HUMAN INFESTATION WITH FASCIOLA GIGANTICA *

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Single cases of human infestation with the liver fluke, *Fasciola gigantica,* have been reported from Indo-China, Central Asia, and Africa.[1] Alicata[2] recently reviewed 18 cases of Fasciola infestation that had been reported in the Territory of Hawaii and decided that probably all of them had been due to this species. This fluke is closely related to *Fasciola hepatica,* both organisms being naturally parasitic in cattle, sheep, and swine. The available clinical information from 11 of Alicata's cases, plus 3 additional cases noted by me, are included in Table I. The remainder of Alicata's cases have been omitted because of lack of clinical detail. The detailed histories of 5 cases, including 2 cases cited by Alicata, are included in this study. Since Alicata's cases occurred over a period of 50 years and since they were reported from more than one island in the well populated Hawaiian group, it would seem that the disease does not have a high incidence in endemic areas. The present study, however, reveals that the disease occurs in an abortive form, and that it is probably more frequent than the above figures would indicate.

LIFE CYCLE AND MORPHOLOGY

Alicata,[2-4] in a series of papers upon *F. gigantica,* reviewed the available information relating to geographic distribution, the hosts, and the morphology of the parasite. He also reported his observations upon flukes within the Hawaiian environment. He noted that almost all flukes found in cattle in this region are *F. gigantica.* Review of the flukes from human cases in his paper revealed that all were *F. gigantica,* although some had previously been labeled *F. hepatica.* The following data are derived from these sources:

1. *The Egg.* In a series of measurements of 100 eggs recovered from cattle, the eggs varied from 156 to 197 μ in length and 90 to 104 μ in diameter. They are light golden brown, and oval to elliptical. They develop rapidly in tap water at room temperature and hatch after 14 days. It is of interest that only one of the adult flukes recovered from human cases contained eggs. It is possible that since man is not a natural host to this parasite, egg formation is suppressed. This finding is of importance, since it means that a search for eggs in the stool has little practical value in establishing a diagnosis.

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2. *The Miracidium.* The newly hatched miracidia of *F. gigantica* are similar in structure to other fascioloid miracidia. Copper sulfate in dilutions of 1:120,000 and water of slight salinity is not lethal to these organisms.

3. *Developmental Stages in Intermediate Host.* In Hawaii the intermediate host is the snail, *Fossaria ollula* (Fig. 1). After penetration the miracidia are transformed into sporocysts which enclose mother redia.

a. *Mother Redia.* Mother rediae escape from the sporocyst. Fully developed, they measure 2.05 mm. in length by 250 μ in width and contain daughter rediae.

b. *Daughter Redia.* Daughter rediae resemble mother rediae. Fully matured, they contain motile cercariae and may measure 4.5 mm. long and 450 μ wide.

4. *Cercariae.* Cercariae may emerge from the snail 39 days after infection. They are actively motile and encyst on vegetation near the level of the water.

5. *Metacercariae.* Metacercariae, or fluke cysts, have a hard outer cyst wall and an elastic inner wall. They measure approximately 238 to 268 μ in diameter. Under favorable conditions these cysts are infective after 122 days.

6. *Maturation in the Final Host.* Maturity as indicated by the recovery of eggs from feces is reached as early as 77 days after infection.

The route taken by the fluke in reaching the bile ducts of the final host is not definitely established. Most investigations into this phase of the parasitic life cycle have been done with *F. hepatica.* In view of their similarity, it is probable that a similar route is used by both species. Ssinitzin[5] found the larval flukes of *F. hepatica* in the peritoneal cavity of rabbits experimentally infected with encysted cercariae. This work was confirmed by Shirai.[6] Shaw[7] injected larval flukes directly into the peritoneal cavity of rabbits, guinea-pigs, and lambs. Young flukes were later recovered from the liver. Krull and Jackson[8] confirmed Shaw's work and further demonstrated that fluke larvae implanted in the thoracic cavity also found their way to the liver. These authors believed that infection via the peritoneal cavity is the principal, if not the sole, route. Necropsy of animals a few days after experimental infection with *F. hepatica* revealed the presence of entrance sites on the capsular surface of the liver. It is believed that after perforation the fluke larvae migrate inward until they reach a bile duct. Once this is entered they migrate downward to the larger

ducts in the region of the porta hepatis. The mature fluke, *F. gigantica* (Fig. 2), may be distinguished from *F. hepatica* on the basis of size and shape. *F. hepatica* is leaf-like and reaches a maximum length of 3.0 cm. The ova range from 130 to 150 μ by 63 to 90 μ. *F. gigantica* is usually more elongate than *F. hepatica* and reaches a maximum length of 5.0 cm.

In order to trace the development of the granulomatous lesions caused by the migrating flukes, I infected 6 guinea-pigs with encysted cercariae. These animals were chosen because they are not normal hosts to the parasite. The fluke does not reach maturity in the guinea-pig, nor does it produce eggs. Each animal was fed blades of grass, to which were attached 15 to 20 cysts. Four animals were sacrificed on the 2nd, 5th, 10th, and 20th days after ingestion. Two other animals were followed until they died on the 58th and 72nd days.

At necropsy the gross appearance of the livers was similar to that reported by other authors. The earliest gross lesions were noted on the second day, at which time subcapsular burrows could be seen. These burrows measured approximately 1 mm. in diameter. They pursued a serpiginous course and measured approximately 1 cm. in length. They were sharply defined and somewhat depressed from the adjacent intact parenchyma. These yellow zones became more numerous and larger at later stages of infection (Fig. 3). Examination of the livers of the animals that survived until the 72nd day revealed broad, poorly defined, yellow areas. The largest of these involved entire hepatic lobes. Individual subcapsular tracks were noted in which there was central softening and liquefaction. It was believed that the necrotic areas were of sufficient extent to account for the deaths of the last 2 animals in this series.

Microscopic examination of the hepatic lesions revealed the mode of development of the grossly visible lesions. In the earliest phase of infection the migrating larva was found within the hepatic parenchyma (Fig. 4). It was bordered by well stained cord cells, and there was little cellular reaction adjacent to the parasite. In the next phase a broad band of parenchyma adjacent to the parasite appeared congested, with the central veins and the hepatic sinusoids greatly distended. Occasional focal collections of neutrophils were noted within the sinusoids at this time. Areas of necrosis appeared next. The outlines of the liver lobules were well defined. The cord cells took a pale pink stain, and their nuclei were shrunken and dark staining. Occasional neutrophils were found along the intact sinusoids. Areas of this type were noted as early as the second day after infection. Collections

of serum containing neutrophils, eosinophils, and nuclear fragments then appeared in the central portions of the necrotic zones. Dense collections of eosinophils, histiocytes, and neutrophils were present in the intact liver parenchyma bordering the zone of necrosis. These cellular aggregates were most numerous in the portal regions. Portal veins in the central portions of the necrotic areas contained plugs of fibrin and neutrophils. These clots extended into segments of the vessels which traversed adjacent areas of viable parenchyma. In some areas there was extensive tissue liquefaction in the central aspects of the necrotic zones. This liquefaction was well established by the 20th day after infection. Wherever flukes were noted during the early periods after infection, the liver parenchyma adjacent to them appeared to be intact. Step and serial sections of the necrotic zones failed to reveal the presence of larvae. From this it may be inferred that the parasite elaborates a toxic substance which causes coagulation necrosis at some distance from its outer surface. Infarction due to obstruction of the portal venules may also contribute to the development of necrosis. Migrating parasites were not noted within either the biliary duct system or the portal venous system, but appeared to be making their way through lobular tissue.

An indication that necrosis during early phases of migration is due to the elaboration of an exogenous toxin rather than sensitivity to the foreign protein of the degenerating body of the fluke was furnished by another experiment. One gram of dried, powdered fluke antigen was placed in the soft tissues of the back of another guinea-pig. Two months later this animal was fed infected grass. It was sacrificed 30 days later. The resulting hepatic lesions were identical in appearance and extent to those noted in the non-sensitized animals.

The histologic appearance of the livers removed from the animals which died on the 58th and 72nd days was similar to that noted at earlier stages, except that the areas of necrosis were of greater extent and early reparative changes could be found. Some of the zones of necrosis were surrounded by well defined vascular granulation tissue containing many histiocytes, plump fibroblasts, and eosinophils. The periportal connective tissue was greatly increased in some areas. In this connective tissue there were many eosinophils, monocytes, and plump fibroblasts. The biliary channels were more numerous, and small tufts of regenerating hepatic cord cells were noted within some portal areas. Thrombi of portal veins similar to those noted in the earlier cases also were found, but the thrombi were noted in vessels of larger caliber. In one animal these thrombi reached the porta hepatis.

