There appears, however, to be a factor common to both diseases—an aberration of carbohydrate metabolism. This finding may pave the way towards determining the missing factor which results in the development of malignancy. Such disturbances in carbohydrate metabolism may be the cause or result of benign glandular hyperplasia and may render the patient more liable to develop carcinoma, in a way similar to that whereby diabetes predisposes to certain infections. Underlying pituitary or adrenocortical dysfunction may be involved.

Summary

Studies in glucose tolerance have been extended to embrace all cases with abnormal uterine bleeding at the time of the climacteric, both benign and malignant. Similar investigations are proceeding in other age-groups. The results have been correlated with the histological appearances of the endometrium.

Conflicting reports have appeared in recent years with regard to the incidence of abnormal glucose tolerance in patients with carcinoma of the body of the uterus. Such cases were therefore investigated by glucose-tolerance tests and compared with control subjects of the same age-group (it is known that age has an important bearing on glucose tolerance). 52% of patients with cancer of the endometrium showed impaired glucose tolerance, compared with 22% in the control group. These figures, on analysis, are most significant statistically.

Patients with proved benign glandular hyperplasia were similarly investigated and compared with controls (both normal subjects and patients with uterine bleeding due to other causes). The incidence of abnormal glucose tolerance (84%) in cases of benign glandular hyperplasia was found to be striking and much higher than in the two control groups and higher than in cases of cancer of the endometrium. These figures are very significant statistically.

The possible significance of these findings is discussed.

It is submitted that further research along these lines is warranted. Such studies may throw more light on problems such as (a) the alleged association between benign glandular hyperplasia and cancer of the endometrium, and (b) the unknown factors that determine the onset of benign hyperplasia and the development of malignancy in some of these cases.

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REFERENCES

- Barr, W., and Charteris, A. A. (1955). *J. Obstet. Gynaec. Brit. Emp.*, **62**, 187.
- Brewer, J. I., and Foley, T. J. (1953). *Obstet. and Gynec.*, **1**, 67. *Brit. med. J.*, 1952, **2**, 712.
- (1959). *1*, 1340.
- Brown, J. B., Kellar, R., and Matthew, G. D. (1959). *J. Obstet. Gynaec. Brit. Emp.*, **66**, 177.
- Duncan, G. G. (1952). *Diseases of Metabolism*, 3rd ed. Saunders, Philadelphia.
- Garnet, J. D. (1958). *Amer. J. Obstet. Gynec.*, **76**, 11.
- Hertig, A. T., and Sommers, S. C. (1949). *Cancer*, **2**, 946.
- Hoet, J. P., and Lukens, F. D. W. (1954). *Diabetes*, **3**, 1.
- Hunter, R. M., Ludwick, N. V., Motley, J. F., and Oaks, W. W. (1954). *Amer. J. Obstet. Gynaec.*, **67**, 121.
- Jackson, W. P. U. (1952). *Brit. med. J.*, **2**, 695.
- (1953). *S. Afr. med. J.*, **27**, 795.
- (1957). *Lancet*, **1**, 617.
- Jacobson, P. H. (1948). *Milbank med. Ed Quart.*, **26**, 90. Quoted by J. B. Vander, *Amer. J. Obstet. Gynec.*, 1959, **77**, 243.
- Jones, H. O., and Brewer, J. I. (1941). *Amer. J. Obstet. Gynec.*, **42**, 207.
- Joslin, E. P., Root, H. F., White, P., and Marble, A. (1952). *The Treatment of Diabetes Mellitus*, 9th ed. Lea and Febiger, Philadelphia.
- Kritzer, M. D. (1952). *Med. Clin. N. Amer.*, **36**, 1151.
- Lawrence, R. D. (1947). *Ibid.*, **31**, 289.
- Louw, J. T. (1958). *Transactions 2nd World Congress of International Federation of Gynaecology and Obstetrics*, Montreal.
- Lund, C. J., and Weese, W. H. (1953). *Amer. J. Obstet. Gynec.*, **65**, 815.
- McBride, J. M. (1955). *J. Obstet. Gynaec. Brit. Emp.*, **62**, 574.
- Marble, A. (1934). *New Engl. J. Med.*, **211**, 339.
- Mazzola, V. P. (1938). *Amer. J. Obstet. Gynec.*, **36**, 698.
- Moss, W. T. (1947). *Amer. J. Roentgenol.*, **58**, 203.
- Moyer, J. H., and Womack, C. R. (1950). *Amer. J. med. Sci.*, **219**, 161.
- Noble, M. J. D., and Attwood, M. E. (1958). *J. Obstet. Gynaec. Brit. Emp.*, **65**, 64.
- and Richardson, E. H. (1941). *Amer. J. Obstet. Gynec.*, **42**, 564.
- Novak, E., and Novak, E. R. (1958). *Gynecologic and Obstetric Pathology*, 4th ed. Saunders, Philadelphia and London.
- and Yui, E. (1936). *Ibid.*, **32**, 674.
- Orrahood, M. D., and Wyatt, J. P. (1953). *J. Obstet. Gynaec. Brit. Emp.*, **60**, 859.
- Palmer, J. P., Reinhard, M. C., Sadugor, M. G., and Goltz, H. L. (1949). *Amer. J. Obstet. Gynec.*, **58**, 457.
- Purdie, A. W. (1945). *J. Obstet. Gynaec. Brit. Emp.*, **52**, 575.
- Scheffey, L. C., Thudium, M. J., and Farrell, D. M. (1943). *Amer. J. Obstet. Gynec.*, **46**, 786.
- Smith, G. V. S. (1941). *New Engl. J. Med.*, **225**, 608.
- Speert, H. (1949). *Surg. Gynec. Obstet.*, **89**, 551.
- Strachan, G. I. (1936). *J. Obstet. Gynaec. Brit. Emp.*, **43**, 749.
- Turnbull, A. C. (1956). *Ibid.*, **63**, 179.
- Vander, J. B. (1959). *Amer. J. Obstet. Gynec.*, **77**, 243.
- Way, S. (1954). *J. Obstet. Brit. Emp.*, **61**, 46.

