia between 2,880-6,000 per cu.mm. was present in all. Ova were found in the stools of one patient. The complement fixation test was positive between 1/20 and 1/80 in three. The double diffusion test was positive in all.

Treatment and follow-up details

Case 1.—This patient was treated in hospital with emetine hydrochloride 60 mg. daily, the 10-day course being interrupted for 48 hours because of atrial ectopic beats. Within a week there was definite symptomatic improvement and ova were no longer found in the stools. After three months she relapsed with abdominal pain for a few days; her erythrocyte sedimentation rate was 40 mm. in the first hour and the eosinophil count was 1,300 per cu.mm. After eight months she was well and had a normal eosinophil count, but precipitin and complement fixation tests were still positive. The Wassermann reaction was negative and the serum alkaline phosphatase normal.

Case 2.—This man was treated with bithionol, 1 g. three times daily orally on alternate days. A few hours after the first dose he had very severe pain in the right hypochondrium and treatment was stopped. Within 10 days of restarting he was symptom-free and ova were not present in his stools. Severe nausea limited the total dosage to 22.5 g., but he recovered completely in six weeks. After eight months he was well, had a normal eosinophil count, but was positive serologically.

Cases 3-5.—Two received 45 g. of bithionol, but the dose for the girl aged 14 was limited to 22.5 g. All returned to normal health but experienced nausea and vomiting on the drug. The eosinophil counts returned to normal but the serological reactions remained unchanged after eight months.

* Veterinary Investigation Centre, Woodthorne, Wolverhampton.

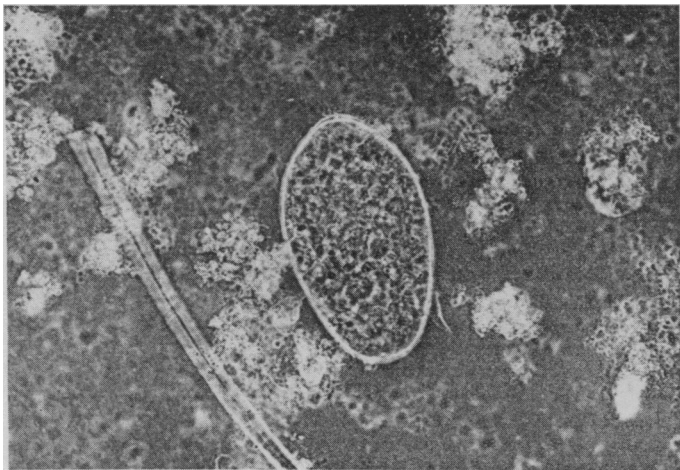
† Consultant Physician, Royal Salop Infirmary, Shrewsbury.

‡ Medical Registrar, Royal Salop Infirmary, Shrewsbury.

§ Technical Officer, Royal Salop Infirmary, Shrewsbury.

|| Consultant Physician, Royal Salop Infirmary, Shrewsbury.

¶ Present address: Queen Elizabeth Hospital, Birmingham.



Egg of *Fasciola hepatica* in faeces.

Laboratory diagnosis

Faeces were examined for ova (see Fig.) after concentration by a modification of the formol-ether centrifugation method (Ridley and Hawgood, 1956). Complement fixation tests were performed by Dr. D. S. Ridley at the Hospital for Tropical Diseases, London. Double diffusion precipitin tests were carried out on the sera of patients and contacts, using as antigen a crude saline extract of adult flukes obtained from the abattoir (Everall, 1970).

Epidemiology

The liver fluke, *F. hepatica*, is an unsegmented hermaphroditic flatworm of the class Trematoda. It has an indirect life cycle, the adult worm living in the bile ducts of the definitive host, usually a sheep or cow but occasionally man, and the larval form in the intermediate host, which in this country is a small mud-living snail, *Limnaea truncatula*. From the eggs that are passed out of the faeces of the definitive host ciliated larvae develop under suitable conditions. These are the miracidia, which find and penetrate the body of the host snail. Further metamorphoses take place in the body of the snail, culminating in the production of small tadpole-like creatures, cercariae, which leave the snail and encyst on waterside plants.