Dense collections of extravasated red blood cells were found within the central portions of the necrotic areas. The capsular surfaces were covered by a thick layer of fibrin, neutrophils, and nuclear débris.

Epidemiology of Human Infection

Alicata[2] searched the Hawaiian records for cases of fluke infestation and was able to discover 18 cases, of which 17 had been confirmed by recovery of flukes from the infected patients. I have seen 3 additional cases, bringing the total to 21. Table I gives the clinical data in 14 of these cases, the remainder of Alicata's cases having inadequate histories. The detailed histories of the 5 cases seen by me (cases 10 to 14, Table I) are included in this study.

Most cases occur among patients who have eaten uncooked watercress derived from endemic areas, although one of Alicata's[2] cases probably was derived from contaminated water. Since the number of human cases is proportional to the degree of infestation in cattle ranging in areas where watercress is grown, a short summary of this facet of the problem follows.

The islands of the Hawaiian group represent the summits of a 2,000-mile range of volcanic mountains. They have a mild and uniform climate because of their position in the midst of a large body of water and because they are in the path of the northeast trade winds. These winds cause a heavy rainfall on the windward slopes of the islands. Where drainage is poor, extensive swamps and bogs occur. The poorly drained lowlands and the mild climate make this region suitable for snail production the year round and increase the longevity of fluke cysts on vegetation. These areas have a rich vegetation, and cattle are permitted to graze continually in infected areas.

All of these conditions are met in and about the city of Hilo which is situated on the windward slopes of the island of Hawaii. Many cattle graze in the hills overlooking the city. The grazing areas receive an annual rainfall of 200 inches. Eighty per cent of the cattle in this area are fluke-infested. The sluggish streams draining into this region are also favored by growers of watercress. One such patch was found to be heavily infested with snails (*F. ollula*) of which 5 per cent were infected. It is estimated that this one patch furnished the Hilo market with 35 pounds of watercress each day.[9]

In view of the fact that cattle are permitted to range in the same drainage areas used for the production of watercress, it is less surprising that human infection occurs, and it is remarkable that such a small number of human cases have been discovered. It seems likely

TABLE I

Fasciola gigantica Infestation in Hawaii

Case	Age	Race	Sex	Fever	Pain	Nausea, vomiting	Jaundice	Other symptoms	Granuloma	Recovery of fluke	Eosinophilia	Known duration	Course	Skin test	Remarks
1	?	?	F	?	Girdle pain	?	?	Weight loss	o	Coughed up	?	3 yrs.	Recovery	−	
2	Child-bearing	?	F	−	−	−	−	−	−	Subcutaneous tissue	?	?	Recovery	−	
3	Young	?	M	?	?	?	?	Pleural effusion with bile fistula	"Fluky" liver recovered at necropsy	None found	?	Approx. 1½ yrs.	Death	−	No fluke found, no tissue for study
4	7	?	M	+	Abdominal	−	−	Migrating subcutaneous mass	−	External ear	?	2 yrs.	Recovery	−	
5	40	?	M	+	Rt. chest and epigastrium	−	−	Recurrent laryngeal palsy	Liver	Sneezed out	?	3 mos	Recovery	−	No tissue available for study
6	Child-bearing	Caucasian	F	?	Lt. chest and epigastrium	−	−	Weight loss, hemoptysis	−	Subcutaneous tissue, abdomen	?	2 yrs.	Recovery	−	
7	10	?	M	?	?	?	?	?	?	Gallbladder	?	?	Recovery presumed	−	
8	?	?	F	?	?	?	?	?	?	Abdominal cavity	?	?	?	−	
9	29	?	F	?	?	?	?	?	?	Common bile duct	?	?	Recovery	−	Infected by contaminated water
10*	16	Caucasian	F	+	Epigastric	+	Transient at onset	−	Hepatic calcification	Coughed up	60%	8 yrs.	Recovery	−1:2500	
11*	51	Japanese	F	+	Epigastric and lt. upper quadrant	+	Terminal	Flatulence, abdominal distention	Liver	Several from bile ducts	24% at onset	10 yrs.	Death	+1:5000 in one member of family	Daughter died of liver trouble, no necropsy
12*	27	Puerto Rican	F	−	Epigastric and rt. upper quadrant	−	−	Migrating subcutaneous mass	Subcutaneous fat, hip	−	60%	1 yr.	Still symptomatic	+1:5000	
13*	37	Japanese	F	+	Epigastric and rt. upper quadrant	+	−	−	Liver	−	38%	3 mos.	Still symptomatic	−1:5000	
14*	66	Caucasian	F	−	Epigastric	+	−	General malaise	Pancreas	−	53%	3 mos.	Still symptomatic	−1:2500	

* Observed by the author and described in this study.

that man is not a natural host to *F. gigantica* and that abortive infestations may occur. This supposition is based upon the observation that most flukes derived from human beings are not fertile. For this reason, studies of the feces for ova and parasites are not likely to be of value and only symptomatic cases would be discovered.

REPORT OF CASES

Case 10

J. M., a girl of Portuguese ancestry, was first seen in 1941, at 16 years of age. She complained of severe frontal headache, sweating, vomiting, and constipation. She had a daily spiking fever from 99° to 104° F. Physical examination revealed an icteric tint to the sclerae. The smooth, tender liver was felt 2 fingerbreadths below the costal margin. All other physical findings were essentially normal. Laboratory reports at this time revealed a white blood cell count of 11,000 (neutrophils, 59 per cent; staff cells, 10 per cent; juveniles, 6 per cent; lymphocytes, 21 per cent; eosinophils, 4 per cent). Urinalysis, stool examination, blood culture, and febrile agglutination were negative. After 4 days the fever and symptoms subsided, and she was discharged after 1 week.

She was readmitted 4 days later with the same complaints. She had fever of 103° F. on the first 2 days. The following changes were noted: (1) Jaundice had disappeared. (2) Eosinophils now were 10 per cent of the total white blood cell count. (3) The liver was no longer palpable nor tender. Her symptoms again receded and she was discharged on the fifth hospital day.

Four days after discharge she again entered the hospital. Her symptoms were now limited to a spiking fever which reached 104° to 105° F. every 5 to 7 days. Each febrile episode was associated with nausea, vomiting, and headache. The liver was not enlarged nor tender, and jaundice was not noted. Eosinophils fluctuated from 8 to 20 per cent. Roentgenograms of the chest were negative for pulmonary or cardiac disease. She remained hospitalized for 3 months. During the last 2 weeks she was symptom-free and was discharged apparently well.

The patient remained in good health for 4 years. In March of 1946 she suffered for 2 weeks from constipation, wave-like epigastric pain, nausea, and vomiting. Her temperature was normal. Roentgenograms of the chest revealed no evidence of pulmonary or cardiac disease. However, a recent review of the films taken at that time revealed an opaque, 2 cm. density in the region of the right lobe of the liver. The liver was not palpable, nor was there abdominal tenderness. Without therapy the patient spontaneously improved and was well for 7 days. She was then admitted to the hospital because of epigastric pain radiating to the back, nausea, and vomiting. Temperature was 103.2° F. She had a slight cough. Crepitant râles were noted in the midscapular area bilaterally. The epigastrium was tender to palpation. Urinalysis was negative; red blood cells, 3.8 millions; hemoglobin, 67 per cent; white blood cells, 13,300 (neutrophils, 72 per cent; lymphocytes, 11 per cent; eosinophils, 3 per cent; staff cells, 14 per cent). On the second hospital day she coughed up an intact fluke (*F. gigantica*). The symptoms receded abruptly. However, on the fifth hospital day eosinophils rose to 42 per cent and on the eighth day reached 60 per cent. No ova were noted in the stool at this time. She was discharged apparently well on the 16th hospital day.

Until 1950 she continued to have occasional sudden attacks of epigastric pain and fever which lasted from 2 to 5 days. Subsequently she has been well. Roentgenograms of the liver taken in 1952 in the anteroposterior and lateral planes revealed

a lobulated, opaque density, 4 cm. in diameter, in the right lobe of the liver (Fig. 6). This was more prominent than in 1946. A skin test with *F. gigantica* antigen in 1952 was negative.

Summary. A young woman suffered from periodic attacks of severe epigastric pain, fever, nausea, and vomiting over a period of 8 years. This was associated with eosinophilia. Each attack seemed self-limited, and in one of these the patient coughed up or vomited a mature fluke (*F. gigantica*). A calcified area developed in her liver which probably represented a healed granuloma similar to that noted in other cases in this report. The episodic nature of this patient's illness is typical of that noted in all cases which I have seen. A skin test with *F. gigantica* antigen was negative.