HYDATID DISEASE IN NORTH WALES

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This paper presents certain epidemiological and surgical aspects of hydatid disease as seen during recent years in North Wales; it does not give a detailed account of the life-cycle of the parasite or pathology of the disease, since authors from countries where the disease is far commoner have contributed to a voluminous literature on these aspects of the subject.

In 1937 Professor Lambert Rogers drew the attention of the Welsh Board of Health to the relatively high incidence of hydatid disease in South Wales. Howell (1938), reporting the results of the inquiry, showed that 144 cases were admitted to hospitals in Wales during the period 1927–36. Most of these patients came from the industrial areas of Glamorgan and Monmouth. Wolfe (1943) reported another 34 cases treated in the Cardiff Royal Infirmary between 1926 and 1938. I was prompted to conduct this further survey of what appears to be a continuing prevalence of the disease after personal observation of several cases in South Wales and later in North Wales. Data concerning 44 cases, hitherto unpublished, treated in hospitals serving the North Wales area during January, 1948, to December, 1957, have been collected. It is probable that the number of patients treated is larger, since many hospital records only extend back over a five-year period.

Pathological Features

Hydatid disease is caused by cysts which are formed in various tissues by the developing larvae of the dog tapeworm, *Echinococcus granulosus*. The adult worm is 6 mm. long, and many hundreds are present in the upper small intestine of infected dogs (definitive host). About 500 ova are found in each proglottis. Food contaminated by dog faeces can be ingested by the intermediate host, which may be sheep, cattle, pig, camel, or man.

Ova ingested by man are acted upon by ferments in the stomach and upper part of the small intestine, where the external coat is digested. The freed embryo then burrows through the intestinal mucosa into a portal radicle to gain access to the liver, which is the commonest site of cyst formation; some embryos may filter through the liver sinusoids into the pulmonary capillaries and cysts develop in the lungs. Less commonly, cysts develop elsewhere—namely, kidney, spleen, pelvis, heart, bone, and central nervous system.

Hydatid cysts may reach the size of an orange or a baby's head, and are usually filled with a clear fluid. They are enclosed by an outer coat or adventitia, which is formed of fibrous tissue derived from the cellular reaction in the host tissue. The wall of the cyst proper is composed of an outer chitinous layer known as the laminated membrane; this layer is mainly responsible for the thickness of the cyst wall. The germinal layer, or endocyst, forms the lining membrane, and from it arise buds about the size of grains of sand, which grow into brood capsules containing a larger number of scolices. These are destined to grow into mature worms in the intestine of the dog. In man they are capable of developing into fully formed daughter cysts within the primary cyst, or elsewhere should rupture into serious cavities or the blood-stream occur. Insult to a simple or univesicular cyst by trauma, lack of nourishment, infection, or a foreign substance such as bile, may also result in the formation of daughter cysts. This tendency to multivesiculation appears to increase with age and is also more apparent in liver cysts. For instance, in 34 patients operated upon in the present series, 14 out of 19 liver cysts contained daughter cysts, whereas only 3 out of 10 pulmonary cysts were multivesicular. The contents of such cysts may be clear, caseous, or purulent.

Epidemiological Aspects

Occurrence.—Hippocrates first described the disease, which occurs throughout the world in sheep-rearing countries. It is relatively common in Australia, South America, Greece, Southern Italy, and in some countries of the Middle East; it is rare in the United States, but not uncommon in the native population of Canada. In Great Britain the incidence of the disease is low and, as was noted by Howell (1938), Wolfe (1943), and Barrett and Thomas (1952), largely confined to the Welsh area. Stringent public health measures have reduced the disease to a rarity in Scotland and the Shetlands.