If swallowed by the definitive host these encysted stages—metacercariae or immature flukes—undergo further development until some six weeks later, having crossed the abdominal cavity and burrowed through the liver, they enter the bile ducts, where they grow to maturity. At least six weeks after this the first of the new generation of fluke eggs may appear in the faeces. Since apparently healthy cattle and sheep are often infected with small numbers of liver flukes, and since one fluke can lay 20,000 eggs per day (Taylor, 1964), the incidence of fascioliasis is related to the size of the snail population and, in this, rainfall is the critical factor. In the present outbreak the infected patients lived on two adjacent farms and ate watercress between the months of May and October 1968. The watercress grew wild in two ponds and a ditch on these farms. The ponds were filled with water throughout the year and had clearly defined banks which did not merge into marshy areas and did not constitute typical *L. truncatula* habitats. A thorough search around both ponds failed to reveal any snails. The ditch ran alongside the road to the farms and received tributaries from the adjacent fields. Watercress grew conveniently in the ditch by the gate of one farmhouse. A search here in January 1969 revealed numerous live snails identified as *L. truncatula*. Dissection showed that 20 of the 50 snails collected were infected with rediae and cercariae of *F. hepatica*.

Foot-and-mouth disease had been confirmed on both farms

in November 1967. Restocking began in June 1968, when 45 cattle were brought on to the two farms from an area where fascioliasis is endemic. Under favourable conditions eggs can reach the infective metacercariae stage in 11 weeks (Ollerenshaw, 1969). Thus, assuming that the parasite was introduced by the purchased cattle, the human infections could not have occurred before the middle of August. After diagnosis of the human outbreak fascioliasis was confirmed in the cattle on the two farms.

Discussion

All patients had eosinophilia, pain in the right hypochondrium, malaise, and pruritus. Weight loss, pyrexia, tender hepatomegaly, and a diffuse increase of serum gammaglobulin were noted in four. The person with minimal symptoms (Case 5) was treated, in spite of the possibility of spontaneous cure (Taylor, 1961), because of the risk of late bile duct obstruction.

Emetine hydrochloride and chloroquine are the two main therapeutic agents. In this series Case 1 responded to emetine, but its disadvantages are cardiac toxicity and the need for parenteral administration. Facey and Marsden (1960) reported dramatic improvement on chloroquine sulphate, but ova continued to be found in the stools, and a high incidence of side-effects was recorded.

Bithionol is used to treat the lung fluke, *Paragonimus*, side-effects being transient diarrhoea, abdominal pain, nausea, anorexia, and urticaria (Kang, Loh, Ham, and Chyu, 1963). It is effective against induced fascioliasis in rats (Dawes, 1966). Swiezawska, Kaliszewicz, and Grott (1967) have reported success in a case of human fascioliasis. The four outpatients in this series treated with bithionol recovered completely, their eosinophilia resolved, and ova were not detected in the faeces, but complement fixation and precipitin reactions remained positive. Side-effects were nausea, vomiting, diarrhoea, abdominal pain, and pruritus. In one patient the dose had to be limited to 22.5 g., but the response was still satisfactory, suggesting that the effective dose may be lower than that employed. The intense pain that developed in Case 2 a few hours after the initial dose suggested the possibility of a Herxheimer type of reaction.

A minimum of three months elapses between the time of ingestion of metacercariae by the human host and the appearance of eggs in the faeces. In many human infections the larval flukes do not develop to maturity; thus Coudert (1960) recorded that in 30% of over 100 cases eggs were never found in the faeces or bile. Serological tests are therefore of importance in the diagnosis of this disease. The one most commonly used in this country is the complement fixation test. This requires specialized knowledge for antigen preparation and performance if it is to maintain specificity and sensitivity. Double diffusion analysis offers great advantages of speed and simplicity and in addition allows direct comparison between different serum samples. Positive reactions may occur in patients infected with other helminths (Capron, Biguet, Tran Van Ky, and Rose, 1964). However, the production of more than one precipitin line in this test and the reaction of identity support the diagnosis, and in this country at least it appears to be of value as a screening test.