Case 11

Y. N., a 51-year-old woman of Japanese ancestry, was first seen by a physician in 1941, when she complained that for 3 months she had had epigastric pain which radiated to the left lower quadrant. She also complained of anorexia, flatulence, and weight loss. A week before, the patient's daughter died of "liver trouble" in another hospital. Since no necropsy was performed, the exact cause of death was not known. She was admitted to the hospital for observation. Her temperature was 101° F.; pulse, 140; respirations, 30. The abdomen was distended. The left rectus muscle was rigid. The left upper quadrant gave a sense of resistance, suggestive of either an enlarged left lobe of the liver or an enlarged spleen. All other physical findings were within normal limits. Laboratory findings were as follows: red blood cells, 3.64 millions; hemoglobin, 11 gm.; white blood cells, 14,300 (neutrophils, 51 per cent; eosinophils, 24 per cent; lymphocytes, 21 per cent; monocytes, 4 per cent). The urine was amber, slightly cloudy, and slightly acid; specific gravity was 1.017; no sugar or albumin, no casts or crystals, occasional epithelial cells. Serologic test for syphilis was negative. The feces were negative for ova and parasites on one occasion. Roentgenograms of the chest were negative. Examination of the urinary tract with contrast media failed to show any evidence of disease.

A laparotomy was performed. Dense adhesions were found along the sigmoid colon. The omentum and transverse colon were fixed to the left lobe of the liver. The surfaces of both hepatic lobes were studded with round, white nodules. The gallbladder and external biliary tree were normal. Culture of the nodules showed no growth. Biopsy of the liver revealed the presence of numerous, oval, necrotic areas (Figs. 7 and 8). The outlines of the original hepatic architecture could no longer be defined in these zones. Present within the necrotic areas were numerous hexagonal crystals and double-pointed needle crystals (Charcot-Leyden crystals) which were brightly stained by the Ziehl-Neelsen and Gram techniques. The necrotic tissue was surrounded by vascular granulation tissue containing many neutrophils and eosinophilic granulocytes, plasma cells, plump fibroblasts, histiocytes, and

giant cells. Stains of these zones for acid-fast bacilli were negative. Some of these necrotic zones spanned several hepatic lobules. The hepatic architecture of the uninvolved portions was well maintained. The portal connective tissue was scanty, and the biliary ducts were empty. The postoperative course was smooth, and the patient was unexpectedly relieved of her pain. She was discharged 2 weeks after operation.

In 1942, 1945, and 1947 this patient had three admissions for other conditions. On none of these occasions was there blood eosinophilia. Between 1947 and November, 1951, she suffered from periodic attacks of upper abdominal pain, for which she did not go to a physician. On November 26, 1951, she developed a severe, left upper quadrant, abdominal pain. She began to vomit, at first producing recognizable food particles and later a grayish fluid. She vomited ten times prior to admission. She also had several loose, sticky, black stools. Physical examination revealed a well developed, somewhat obese woman, lying on her back. She was moaning and gasping. Pulse and blood pressure were imperceptible, and the fingers were cold and clammy. Except for the scars of previous operations and a slight icteric tinge to the sclerae, the physical findings were limited to the abdomen. The latter was greatly distended so that palpation of the liver and spleen was not possible. There was increased tone of the musculature of the abdominal wall. The left upper quadrant was tender. Laboratory findings were as follows: The urine was yellow, slightly cloudy and acid; specific gravity, 1.014; albumin, 4 plus; sugar, negative. There were 3 to 5 white blood cells per high-power field, 6 to 8 waxy casts, 0 to 1 hyaline cast, and 1 to 3 fine granular casts per high-power field. The urine was indican-positive. Upon examination of the blood the red blood cells were 3.82 millions; white blood cells, 7,600 (neutrophils, 95 per cent, of which there were 14 per cent staff and 5 per cent juvenile cells; lymphocytes, 4 per cent; eosinophils, 1 per cent); hematocrit, 41; specific gravity of the blood was less than 1.054; non-protein nitrogen, 82 mg. per cent; icterus index, 18. A flat plate of the abdomen revealed the loops of the small bowel to be widely dilated.

Despite transfusion the patient never recovered from shock and died 6 hours after admission.

At necropsy there was a slight icteric tint to the skin and sclerae. The left breast was absent (radical mastectomy). No gross or microscopic evidence of residual or metastatic mammary carcinoma was noted in the region of the left breast, the left axilla, or in any organ examined.

The *lungs* weighed 500 gm. Both were well aerated, although the posterior one third of each lower lobe was dark brown and had a boggy consistency. The *heart* weighed 250 gm. It was without evidence of significant pathologic change. The *aorta* showed no evidence of pathologic change.

The *liver* weighed 1400 gm. Its outer surface was smooth, but matted adhesive bands bound the superior surface to the overlying diaphragm. There were many soft, yellow elevations measuring from 2 to 3 mm. in diameter over both lobes. On sectioning the liver many

pus-filled cavities varying from 3 mm. to 2.5 cm. in diameter were noted in both lobes. The smaller cavities had soft, poorly defined, gray walls. The larger cavities, which were noted in the right lobe, had ragged linings and brownish red walls which varied from 1 to 3 mm. in thickness. The intervening parenchyma had a flabby consistency, and the liver markings were indistinct. The intrahepatic biliary ducts were dilated. The common hepatic duct measured 4.1 cm. in diameter. The left hepatic duct measured 2.1 cm. in diameter. Present within the right and left hepatic ducts near their entrance into the liver were mature liver flukes. There were three flukes at this level. Two other flukes were noted within the intrahepatic segments of the right biliary duct. These flukes were classified as *F. gigantica* by Dr. J. E. Alicata. They did not contain eggs. The flukes were not attached to the duct walls, and within the smaller ducts their flat bodies were rolled upon themselves after the fashion of a jelly roll. The ductal linings were granular and red. The ductal walls appeared softer than usual. The ductus choledochus and the gallbladder were filled with a brownish red liquid, and contained no stones. The walls of these structures were purple-red and friable. The common bile duct measured 3.5 cm. in circumference and had a granular red lining.

Microscopic examination of the liver revealed both the smaller and the larger bile ducts to be filled with neutrophils, fibrin, and nuclear débris. The lining epithelium of some ducts was replaced by a vascular granulation tissue. The lumina of some ducts communicated with small abscess cavities which were filled with necrotic débris, nuclear fragments, and fibrin. These were bordered by dense collections of neutrophils and fibrin. The periportal connective tissue was extremely edematous and contained plasma cells, neutrophils, lymphocytes, and histiocytes. The lumina of the portal veins adjacent to the pus-filled ducts were occluded by clumps of fibrin and nuclear débris. Large areas of the liver had undergone necrosis. The cellular and reticular outlines persisted in these zones, and numerous neutrophils were arranged along the persisting reticular framework. These necrotic zones blended with the abscess cavities previously noted. Sections of the fluke-bearing portions of the intrahepatic and extrahepatic biliary tree revealed a similar appearance throughout. The ductal walls were greatly thickened. The lining epithelium was intact and thrown into folds. Numerous coiled and branching sinuses lined by epithelium extended from the mucosal surface into the underlying ductal wall. The connective tissue beneath and between these tracts was extremely edematous and contained large numbers of lymphocytes, plasma cells, and occa-

sional bile-laden histiocytes. Present within the outer aspects of the ductal wall were small areas of tissue liquefaction containing dense collections of neutrophils, plasma cells, and histiocytes. The lumen of the portal vein in this region was partially filled with fibrin, red blood cells, and nuclear débris. This material was partially surrounded on its endothelial aspects by fibroblasts and histiocytes. In the extrahepatic segments the periductal adipose tissue was extremely edematous and contained focal, perivascular collections of lymphocytes, histiocytes, and plasma cells. Sections of the dilated ductus choledochus in its most distal segments revealed a similar appearance to that just noted, indicating perhaps that at one time flukes had been resident at that site. Microscopic examination of a cross section of a fluke within a bile duct revealed the presence of oblique, hyaline barbs along the body surface (Fig. 9). These cuticular spines did not appear to be imbedded within the duct wall. Where they impinged upon the mucosal surface, the latter appeared to be pushed downward.

The *pancreas* showed no gross evidence of pathologic change. Microscopic examination of the head of the organ revealed the lobular architecture to be preserved. The interlobular connective tissue was edematous and contained scattered neutrophils, plasma cells, and histiocytes. The tail of the pancreas showed neither gross nor microscopic evidence of pathologic change.

The *periportal lymph nodes* varied from 5 mm. to 1.5 cm. in diameter. Microscopic examination revealed their stroma to be edematous and pale staining. Germinal centers were numerous and sharply defined. The nodal sinusoids were distended with serum. The *spleen* weighed 100 gm. It showed neither gross nor microscopic evidence of pathologic change. The *genito-urinary system* showed no evidence of pertinent pathologic change.