Source and Reservoir of Infection.—Ova from dogs infected with the adult worm are ingested by sheep or man. The dog-sheep-dog cycle is responsible for perpetuating the infection in endemic areas.

As noted by Wolfe, inadequate supervision of the disposal of offal is the main factor responsible for

transference of the disease. It would appear that approximately 4% of the sheep slaughtered in abattoirs of the Wrexham rural district area are infected with liver hydatid disease. The significance of cysts in some sheep livers is well understood by public abattoir staffs in North Wales, and, in general, offal is carefully disposed of at a central depot. In the industrial areas of Flintshire and Denbighshire, however, the multiplicity of small slaughterhouses makes strict supervision difficult. There are, for example, 13 slaughterhouses in one area with a population of 90,000; it is of interest to note that this number presents a considerable reduction on the pre-war figure of 57 slaughterhouses in the same area. Stray dogs undoubtedly gain access into substandard abattoirs where, because of the sheep infestation, the infectivity rate must be high.

Other practices, such as the occasional slaughtering on farms and the sale of offal as manure, are known to occur. Another old custom exists among shepherds in some areas of feeding dogs with dead sheep carcasses. Obviously, therefore, there are abundant sources from which dogs are continually infected, with the consequent increased opportunity for human infection.

Veterinary surgeons in North Wales give a low incidence of infestation among domestic dogs, but no detailed investigation has, to my knowledge, been conducted on stray dogs. Three patients in the present series lived in a small mining village in the North Wales coalfield, which is noteworthy for its population of stray dogs.

As shown in Fig. 1, a high proportion of the cases in this series occurred in and around the industrial areas of Flintshire and Denbighshire and along the more heavily populated North Wales coast. A similar geographical distribution was noted in South Wales by Howell, and many causes have been postulated to account for it. The close proximity of grazing land to an industrial

an industrial community with a large canine population must be a factor, especially as some of these areas have an increased number of stray and unlicensed dogs. Furthermore, domestic animals come into close contact with children and adults in the more crowded living conditions of an industrial community. Twenty-four patients in the present series were dog-owners. It should be remembered that, in addition to the excreta, the hair, paws, and muzzle of a dog may be infected. The increased fondling of dogs by children as well as their lower standard of hygiene, probably explains why hydatid disease is most often acquired during childhood. Others possible sources of human infection are green vegetables and spring water. Greenstuffs are occasionally contaminated with excreta, when infected dogs gain access into unfenced allotments and kitchen gardens.

FIG. 1.—Geographical incidence (44 cases). Shading denotes more heavily populated areas.

Incidence of the Disease

The annual incidence between 1948 and 1957 appears to have remained fairly constant (Table I). The sex incidence shows a slight female preponderance, 23 being

TABLE I.—*Annual Incidence*

	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957
No. of cases	3	5	2	6	5	5	4	5	4	5

female and 21 male. In most other series the sexes are about equally affected. Wilson (1950) attributed a high incidence amongst Arab women to their extreme domesticity, which resulted in a greater liability to infection.

The ages of the patients at the time of diagnosis of the disease is shown in Table II; the maximum age incidence occurred in the fourth, fifth, and sixth decades.

TABLE II.—*Age Distribution at Time of Diagnosis*

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+
No. of patients	1	3	3	5	9	7	12	4

The age of clinical presentation, however, is no criterion of the duration of the disease, which according to most authors is acquired during childhood or early adult life (Dew, 1928). The age of a cyst is indicated by such features as multivesiculation, calcification, sterility, and the onset of complications.

Surgical Manifestations

Dew (1930) has stressed that it is the onset of complications such as trauma, spontaneous rupture of cysts, and infection which determine the first clinical manifestations of hydatid disease. The disease may remain dormant for many years and be revealed only at necropsy. Hydatid cysts have been described in almost every organ in the body, but the liver and lungs are most often affected (Table III). The anatomical distribution of cysts in the present series is shown in Table IV.

TABLE III.—*Distribution of Cysts in Liver and Lung (Meltzer et al., 1956)*

	Liver	Lung
Lebanon	56%	30%
Greece	51%	30%
Turkey	51.7%	29%
Australia	76.6%	9.4%
S. America	70%	15%
Present series	59%	29%

TABLE IV.—*Anatomical Distribution of Cysts in 44 Patients*

Site of Disease	No. of Patients	Details
Liver	28	Right lobe, 23. Left lobe, 3. Both lobes, 2
Lung	13	Right lung: 4 lower lobe, 2 middle lobe, 1 upper lobe, 1 middle + lower lobe. Left lung: 3 lower lobe, 1 upper lobe. Right + left lungs: 1 (right middle lobe and left lower lobe)
Spleen	3	Whole spleen replaced by multivesicular cysts in 2 cases. Bipolar cysts in 1 case
Muscle	1	One cyst invaded abdominal wall in continuity with liver cyst
Peritoneal cavity	3	(1) Great omentum. (2) Behind bladder. (3) Multiple peritoneal

In four cases cysts were multiple: liver and bilateral lung cysts; liver and omentum; liver and multiple peritoneal; and liver and abdominal wall.