During 1969 there were at least three other outbreaks of liver fluke disease in man in the United Kingdom, a feature common to all being a history of eating wild watercress (Tee, 1969). In general, cultivated watercress is safe (Public Health Laboratory Service, 1966; *Lancet*, 1969). After wet summers, however, when an increase in the incidence of fascioliasis can be predicted, the danger of eating wild watercress or watercress of unknown origin should be publicized.

We wish to thank Dr. D. S. Ridley for his help and to acknowledge the assistance of all sections of the department of pathology at the Royal Salop Infirmary.

REFERENCES

- Capron, A., Biguet, J., Tran Van Ky, P., and Rose, E. (1964). *Presse Médicale*, 72, 3103.
- Coudert, J. (1960). *Pathologie et Biologie*, 8, 145.
- Dawes, B. (1966). *Nature*, 209, 424.
- Everall, P. H. (1970). *Journal of Clinical Pathology*. In press.
- Facey, R. V., and Marsden, P. D. (1960). *British Medical Journal*, 2, 619.
- Kang, S. Y., Loh, I. K., Ham, E. K., and Chyu, I. (1963). *Journal of the Korean Medical Association*, 6, No. 8, p. 59.
- Lancet* (1969), 1, 658.
- Ollerenshaw, C. B. (1969). Personal communication.
- Public Health Laboratory Service. (1966). *Monthly Bulletin of the Ministry of Health and the Public Laboratory Service*, 25, 146.
- Ridley, D. S., and Hawgood, B. C. (1956). *Journal of Clinical Pathology*, 9, 74.
- Swiezawska, E., Kaliszewicz, S., and Grott, J. W. (1967). *Wiadomości Parazytologiczne*, 13, 707.
- Taylor, A. W. (1961). *Lancet*, 2, 1334.
- Taylor, E. L. (1964). *Fascioliasis and the Liver Fluke*. Rome, F.A.O.
- Tee, G. (1969). *Lancet*, 1, 778.

Fascioliasis—A Large Outbreak

E. W. HARDMAN,* M.B., CH.B. ; R. L. H. JONES,* M.B., B.CH. ; A. H. DAVIES,* M.B., D.OBST.R.C.O.G.

British Medical Journal, 1970, 3, 502-505

Summary: Forty-four cases of liver fluke infestation (*Fasciola hepatica*) were diagnosed near Chepstow, Monmouthshire, in 1968. Intramuscular emetine hydrochloride and oral chloroquine given to the adults and children, respectively, were well tolerated. Assessment by repeated stool examination, complement fixation and liver function tests, and full blood counts indicated that treatment had been effective in most cases. It is recommended that both the growth and the sale of watercress should be strictly controlled.

Introduction

The outbreak reported here is by far the largest to have occurred in Britain. Facey and Marsden (1960) described six cases in Hampshire in 1959. Apart from this outbreak, human generalized fascioliasis has been described only in isolated cases in the United Kingdom. Two cases have been reported in Kent (Taylor, 1961) and one in a farm worker from Scotland (Jones and Smith, 1963). The disease is much more common abroad, a well-documented outbreak of 53 cases having occurred in France (Pautrizel *et al.*, 1964), as well as 12 cases in Algeria (Coumbaris, 1966). One interesting case was that of an 8-year-old boy who was treated with intravenous emetine with apparently good results (Quaiser, 1956).