The *esophagus, stomach,* and *proximal duodenum* showed no evidence of gross or microscopic disease. The *distal duodenum* and the entire small intestine were widely distended with gas and liquid intestinal contents. Dense, gray adhesions bound the small bowel loops to one another so that they had a plicated appearance. The mucosa of the small intestine showed no gross or microscopic evidence of pathologic change. The appendix measured 7 cm. and showed no pathologic change. The entire large intestine was distended. Present on the mucosal aspect of the descending and sigmoid colon were numerous shallow, dark red ulcers which varied from 3 to 5 mm. in length. These had a granular red base and ill defined edges. Microscopic examination of these ulcers revealed the superficial one third of the mucosa in these

areas to be intact but necrotic. This zone of necrosis included the lamina propria and was covered by a layer of fibrin and nuclear débris. The deeper portions of the crypts were filled with neutrophils, fibrin, mucus, and red blood cells. The intact lamina propria was edematous and contained numerous neutrophils and histiocytes. The muscularis mucosae was intact. The lymphatic channels of the submucosa were widely distended with serum. Search for amebae failed to reveal these organisms.

The *thyroid, parathyroid,* and *adrenal glands* showed no evidence of pertinent pathologic change.

Permission to examine the head was not obtained.

Summary. This 51-year-old woman died 10 years after the onset of a disease characterized by episodes of intense upper abdominal pain, fever, flatulence, and nausea. During the first year of the disease there was an associated eosinophilia of 20 per cent. Laparotomy in the first year of the disease revealed the presence of granulomata within the liver. Death was due to shock and paralytic ileus secondary to diffuse suppurative cholangitis and massive necrosis of the liver. Mature flukes (*F. gigantica*) were noted in the bile ducts at death. The patient's daughter died of an obscure liver disease at the time that the patient first developed her disease.

Case 12

F. P., a 27-year-old housewife of Puerto Rican ancestry, was well until July, 1951, when she noticed a lump in the right upper quadrant of the abdominal wall. This was associated with marked right upper quadrant pain that radiated to the back. The abdominal wall adjacent to the lump was tense and red. The abdominal pain was most intense at night, was not associated with meals, and was accompanied by profuse sweating. The pain came in waves during which she felt cold. After they subsided she had a hot, burning sensation in the epigastrium. She was seen by a physician in September. At this time the mass had elongated and reached the right iliac crest, to which it appeared fixed.

Physical examination in November, 1951, revealed a fixed, moderately tender mass, 15 by 4 cm., to the right of the umbilicus. A thin cord or band seemed to fix it to the region of the right iliac crest. The liver and kidneys could not be palpated. There was no rigidity of the abdominal wall or any deep tenderness. All other systems were negative to physical examination.

Laboratory findings were as follows: On October 18, 1951, the specific gravity of the urine was 1.011; albumin, 1 plus; sugar, negative; white blood cells were 5 to 10, red blood cells, 10 to 15 per high-power field. Examination of the blood revealed red blood cells, 3.6 millions; white blood cells, 8,800 (neutrophils, 14 per cent; lymphocytes, 35 per cent; eosinophils, 51 per cent); hemoglobin, 9.2 gm. Icterus index, 1. Total serum protein, 8.65 gm. per cent; albumin, 4.29 gm. per cent; globulin, 4.36 gm. per cent; albumin-globulin ratio was 0.99. A serologic test of the blood was negative. On October 22, 1951, examination revealed the red blood cells to be 3.7 millions; white blood cells, 11,500 (neutrophils, 24 per cent; lymphocytes, 36 per cent; eosinophils, 38 per cent; basophils, 2 per cent); hemoglobin, 9.5 gm.

Roentgenograms of the chest, gallbladder, and gastrointestinal tract were negative.

The patient was in the hospital for 7 days, during which time she was afebrile, but continued to complain of severe upper abdominal pain. She then left against medical advice.

During the succeeding 7 months the abdominal mass gradually moved downward and laterally. She was next seen in June, 1952, when it lay over the outer surface of the right gluteal region. It measured approximately 10 by 5 cm. It was indurated, hot, and tender. At the sites where the mass had previously been felt in the abdominal wall, the skin was soft and nontender. There was slight epigastric tenderness. The patient complained of epigastric pain.

Blood studies at this time revealed the red blood cells to be 3.2 millions; white blood cells, 10,150 (neutrophils, 18 per cent; eosinophils, 60 per cent; lymphocytes, 21 per cent; basophils, 1 per cent); hemoglobin, 9.1 gm.

On the day after admission the mass over the hip was removed. It was found to lie in the subcutaneous fat. The excised tissue mass measured 6 by 4 by 2 cm. It was composed of fat. Present in the central portion of the specimen was a sinus tract which traversed its full length. The tract was filled with a soft, reddish brown material. It had an extremely ragged periphery. The wall of the tract was firm and composed of dense, gray tissue. The tract with its wall measured 2 cm. in its greatest diameter.

Microscopic examination of sections of the tract revealed its central portions to be composed of necrotic adipose tissue which in some areas had undergone further degeneration (Figs. 10, 11, and 12). Dense collections of neutrophils, serum, red blood cells, frayed collagen fibers, plasma cells, and numerous Charcot-Leyden crystals were noted in this tissue. In cross section this necrotic zone had a stellate outline, not unlike that seen in the early phases of cat-scratch fever and lymphopathia venereum. Bordering the necrotic zone was vascular granulation tissue of varying width and composed of histiocytes, plasma cells, eosinophils, lymphocytes, fibroblasts, and collagen fibers. Present at the junction of the zone of necrosis and the granulation tissue were occasional, irregular clumps of hyaline material. Within the intact adipose tissue adjacent to the mass were dense collections of plasma cells and eosinophils.

Subsequent to this procedure the patient's epigastric symptoms have abated somewhat, although they still persist 1 month after surgery. It is probable that additional intra-abdominal granulomata are present. The surgical wound healed *per primum*. A blood study on the tenth postoperative day revealed the red blood cells to be 3.9 millions; white blood cells, 17,600 (neutrophils, 64 per cent; lymphocytes, 17 per cent; eosinophils, 19 per cent); hemoglobin, 11.1 gm.

This patient was given a skin test with *F. gigantica* antigen. A strong positive result was obtained.

Summary. This 27-year-old woman suffered from epigastric pain, fever, nausea, and a migrating mass for 11 months. This was associated

with eosinophilia. Removal of the mass revealed a granuloma similar to that noted in the liver of case 10. Skin testing with *F. gigantica* antigen was positive.

Case 13

M. Y., a 37-year-old Japanese woman, was seen by a physician in May, 1952, because of an attack of intense right upper quadrant pain which radiated to the back. She had suffered from intermittent attacks of similar pain for several months. This was associated with flatulence and was most intense after the ingestion of fats. At times the pain was intense. It was most severe when she coughed. It was associated with anorexia and nausea, and radiated to the back. On physical examination there was exquisite tenderness in the region of the gallbladder and over the epigastrium. There was no splinting of the abdominal wall, and no masses were noted. The patient had a temperature of 100° F. Other physical findings were within normal limits.

Examination of the blood on May 17, 1952, revealed the white blood cell count to be 8,900 (neutrophils, 56 per cent; lymphocytes, 26 per cent; eosinophils, 18 per cent). On May 28, 1952, the white blood cell count was 12,300 (neutrophils, 31 per cent; lymphocytes, 32 per cent; eosinophils, 37 per cent); hemoglobin, 10.4 gm.; hematocrit, 36 per cent. Urinalysis was negative. There was good visualization of the gallbladder in a roentgenographic series, and there was no evidence of biliary concretions.

Because of the eosinophilia and the clinical appearance, a diagnosis of fluke granuloma was made. Laparotomy was performed on June 3, 1952. The gallbladder and the external biliary tree did not appear diseased. Present on the diaphragmatic surface of the liver were several slightly raised, poorly defined, soft areas which varied from grayish yellow to dark red. They measured approximately 1 cm. in diameter. Incision of these zones revealed them to be filled with cheesy, brown material. A portion of one of these was removed for microscopic examination, which revealed a granuloma similar in appearance to that found in the liver of case 10.

Subsequent to operation, examination of the feces by the acid-ether and the zinc sulfate concentration methods for eggs was fruitless on four occasions. The patient recovered from the operation without ill effects. Her course after operation is still marked, after 2 months, by paroxysms of right upper quadrant pain which radiates to the back. On July 24, 1952, eosinophilia had disappeared.

Summary. This patient had a typical train of symptoms characterized by intense, intermittent, upper abdominal pain, associated with eosinophilia, fever, and nausea. Laparotomy revealed the presence of multiple granulomata of the liver histologically similar to those noted in cases 10 and 12.