Liver Cysts

The latency of hepatic hydatid disease is well recognized. A long period usually elapses between infection during childhood or early adult life and the

development of symptoms of the disease. Of 26 patients with liver cysts, 21 had complained of symptoms for less than six months. Three others had been aware of a symptomless abdominal swelling for 4, 8, and 15 years respectively. The frequency of various symptoms is enumerated in Table V, and is compared with two other series.

TABLE V.—*Comparison of Frequency of Symptoms in Liver Hydatid Disease*

Present Series	Kneebone (1937)	Wilson (1950)
Pain and jaundice ..	8	Pain and jaundice .. 2
Anaphylactic	1	Anaphylactic 0
Pain or discomfort ..	5	Pain and discomfort .. 8
Swelling and cough ..	1	Swelling 4
Swelling	3	Pain and cough .. 1
Swelling and pain ..	6	Swelling and pain .. 10
Weak feeling	2	Weak feeling 0
Totals	26	40
		25

It is evident that the commonest single symptom in all three groups of patients was abdominal swelling with or without pain. Characteristically, the pain simulated that of gall-bladder disease and was most often situated in the right hypochondrium; it was of a dull aching type, and was sometimes associated with pain in the right shoulder. Nausea and vomiting were rare symptoms except in the jaundiced patients. Two patients were admitted as acute abdominal emergencies following traumatic rupture of liver cysts. In one, a boy of 14 years, generalized abdominal pain occurred half an hour after a fall during a long-jump competition; an urticarial eruption also developed over the neck, chest, and abdomen. A pre-operative diagnosis of ruptured hydatid cyst was confirmed at operation. The other patient, a man of 48, complained of severe abdominal pain and vomiting following a crush injury between a tractor wheel and a motor truck. At laparotomy a ruptured hydatid cyst 3 in. (7.5 cm.) in diameter was found in the postero-inferior aspect of the right lobe of the liver, and the peritoneal cavity contained free fluid and many daughter cysts; anaphylactic symptoms did not occur.

Jaundice.—Rupture into or compression of the biliary system was thought to be the cause of jaundice in six patients. In addition, there were two cases of jaundice associated with infected hydatid cysts.

Intrabiliary Rupture.—This occurred in four patients, and daughter cysts were discharged along the common bile-duct. In three patients erosion of the right hepatic duct occurred and in the fourth an infected cyst of the left lobe of the liver had ruptured into the left hepatic duct. A noteworthy feature in one patient was a shrunken right lobe the substance of which had been entirely replaced by a multivesicular cyst which communicated with the right hepatic duct; the left lobe of the liver had undergone compensatory hypertrophy, and was at least the size of a normal right lobe.

Compression of Bile-ducts.—There were two cases in which large cysts of the right lobe of the liver had produced pressure deformity of the biliary system. One male patient, whose sister had already undergone treatment for hydatid disease five years previously, was found to have a large cyst in the quadrate lobe compressing the porta hepatis. In the other case jaundice subsided after draining a large cyst situated in the right lobe of the liver near the gall-bladder; the latter was distended, but no communication between the cyst and the bile-duct was demonstrated.

Suppuration.—In two patients jaundice was thought to be due to infective cholangitis. In one an intermittent pyrexia with jaundice continued for 10 days after draining a large infected cyst of the right lobe of the liver. In the

other patient jaundice and pyrexia occurred two months after drainage of a hydatid cyst situated high up under the diaphragm. The symptoms subsided after further drainage extrapleurally through the bed of the eleventh rib.

Pulmonary Cysts

There were 13 cases of pulmonary disease. The patients in the group were rather younger, six of them being under 30. With two exceptions the cysts were unilateral and solitary, the lower lobe of the right lung being most commonly affected (Table VI). In the

TABLE VI.—Frequency of Symptoms in 13 Patients with Pulmonary Hydatid Disease

Cough and haemoptysis	2
" " pain	2
" " dyspnoea	3
Chest pain	3
Cough and abdominal swelling	1
Asymptomatic (mass radiography)	2

experience of Barrett and Thomas (1952), multiple lung cysts are unusual in patients who have liver cysts as well, and are probably the result of simultaneous multiple infestation, thus enabling more than one embryo to penetrate the liver capillary barrier. Another possibility is that live elements are shed into the hepatic vein from a complicated liver cyst.

The commonest symptom was a paroxysmal cough, which was associated in two patients with slight haemoptysis. Two patients also gave a history of having coughed up hydatid "grapeskins." Chest pain, alone, occurred in three patients; in two of them it was the result of rib erosion by peripheral cysts.

The length of history varied for a few days or weeks to three months, the average duration being about one month. Cysts grow rapidly in the lung, since there is less limitation to expansion than in liver tissue. Symptoms therefore occur earlier than in liver disease.