Adult flukes may be found in widespread sites—for example, subcutaneous tissue, brain, and bladder—and several cases of ectopic fascioliasis have been described (Bürgi, 1936; Catchpole and Snow, 1952); one of the cases in this present outbreak may have been a further example. Furthermore, adult liver flukes have been found in the common bile duct and removed during surgery for obstructive jaundice (O'Donnell, 1949; Murphy and Pascall, 1950; Ramage, 1951; Sagar, 1962; Munroe, 1965).

The Outbreak

All 44 patients admitted to having eaten wild watercress from a bed, which was near infected cattle and sheep, during September and October 1968, some two to three months before the onset of their symptoms. The intermediate host, the snail *Limnaea truncatula*, was found in the watercress bed concerned (Figs. 1 and 2). The degree of severe liver damage suffered by cattle is illustrated in a section of a calf's liver, which shows the gross macroscopic disorganization with thick cyst formation (Fig. 3); in one cyst a fluke can be clearly seen. An adult form of the liver fluke is shown in Fig. 4.

The large number of cases discovered has given us an opportunity to assess the difficulties in establishing an exact diagnosis at the onset of the outbreak. Even when the possi-

bility of the correct diagnosis was considered, the typical diagnostic criteria were not always present in subsequently proved cases. Moreover, several completely asymptomatic cases were discovered solely by routine checking of possibly infected patients.

Symptomatology.—Manifestations of the illness were malaise, intermittent fever, night sweats, weight loss, and pain under the right costal margin. Urticaria with dermatographia was a distinctive feature in some of the cases. Coughing was an occasional symptom, and was sometimes severe and persistent though non-productive. Clinical jaundice was not generally noticed, and in several patients erroneous initial diagnoses were made early in the outbreak (see Table).

Investigations.—Laboratory investigations included full haematological examination, liver function and complement

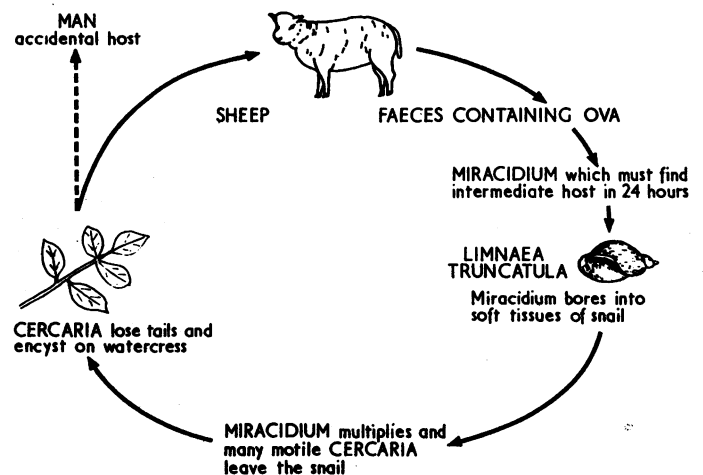


FIG. 1.—Life cycle of the liver fluke (*Fasciola hepatica*).

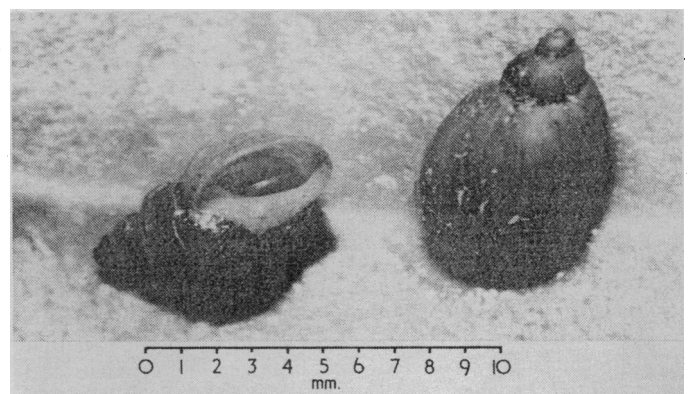


FIG. 2.—Intermediate host, the *Limnaea truncatula*.

* General Practitioner, Chepstow, Mon.