Case 14

The patient was a 66-year-old woman of English ancestry who came to her physician on July 6, 1952, because of fever, general malaise, and upper abdominal pain. These complaints commenced on May 5, 1952. The patient seldom ate water-

cress, but she reported that she had eaten some 20 days before the onset of her symptoms. The fever was intermittent, associated with profuse sweating, accompanied by nausea, and ranged from 102° to 103° F. Physical examination revealed mild tenderness in the epigastrium. There were no other pertinent findings. Laboratory studies revealed the following: Urine showed a slight trace of albumin but was otherwise normal. The blood on July 7, 1952, showed a white cell count of 7,400 (neutrophils, 40 per cent; lymphocytes, 12 per cent; eosinophils, 48 per cent). On July 12, 1952, the white blood cells were 11,000 (neutrophils, 18 per cent; lymphocytes, 26 per cent; monocytes, 2 per cent; eosinophils, 53 per cent; basophils, 1 per cent); hematocrit, 37; hemoglobin, 10.5 gm. The urine urobilinogen was positive in a 1:10 dilution, negative in a 1:20 dilution. The direct Van den Bergh test showed negative immediate and delayed reactions. The indirect test indicated 0.2 mg. per cent of bilirubin. Thymol turbidity test gave a value of 3 units; gamma globulin, 7 units; and the Eagle test was negative. On three occasions, examination of feces for ova and parasites gave negative results.

Roentgenologic examination of the biliary tree revealed two large nonopaque stones with partially calcified centers within the gallbladder. After a fatty meal the gallbladder contracted approximately 50 per cent. A gastrointestinal series demonstrated no lesions in the stomach or duodenum.

In view of the intermittent character of the patient's disease, and because it was associated with eosinophilia in the absence of ova or parasites in the feces, it was believed that she probably had a fluke granuloma in addition to the demonstrated cholelithiasis. An operation was performed on July 18, 1952.

The gallbladder was found to be filled with faceted, green stones which varied from 1.1 to 2.2 cm. in diameter. Its lining was green and granular. The wall measured 1 mm. in thickness. Subsequent histologic examination of the gallbladder revealed the lining epithelium to be intact. The gallbladder wall was thickened by dense, collagenous connective tissue which contained dense, perivascular collections of lymphocytes. Exploration of the biliary tree revealed it to be patent throughout and to contain no parasites. The surface of the liver was not unusual. Further search of the upper abdomen for granulomata was made. One was found in the tail of the pancreas adjacent to the hilus of the spleen and adjacent to the left kidney. This general area was firm and surrounded by bands of dense, gray tissue. The mass was estimated to measure approximately 5 cm. in diameter. Incision revealed it to have a soft, liquid, black center. Microscopic examination revealed a granuloma which was histologically identical with that noted in the soft tissue in case 12. An imprint of the cut surface of the mass revealed many Charcot-Leyden crystals.

The patient's postoperative course has been uneventful. She continues to have epigastric pain associated with nausea, but there has been no recurrence of fever.

Summary. This 66-year-old woman was diagnosed preoperatively as having fluke granuloma despite the presence of proved chronic cholelithiasis. She had symptoms of fever, malaise, nausea, mild epigastric

pain, and eosinophilia. A large granuloma was found in the tail of the pancreas. This granuloma was histologically similar to those noted in all previous cases. It is probable that the mildness of the patient's pain was due to the retroperitoneal location of the lesion.

SUMMARY OF CLINICAL FINDINGS

There appears to be a definite clinical pattern associated with the migratory phase of *F. gigantica* infestation. This pattern consists of intermittent bouts of fever and upper abdominal pain, associated with eosinophilia. Other factors may be added in individual cases. A review of the 5 cases in this series and of the cases in Alicata's study in which any clinical details are available reveals the following facts.

Pain. Pain occurred in 6 of the 8 cases in which information is available. It usually was centered in the epigastrium or in the right upper quadrant. It was noted in the chest on two occasions. It has been noted to radiate to the chest, back, and lower abdominal quadrant. It was described as wave-like, cramp-like, or burning. One patient noted that it was most severe when she coughed. This was probably due to irritation of the diaphragmatic peritoneum and might have been elicited more frequently, had it been searched for. The pain often was associated with abdominal tenderness in the region of the epigastrium, liver, and gallbladder. It appeared suddenly, lasted for a few hours, and disappeared abruptly. Some of the patients associated this pain with ingestion of fatty foods, but this was inconstant.

Fever. Body temperature noted during the attacks varied from 100° to 105° F. Chills were not conspicuously associated with this fever. The fever had a tendency to subside gradually, returning to normal within 24 hours of the end of an attack. The fever and pain frequently were associated with profuse sweating.

Nausea and Vomiting. Four of the 5 patients observed by me were subject to nausea or vomiting, or both, during episodes of pain. Flatulence and anorexia were noted frequently during remissions.

Jaundice. Grossly visible jaundice was noted in only 2 of these cases (10 and 11). In case 10 it was transient and occurred during the early phase of the disease. In case 11 it occurred during the terminal phase and was associated with obstruction of the biliary tree by mature flukes.

Hemoptysis, weight loss, general malaise, hoarseness secondary to recurrent laryngeal nerve palsy, and *abdominal distention* have been noted in individual cases.

A *subcutaneous mass* was noted in 5 cases (2, 4, 5, 6, and 12) and

in 2 of these (4 and 12) it migrated. In case 5 the mass appeared in the neck and was associated with paralysis of the recurrent laryngeal nerve.

Mature flukes were recovered from the upper respiratory system in 3 cases (1, 5, and 10). The parasite was coughed up twice and sneezed out once. It was plucked from the external ear on another occasion (case 4).

LABORATORY FINDINGS

Blood. Eosinophilia was present at some stage of the disease in all 5 cases observed by me. It varied from 24 to 60 per cent. In the one case in which the hepatobiliary phase was reached (case 11), eosinophilia disappeared after the migratory phase was completed.

There was considerable variation in the respective white blood counts of individual patients. During the first attacks the count tended to be low, reaching its highest level after several months. This increase in white cells could not be accounted for on the basis of increase in eosinophils alone, although this was certainly a contributing factor. For instance, in case 12 serial counts revealed lymphocytosis and eosinophilia (14 per cent neutrophils, 35 per cent lymphocytes, 51 per cent eosinophils) when the white cell count was 8,800 in October, 1951. The next count taken 4 days later revealed 11,500 white blood cells (24 per cent neutrophils, 36 per cent lymphocytes, 38 per cent eosinophils, 2 per cent basophils). A count taken 8 months later revealed 17,000 white blood cells (64 per cent neutrophils, 17 per cent lymphocytes, 19 per cent eosinophils). Blood studies during the hepatobiliary phase in case 11 revealed 7,600 white blood cells, of which 95 per cent belonged to the neutrophilic granulocyte series. There was a marked shift to the left in this case, which was consistent with the clinical state. There was a mild secondary anemia in each of the 5 cases of this series. The icterus index was elevated during the terminal phase of case 11. A normal icterus index was recorded in case 12. A normal van den Bergh reaction was noted in case 14. No chemical tests were done in case 10 to gauge the type and amount of jaundice present during the initial attacks.

Urine. There was a slight albuminuria in 2 cases during the migratory phase, and a high degree of albuminuria in the terminal phase of case 11.

Feces. No Fasciola eggs were recovered from the stools of any of the patients in my series. However, an intensive search for these eggs was carried out only in cases 13 and 14.

Skin Testing. Dr. J. E. Alicata has prepared a skin testing antigen from *F. gigantica.* At the present time I have used this material in

testing a selected group of patients, but the number of cases has been insufficient to make a proper evaluation of its reliability. In addition we have yet to arrive at the correct testing dosage. This work will be reported in greater detail when a sufficient number of cases have been tested. Four living members of the family of the patient known as case 11 were tested. Only the patient's father was positive. A strongly positive skin test was noted in case 12. A negative test was obtained in case 10, the only living patient in this series from whom a fluke was recovered and identified. Negative tests were recorded also in cases 4 and 5.

Summary and Discussion of Pathologic Findings

The Granuloma

The granulomatous lesions are similar in appearance, regardless of their site. Recent lesions have a stellate or scalloped outline not unlike those noted in lymphopathia venereum. The central portions of the granuloma are composed of necrotic material containing cytoplasmic and nuclear débris, eosinophilic and neutrophilic granulocytes, and Charcot-Leyden crystals. The original tissue architecture is wiped out in the central portion of the granuloma. Surrounding the necrotic area is a granulation tissue which varies in size and prominence, probably with the age of the lesion. There were areas in case 12 in which the necrotic subcutaneous tissue blended imperceptibly with the intact tissue without any intervening granulation tissue. Where a granulation tissue exists, it is separated from the necrotic zone by a well defined layer of pink, fibrinoid material, within which there are few cells. Imbedded within this material are many Charcot-Leyden crystals and occasional large, pink, hyaline bodies of irregular outline. These probably represent remnants of the original collagenous framework at the site of inflammation. The vascular granulation tissue is composed predominantly of fibroblasts, although epithelioid cells, eosinophils, plasma cells, and neutrophils are noted also. Giant cells of the Langhans or foreign body type are not noted in this tissue.