Complications.—Intrabronchial rupture of pulmonary cysts occurred in two patients. Both gave a history of expectoration of fragments of hydatid cyst, and in each case a fistula between the cyst and a bronchus was demonstrated at operation. Intrapleural rupture occurred in two patients. In the first, a multivesicular cyst of the lower lobe of the left lung had partially ruptured into the pleural cavity, producing rib erosion and a localized bulging of the overlying chest wall. In the second patient, a large cyst 4 in. (10 cm.) in diameter, which was attached to all three lobes of the right lung, had eroded the posterior ends of the sixth, seventh, and eighth ribs, giving rise to new bone formation; many daughter cysts were evacuated from the cyst cavity.

FIG. 2.—A grossly enlarged spleen whose substance has been entirely replaced by a calcified multivesicular hydatid cyst. Daughter cysts are seen within one of the larger cavities. (Case 31.)

Splenic Cysts

There were three examples of primary cysts in the spleen, a higher incidence than the 3% quoted in the literature. All three patients complained of periodic pain in the left lower chest and abdomen. In one patient who also complained of an ulcer type dyspepsia and left shoulder pain there was a large abdominal mass visibly distending the left loin. At operation this was found to be grossly enlarged calcified spleen containing hundreds of daughter cysts (Fig. 2).

Secondary Cysts

Two patients in this series were admitted because of symptoms attributable to secondary cysts. One complained of a large fixed rounded swelling in the lower abdomen which had been present for about three months. At operation a large cystic mass was found arising out of the pelvis which was adherent to the posterior surface of the bladder; there was also a fibrosed remnant of a hydatid cyst in the liver. The second patient presented with symptoms of subacute intestinal obstruction. At operation multiple cysts were found in the liver, in the mesentery of the terminal ileum, and in the pelvis anterior to the sacrum.

Diagnosis and Treatment

In this series of 44 cases, 10 were not subjected to operative procedures for various reasons. In these 10 patients, however, the diagnosis of hydatid disease was substantiated by means of radiological, serological, and haematological investigations. Six patients in whom symptoms were minimal were not operated upon for reasons such as old age, obesity, congestive heart failure, and pneumoconiosis; three patients refused treatment, and in one case the diagnosis was made at necropsy. A correct pre-operative diagnosis was made in 21 of the 34 cases treated surgically, which suggests that clinicians in North Wales are not unaccustomed to hydatid disease.

Common diagnostic features of hepatic cysts were abdominal pain, palpable swelling, and jaundice. The swelling was smooth, lobulated, and usually firm rather

FIG. 3.—Antero-posterior radiograph showing the calcified shadow of a large hydatid cyst in the right lobe of the liver. This patient was 70 years of age, strongly positive to Casoni test. Symptoms were minimal and operation was not performed.

than cystic; in one case it was described as hard and nodular. Fluctuation with a so-called hydatid thrill was demonstrated on only one occasion. Probably the most important confirmatory finding was radiological evidence of calcification in the liver region (Fig. 3); this was present in 17 out of 28 cases of liver disease, and in all three patients with splenic cysts (Fig. 4). In lung cysts the x-ray appearance of a sharply demarcated opacity, often lobulated, suggested hydatid disease (Figs. 5 and 6). Calcification of the cyst wall occurred in only one case.

FIG. 4.—Radiograph showing relationship of a large calcified splenic cyst to the fundus of the stomach during a barium-meal examination. There was a second cyst in the lower pole of the spleen. (Case 30.)

FIG. 5.—Antero-posterior radiograph showing a hydatid cyst in the lower lobe of the right lung (Case 20.)

FIG. 6.—Antero-posterior radiograph of the chest of a child showing bilateral hydatid cysts of the lung. This film demonstrates the typical lobulated appearance of large pulmonary cysts. (Case 19.)

The Casoni intradermal test was of diagnostic value, though occasionally misleading. It was performed in 35 cases, the remaining nine patients being among those diagnosed at operation. As shown in Table VII, a

TABLE VII.—Results of Casoni Intradermal Test (35 Patients)

	No. of Tests	Positive	Negative
Liver cysts ..	22	21	1
Lung " ..	11	7	4
Spleen " ..	2	2	0

negative Casoni reaction was noted in four cases of pulmonary hydatid disease. Dew (1928) attributed an occasional negative Casoni test to non-antigenic properties in the fluid injected or to desensitization following rupture of cysts or some other complication. In the present series, complement-fixation tests were rarely performed and no conclusion can therefore be drawn from the results.

The differential leucocyte count showed an eosinophilia varying between 6% and 24% in 16 cases (36% of whole series); this investigation therefore proved helpful in diagnosis.

The results of operative treatment in 34 patients are shown in Table VIII. In a series derived from a number of hospitals there was inevitably some slight variation in the details of surgical management, but, in the main, treatment was conducted along orthodox lines. All the pulmonary cases were treated at the Liverpool Thoracic Centre and two centres in North Wales.

Surgical Management

Liver Cysts

An anterior intraperitoneal approach through a right paramedian or Kocher incision was used in all cases of hepatic hydatid cysts. In two patients, when secondary procedures were necessary, a transthoracic extrapleural incision was made in the bed of the eleventh rib. Care was taken to protect the wound edges and the peritoneal cavity from contamination with hydatid fluid and daughter cysts.

TABLE VIII.—Result of Treatment in 34 Cases

Case No.	Age and Sex	Type of Cyst and Site	Treatment	Result
<i>Liver Cysts</i>				
1	67 M	Multivesicular cyst R. lobe	Cholecystectomy. Removal of parasite. Drainage	Died from reactionary haemorrhage 24 hours after operation
2	60 M	Multivesicular cyst R. lobe infected	Drainage of abscess cavity	Died 48 hours after operation
3	72 M	Multivesicular cyst R. lobe. Rupture into common bile-duct	Removal of parasite. Drainage of cyst and common bile-duct	Died within 48 hours of operation
4	32 M	Univesicular cyst L. lobe	Excision of pedunculated cyst	Follow-up 2 years. No recurrence
5	26 M	Univesicular cyst R. lobe. Jaundice due to extrinsic pressure on common bile duct	Excision of parasite—formation of saline cyst	(1) Evacuation of blood clot 24 hours post-op. (2) Infected cyst recurred 2 months later. Drainage. No recurrence in 4 years
6	35 F	Univesicular cyst R. lobe	" "	Biliary fistula 2 days after operation. Drainage for 2 months. No recurrence in 6 years
7	48 M	Multivesicular cyst R. lobe. Traumatic rupture	Excision of parasite. Marsupialization of cyst. Peritoneal lavage	Follow-up 2 years: well
8	14 M	Univesicular cyst R. lobe. Traumatic rupture	Excision of parasite. Drainage of cyst. Peritoneal lavage	Follow-up 6 years: well
9	59 F	Multivesicular cyst L. lobe communicating with L. hepatic duct. Jaundice. Empyema of gall-bladder	Cholecystectomy. Excision of parasite. Drainage of cyst and common bile-duct	Follow-up 4½ years: well
10	46 F	Multivesicular cyst R. lobe. Jaundice	Incomplete excision of laminated membrane. Drainage of cyst and common bile-duct	Inadequate drainage post-op. necessitated drainage posteriorly through 11th rib bed. Biliary fistula for 3 months. Follow-up 4 years: well
11	64 F	Multivesicular cyst R. lobe. Jaundice	Cholecystectomy. Excision of parasite. Drainage of cyst and common bile-duct	Follow up: well
12	62 F	Multivesicular cyst R. lobe, adherent to duodenum	Excision of parasite. Drainage of cyst	Biliary fistula for 6 weeks. Follow-up 1 year: well
13	45 M	Multivesicular cyst R. lobe	Excision of parasite. Marsupialization of cyst	Untraced
14	40 M	" "	Excision of parasite. Drainage	Follow-up 3 years: well
15	32 M	Multivesicular cyst R. lobe	" "	Drainage for 7 weeks. Follow-up 2 years: well
16	54 M	Multivesicular cyst involving whole R. lobe	Excision of laminated membrane incomplete because of bleeding. Marsupialization of cyst	Biliary fistula necessitated further drainage through 11th rib bed 4 months later. 18 months later hydatid cyst excised from abdominal wound. Liver cyst full of daughter cysts. Further drainage. In poor health 6 months later
17	47 M	Multivesicular cyst R. lobe. Jaundice due to extrinsic pressure on bile-ducts	Excision of parasite. Marsupialization of cyst	Follow-up 2 years: well, but untraced for 2 years subsequently
18	61 F	Two multivesicular cysts in R. lobe. One cyst in L. lobe. One cyst invaded rectus abdominis muscle	Excision of parasite and part of abdominal wall. Drainage	Follow-up 3 years: well
19	4½ F	Univesicular cyst in liver. Bilateral lung cysts	Excision of bilateral lung cysts (monthly interval). Excision of parasite and drainage of liver cyst 2 months later	Follow up 14 months: well

TABLE VIII (continued)