The structures beyond the granulation tissue vary in appearance according to the age of the lesion. The extent and form of this variation are best appreciated in examining the process in the liver. In case 13 it was believed that the granuloma was of recent origin. Within the contiguous hepatic lobules there were small clusters of cord cells which were widely separated by plump fibroblasts, collagen fibers, eosinophils, and plasma cells. Beyond this there was an area in which the hepatic cords persisted. In this zone the cords were separated

by widely distended sinusoids. The latter were filled with dense collections of eosinophils. The periportal connective tissue in this region was scanty and contained many eosinophils. The small bile ducts were empty. The granuloma in case 11 was considered to be an older lesion than that just described. In this case a broad, but poorly defined area, composed of dense collagenous connective tissue surrounded the granuloma. Small nests of cord cells persisted in this region. The connective tissue contained only occasional eosinophils, and the fibroblasts were small and widely spaced. In the intact liver parenchyma there was less sinusoidal distention. There were no eosinophils within these sinusoids or within the periportal connective tissue. The tissue changes noted in these human cases were similar to those noted within experimentally infected guinea-pigs, except for the added finding of Charcot-Leyden crystals in the human lesions.

These granulomata have not received prominent attention in the study of Fasciola infestation. In cases in which *F. hepatica* has been found in aberrant localities, similar lesions have been described. Diss[10] described a case in which a fluke, identified as *F. hepatica* on microscopic section, was surrounded by a granulomatous lesion not unlike that which has just been described, although he did not mention Charcot-Leyden crystals. Neghme and Ossandon[11] also described a subcutaneous granuloma which, on histologic examination, contained a fluke (*F. hepatica*), believed to be in an early phase of development. Catchpole and Snow[12] recently described a patient with a migratory subcutaneous swelling, which on removal was found to be an abscess containing a fluke (*F. hepatica*). These authors have supplied me with a histologic section of the soft tissue adjacent to the fluke. It is identical in appearance with the granulomata just described. Many Charcot-Leyden crystals are present in the zone of necrosis adjacent to the fluke. Lièvre[13] is cited by Diss[10] as having seen similar cases, but Lièvre's article was not available to me. It should be noted that, of the 14 cases outlined in Table I, seven of ten flukes were recovered from aberrant sites, and two of the seven granulomata occurred in such sites.

Histologic Differential Diagnosis of Granulomatous Lesions

There are many parasites which may elicit a granulomatous response during migration within a human host. The parasites may be naturally parasitic to man or to some other mammal. The human parasites which are most frequently found to cause granulomatous lesions are strongyloides, ascaris, schistosomes, and microfilariae. *Toxocara*

canis and *catis,* canine and feline ascarids, have also been found to cause granulomata. Two forms of granulomata may be caused by such parasites. The lesions may be small, oval, and discrete, resembling miliary tuberculous foci. Lesions of this type are noted in the hyperinfective cycle of strongyloidiasis,[14] schistosomiasis,[15] and filariasis.[16] If central necrosis occurs, it is not very extensive and is not associated with tissue liquefaction. The necrotic zone has a pink, fibrinoid appearance, and in strongyloidiasis may contain Charcot-Leyden crystals (my observation). These foci occur about the disintegrating larvae of the parasite, which may be discovered by serial sections of the tissues.[14] Extensive granulation tissue borders the zone of necrosis. This contains many epithelioid cells, eosinophils, and giant cells of the Langhans type. The granulomata of schistosomiasis surround eggs rather than larvae. Each focus is small, bulky granulomata being formed by the presence of many eggs.[15]

Larger lesions, associated with extensive tissue destruction and liquefaction, similar to those in Fasciola infestation may be found in ascaris infection.[17] Remnants of ascarid larvae and Charcot-Leyden crystals may be found within the necrotic tissue. Giant cells of foreign body type may surround the larval remnants when they become enveloped by the reparative granulation tissue surrounding the zone of necrosis. Beaver *et al.*[18] described hepatic lesions which varied from 5 to 10 mm. in diameter in cases of infestation with the canine and feline ascarids, *T. canis* and *T. catis*. In some areas there was total necrosis of the normal cellular elements, which were replaced by amorphous acidophilic material. In other areas necrotic hepatic cells had been almost exclusively replaced by eosinophilic leukocytes and a few foreign body giant cells. No Charcot-Leyden crystals were noted in this description, but in other respects the lesions seemed similar to those noted in *F. gigantica* infestation. Serial section reconstruction of the outline of parasites found within the necrotic areas enabled Beaver *et al.*[18] to make a species identification.

It should be stressed that diagnosis as to the inciting parasite should not be made on the basis of a histologic examination of the granuloma unless an intact parasite can be demonstrated within the lesion. If the granuloma is a very large one, all that may be available for section is a portion of its wall. On the basis of the studies of guinea-pigs, there is no tissue necrosis adjacent to a migrating fluke, so that sections taken of the granulomata have little chance of revealing the parasite unless it has died. Even if parasites are found, they may be too fragmented to allow a specific diagnosis. Diagnosis must therefore

depend upon a combination of clinical, laboratory, and histologic findings.

Hepatobiliary Disease

Only one case in this series was studied extensively from the standpoint of hepatobiliary disease (case 11). The tissue changes in this case were similar to those described in *F. hepatica* infestation[19] and may be divided into those caused by the direct action of the fluke upon host tissue and those which were secondary to obstruction of the biliary tree. The latter changes were more extensive and were the cause of the patient's death. These included diffuse cholangitis with suppuration and abscess formation and thrombosis of the portal vein. Abscesses were present within the walls of the ducts adjacent to the fluke and were present within the liver itself as a result of extension of the suppurative process from the smaller bile ducts. There were, in addition, extensive areas of lobular necrosis which probably resulted from obstruction of the portal vein.

The tissue changes immediately adjacent to the parasite were not as striking as those noted in the granulomata. The epithelium was, for the most part, intact. Epithelium-lined sinuses extended from the surface into the deeper tissues. Histiocytes, occasional neutrophils, lymphocytes, and plasma cells were noted in the underlying connective tissue. The latter was edematous and increased. The difference between the tissue reaction noted in the granulomata and adjacent to the mature fluke in its proper habitation probably stems from the fact that the former occurs during the migrating phase of the disease. Migratory flukes are in intimate contact with host tissue. In addition they probably elaborate digestive enzymes. If the larvae die, the proteins and polysaccharides of the disintegrating body must also elicit a response from the host tissues. When resident within the bile ducts, however, the parasite is separated from the host tissue by a layer of epithelium. Müller's[20] studies (cited by Hoeppli[19]) of *F. hepatica* during this phase of its existence probably apply equally to *F. gigantica*. He noted that the food of the parasite consisted chiefly of bile duct epithelium and leukocytes, but not blood. This separation of the parasite and host probably inhibits the development of the tissue reactions noted during earlier phases of infestation. A further indication of a barrier between host and parasite is the lack of eosinophilia during the latter stages of the disease (case 11).

Summary

Five cases of *Fasciola gigantica* infestation are reported. This para-

site, normally present in cattle and swine, but not in man, is the commonest form of Fasciola in Hawaii.

Infestation is derived from the ingestion of raw watercress grown in areas where infected cattle are allowed to range freely.

Migratory and hepatobiliary phases of the disease occur. The former is marked by the production of granulomata, often in aberrant locations. In addition, mature flukes may be recovered at aberrant sites.

The symptoms of the migratory phase are sufficiently typical to make possible a clinical diagnosis. They consist of intermittent bouts of intense abdominal pain, fever, nausea, and vomiting. These symptoms are associated with profound eosinophilia and may be associated with abdominal tenderness.

The tissue changes during the migratory and end stages of the disease are described, and an attempt is made to explain the difference in the tissue changes noted during these phases of the disease.

I wish to thank Dr. J. E. Alicata for his kind advice in the preparation of this paper and for the illustrations of the fluke and its intermediate host. Thanks are also due Dr. I. L. Tilden for the photomicrographs of the histologic material.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. The snail, *Fossaria ollula,* which is the intermediate host of *Fasciola gigantica* in the Hawaiian Islands. Natural size.

FIG. 2. Mature liver fluke, *F. gigantica.*

FIG. 3. Gross appearance of the liver of a guinea-pig, 20 days after infection, showing numerous subcapsular burrows.

FIG. 4. Migrating liver fluke (*F. gigantica*) in the liver of a guinea-pig, 20 days after infection. Of note is the lack of host tissue destruction or response in the immediate vicinity of the migrating parasite. Hematoxylin and eosin stain. × 120.