Case No.	Age and Sex	Type of Cyst and Site	Treatment	Result
<i>Pulmonary Cysts</i>				
20	44 F	Multivesicular cyst R. lower lobe. Communication with lower lobe bronchus	R. lower lobectomy	Follow-up 3 years: well
21	65 F	Univesicular cyst R. middle lobe	Excision of parasite and obliteration of cavity	Follow-up 7 years: well
22	39 F	Univesicular cyst R. lower lobe	" "	Untraced
23	38 F	Multivesicular cyst R. middle lobe communication with bronchus	Excision of parasite layers and small block of chest wall comprising portions of ribs 6, 7, and 8	Follow-up 6 years: well
24	17 M	Univesicular cyst L. lower lobe	Excision of intact cyst after dissection outside adventitia. Cavity obliterated	"
25	51 M	Multivesicular cyst attached to all three lobes of R. lung—also to ribs 6 and 7. New bone formation	Excision of cyst outside adventitia and portions of ribs 6 and 7. Bleeding controlled by obliteration of dead space	Follow-up 18 months: well
26	64 F	Univesicular cyst R. lung—attached middle and lower lobe	Excision of parasite. Cavity closed	Hydatid cyst recurred in 18 months. Excision performed after. Subsequent follow-up 1 year: well
27	24 F	Univesicular cyst R. upper lobe	Excision of cyst parasite. Closure of cavity	Follow-up 9 years: well
28	12 M	Univesicular cyst L. upper lobe projecting into lingula	Excision of cyst. Closure of cavity	Follow-up 8 years: well
29	28 F	Univesicular cyst R. lower lobe projecting into interlobar fissure	Excision of intact parasite cyst. Closure of cavity	Follow-up 5 years: well
<i>Splenic Cysts</i>				
30	44 M	Multivesicular cysts	Transthoracic splenectomy	Readmitted 6 weeks after discharge from hospital suffering from L. empyema. Recovery satisfactory after drainage. Follow-up 6 months: well
31	61 F	Large multivesicular cyst	Splenectomy	Died 10 days after operation
32	46 M	Multivesicular cyst	"	Follow-up 4 years: well
<i>Secondary Cysts</i>				
33	54 M	Hydatid cyst adherent to posterior aspect of bladder	Cyst wall excised after evacuating contents	Developed post-operative asthma—thought to be allergic response to antizens of hydatid disease. Follow-up 1 year: well
34	59 F	Multiple peritoneal cysts in small intestine, mesentery, and pelvis	One cyst removed. Other cysts fixed and immobile	Follow-up 4 years: well

One-stage operations were performed on all patients, one of three procedures being employed: (1) excision of the entire cyst including the adventitia, (2) excision of the parasitic membranes and conversion of the cavity into a saline cyst, or (3) excision of the parasitic membranes followed by open tube drainage or marsupialization of the residual cavity.

The first method can be accomplished only when a pedunculated cyst is present as severe haemorrhage usually precludes any attempt at dissection outside the adventitia. Such a cyst occurred once in this series, when a large pedunculated cyst of the left lobe of the liver was removed *in toto*. The second method of treatment was used in only two patients; in each the cysts were simple and univesicular. The parasite was

first destroyed by exposing the cyst contents to 2% formalin for 5 to 10 minutes. The parasitic layers were removed by separation along the plane of cleavage between the laminated membrane and the adventitia, and the residual cavity was converted into a saline cyst. The closed cyst was then sutured to the parietes deep to the incision so as to facilitate drainage in the event of a biliary fistula or infection. In fact, both these patients needed post-operative drainage. In one the blood clot was evacuated from the cyst cavity 24 hours after operation, and two months later infection of the cyst necessitated further drainage by marsupialization. In the other a biliary fistula occurred two days after operation; this healed after two months of open drainage. No conclusion can be drawn from the results of this method of treatment in two patients, but other writers (Oulié, 1934; Jenkins, 1949) have found that because of complications, such as haemorrhage and infection, primary closure even in apparently suitable cases is not always satisfactory.

In the remaining patients, the third method of treatment was adopted and on the whole was found to be safe and satisfactory. All cysts were formalized before evacuating the contents, and the residual cavity was either drained or marsupialized. Occasionally, in large multivesicular cysts, complete separation of the laminated membrane from the adventitia was impossible and fragments of the cyst lining were left *in situ*. Care was taken, therefore, to swab the whole interior wall of the residual cavity with 2% formalin.

Table VIII shows that 3 out of 19 patients with liver cysts died in the immediate post-operative period, all three being 60 years of age or over. One died from reactionary haemorrhage following cholecystectomy and drainage of a hydatid cyst; the second died after drainage of an infected cyst occupying the entire right lobe of the liver. The third patient, an obese man of 72 years, died 48 hours after draining a cyst of the right lobe of the liver which communicated with the common bile-duct.

In two cases of traumatic rupture of liver cysts, simple tube drainage was performed after routine treatment of the cyst cavity. So far as was possible the peritoneal cavity was cleared of hydatid fluid and daughter cysts by means of saline irrigation.

The common bile-duct was drained in three jaundiced patients in whom hepatic cysts had ruptured into the main bile-ducts. In one of these patients a persistent biliary fistula necessitated further drainage of the cyst through a posterior incision in the bed of the 11th rib.

Of the remaining eight patients with hydatid cysts of the liver, five were treated by simple drainage of the cavity and in three cases the cyst was marsupialized (Table VIII). In one patient (Case 18) part of the rectus abdominis muscle was excised in continuity with a large multivesicular cyst of the right lobe of the liver which had involved the abdominal wall. In the child with multiple lung and liver cysts (Case 19), successive operations were performed on both lungs and the liver over a period of three months. Each operation was well tolerated and the follow-up since operation has been satisfactory.