FIG. 5. Edge of hepatic granuloma of the liver in a guinea-pig, 20 days after infection. Of note are the central zone of necrosis, the surrounding granulation tissue, and the dense collections of round cells in the adjacent portal connective tissue. Hematoxylin and eosin stain. × 120.

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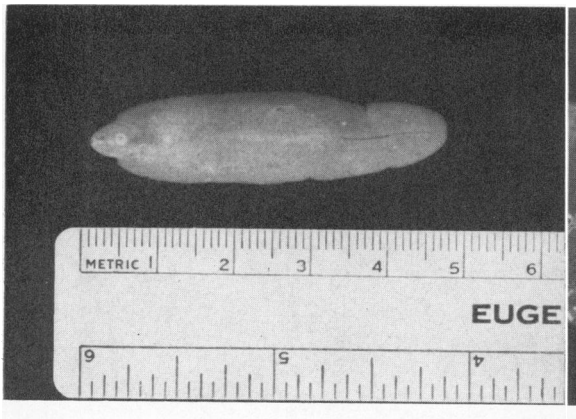

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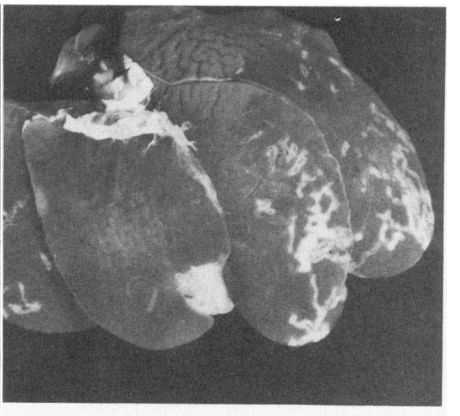

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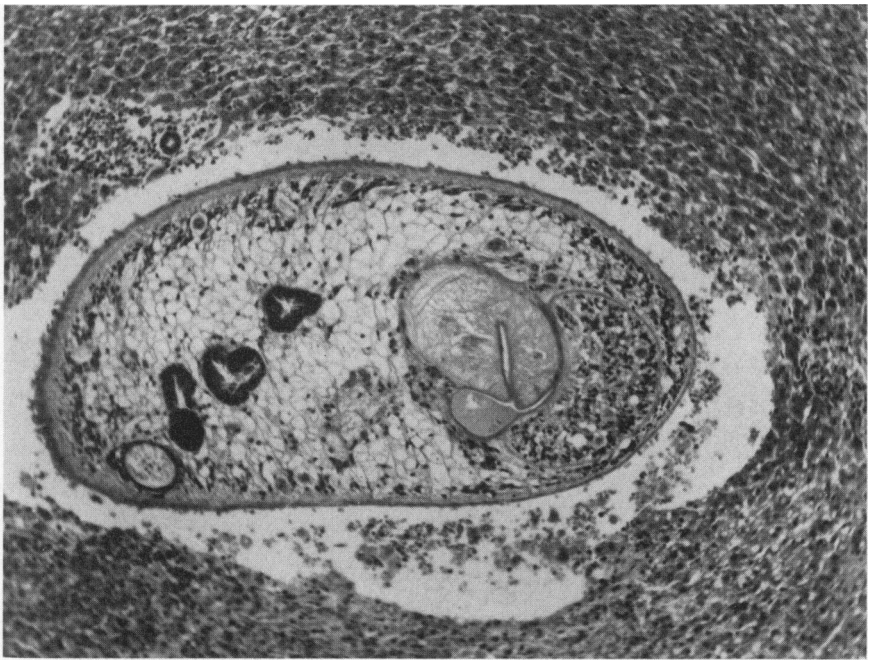

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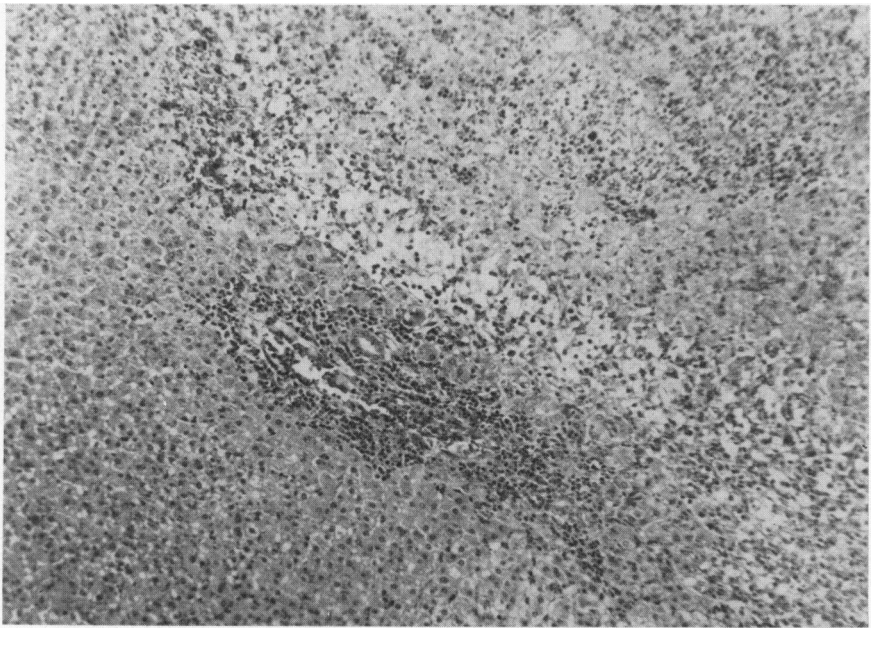
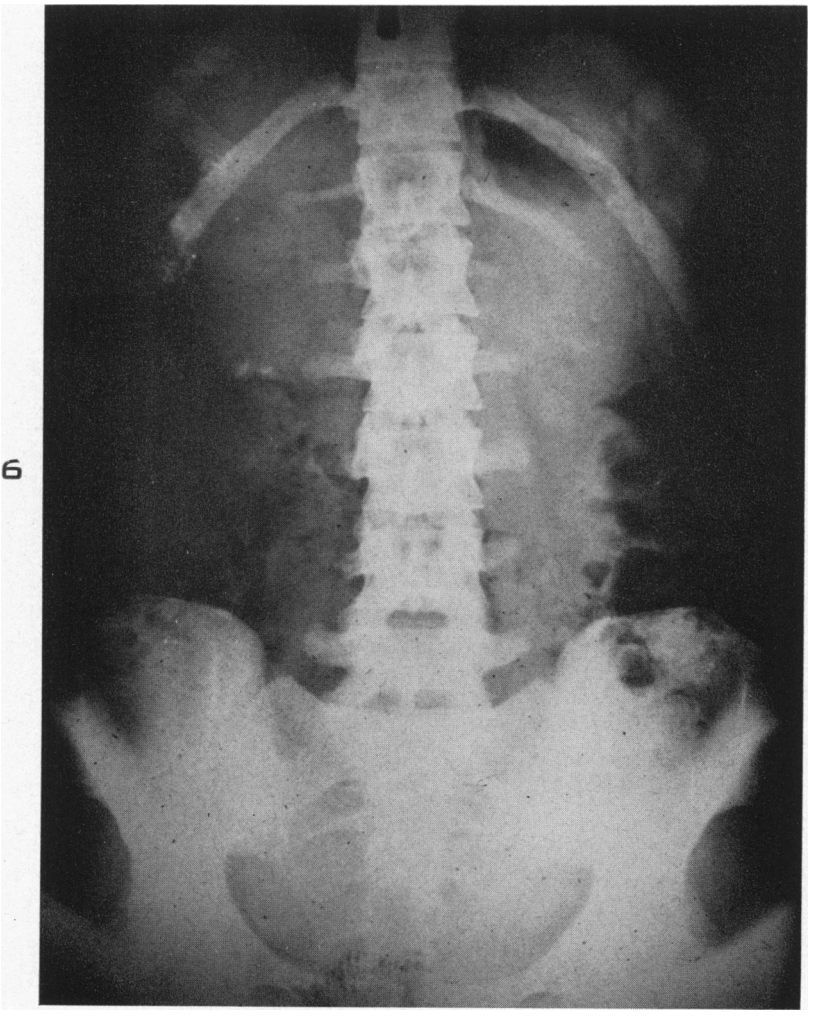


FIG. 6. Flat film, abdomen (case 10). Calcified hepatic granuloma. Film taken 4 years after onset of disease and 2 years after cessation of symptoms.

FIG. 7. Hepatic granuloma, case 11. There is an area of central necrosis with liquefaction surrounded by vascular granulation tissue. Hematoxylin and eosin stain. × 40.

FIG. 8. Hepatic granuloma, case 11. Hematoxylin and eosin stain. × 120.



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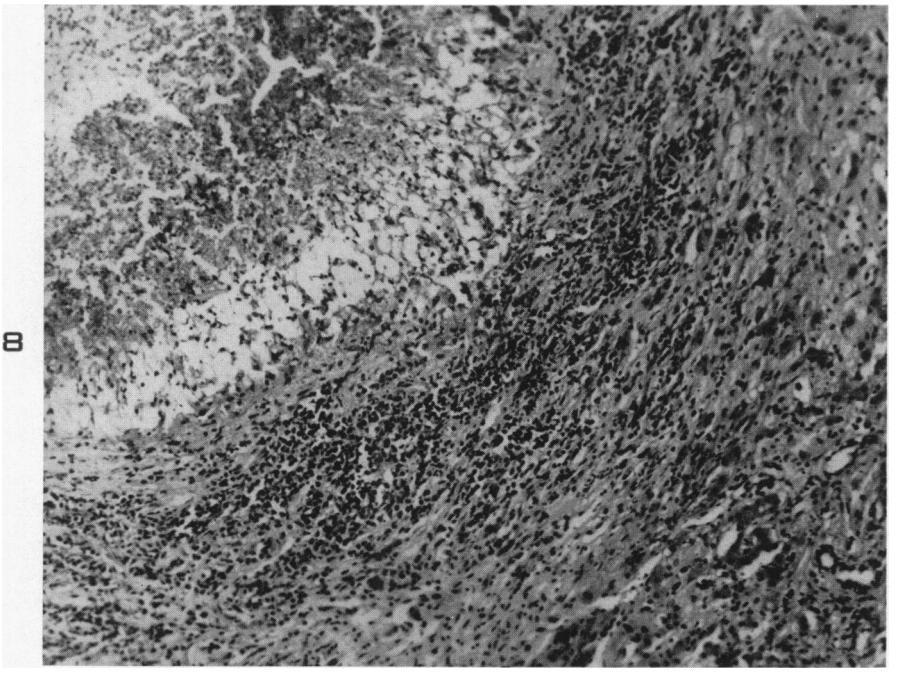

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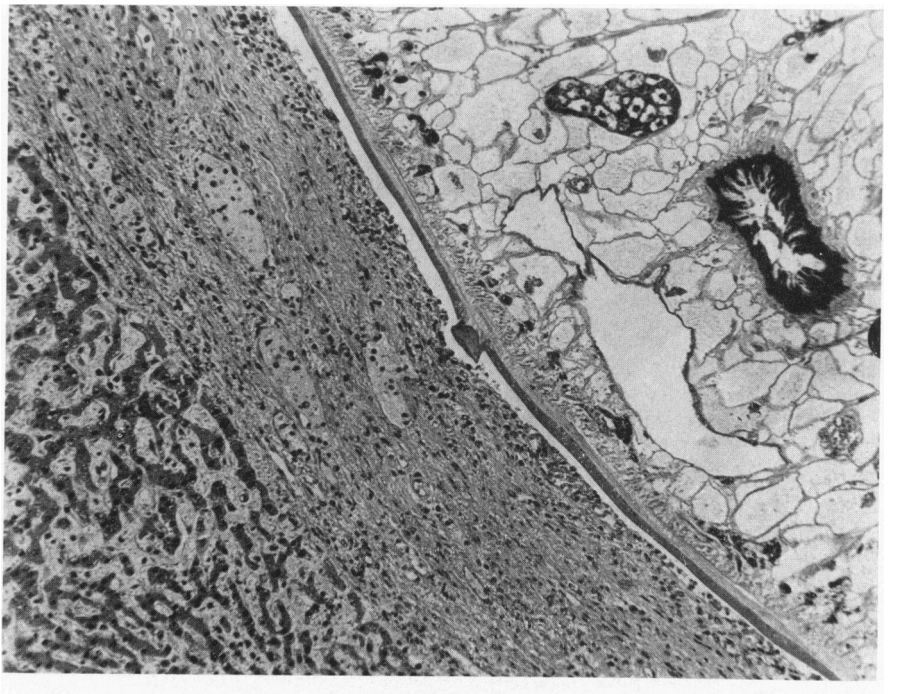
FIG. 9. Mature fluke in hepatic duct, case 11. Hematoxylin and eosin stain. × 120.

FIG. 10. Granuloma, gluteal soft tissue, case 12. Hematoxylin and eosin stain. × 40.

FIG. 11. Granuloma, gluteal soft tissue, case 12. Charcot-Leyden crystals stained by the Ziehl-Neelsen stain. × 205.

FIG. 12. Granuloma, gluteal soft tissue, case 12. Granulation tissue at edge of zone of necrosis. × 95.



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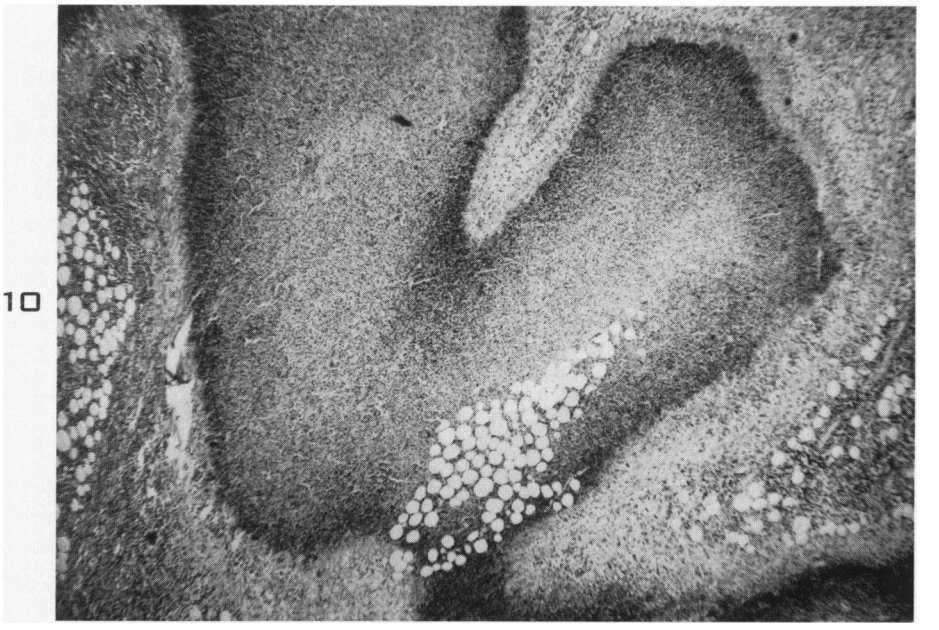

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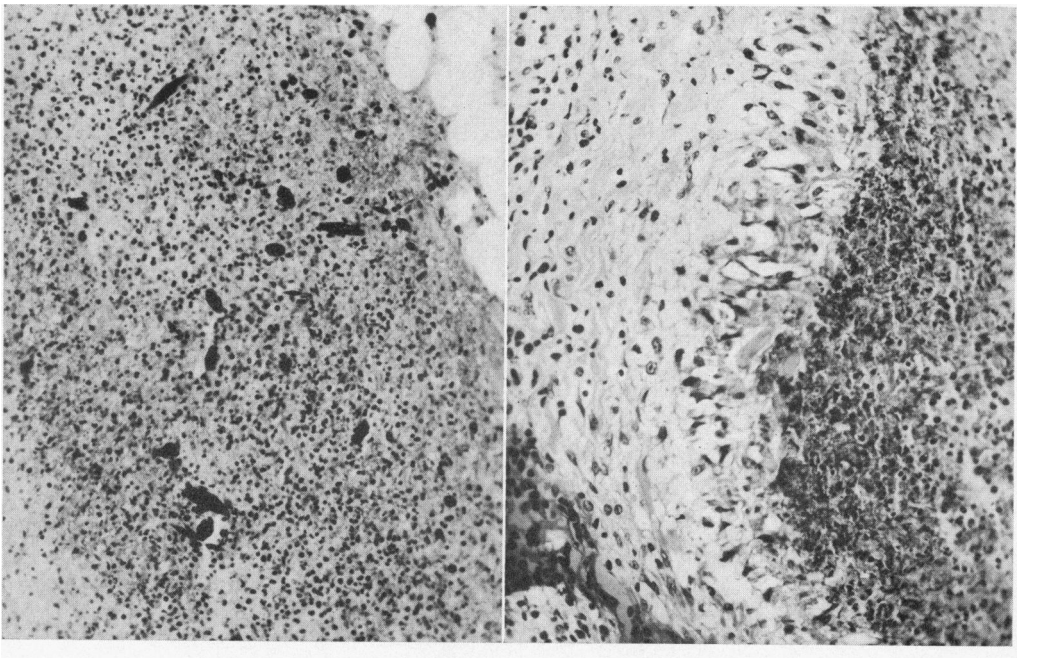

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