Though wound-healing occurred in an average period of three weeks, drainage from one infected cyst continued for as long as two months after operation. In two other patients temporary biliary fistula continued to drain for many weeks. All patients, with two

exceptions, were followed up until July, 1958, recurrence being noted in one patient only (Case 16). The initial operation in this patient was unsatisfactory because bleeding precluded complete removal of the cyst membranes. A recurrence of jaundice necessitated further drainage of the liver cyst three months and again 21 months after the original operation.

Lung Cysts

Ten patients suffering from pulmonary hydatid cysts were treated in addition to the child with multiple lung and liver cysts. Lobectomy was performed once only; in this patient a communication existed between the cyst and the lower lobe bronchus. In two patients large cysts were excised by separating the adventitia or pericyst from the surrounding normal lung tissue and closing the segmental bronchus. In the remaining patients the cysts were removed after incising the adventitial layer. Occasionally extrusion of the intact cyst was accomplished, but usually rupture occurred at some stage of its removal. All bronchial fistulae in the residual cavity were closed and the dead space was either obliterated from within with catgut sutures or, if the cavity was large, the adventitia was simply closed. The residual space usually disappeared within a few weeks. When the lung was not adherent to the parietal pleura, care was taken to protect the open pleural cavity from contamination; in a few cases the mackintosh-bag technique described by Barrett and Thomas (1952) was used. In two patients a small block of the overlying chest wall which had been involved by a multivesicular cyst was removed. Post-operatively, under water seal, drainage of the pleural cavity was carried out in all cases. Because of the danger of entry into the bronchial tree, formalization of the cyst contents was not performed in this series of pulmonary cysts.

There was one recurrence (Case 26), a second cyst being excised from the lower lobe of the right lung 18 months after the first operation.

Splenic Cysts

Splenectomy was performed in all three patients with hydatid disease of the spleen. One patient died from paralytic ileus 10 days after operation. The spleen was found to be entirely occupied by a large multivesicular cyst, and was adherent to the stomach and duodenum. Of the other two patients, one remained well four years after splenectomy; in the other, the spleen, which contained two multivesicular cysts, was removed through a transthoracic incision. Two months after operation the patient was readmitted for drainage of a left basal empyema and has remained well since then.

Secondary Cysts

The treatment of secondary cysts is unsatisfactory, and both patients in this series were operated upon for relief of symptoms due to abdominal cysts. In one patient leakage of hydatid fluid into the peritoneal cavity occurred during separation of a large pelvic cyst, adherent to the bladder. Asthma occurred post-operatively and was thought to be an allergic response to the antigens of hydatid fluid; there was a marked degree of respiratory distress, which, however, responded satisfactorily to treatment. The other patient who was operated upon for subacute intestinal obstruction was found to have multiple fixed peritoneal cysts; one cyst only was removed for diagnostic purposes.

Prognosis

The prognosis in hydatid disease depends upon the presence or otherwise of complicated cysts. In this series of 34 patients treated surgically there were four deaths, an operative mortality of 11.8%. Three patients died from complications of the cyst and one from post-operative haemorrhage. All four patients were 60 years of age or over; there were no deaths at any age in patients with uncomplicated cysts.

The lower mortality and morbidity rates in the post-war era can largely be attributed to the use of antibiotics, both prophylactically and in the control of infection. Antibiotic therapy has certainly lessened the incidence and spread of infection. In the present series there were no instances of subphrenic suppuration, and post-operative chest complications were rare.

Furthermore, improved methods of anaesthesia have made possible a more complete surgical ablation of the disease. This is reflected in the low recurrence rate; so far in this series, cysts have recurred in only two patients.

Summary

A survey is made of 44 cases of hydatid disease treated in hospitals serving North Wales from 1948 to 1957.

Some epidemiological aspects of the disease are described. Attention is drawn to the difficulty of effective supervision of slaughterhouses in some areas.

Hydatid disease is an eradicable disease with a significant mortality rate. Though the incidence in Wales is low compared with many other sheep-rearing countries, it remains higher than in other parts of the United Kingdom.

The clinical features of the various types of cysts seen in this series are discussed. The latency of the disease, particularly in the liver, is stressed. Symptoms are usually the result of complications occurring in the cyst.

The diagnostic criteria are described. Radiological evidence of calcification was observed in a high proportion of liver and splenic cysts.

Details of surgical treatment varied according to the site of the cyst and the complications present, but all methods aimed at a complete removal of the parasitic membranes.

The operative mortality was confined to patients aged 60 or more suffering from complicated multivesicular cysts.

I thank all the consultant surgeons who allowed me to review their cases. I am indebted to Mr. Ivor Lewis for several x-ray plates, and to Mr. Bartholomew and Miss Wadsworth, of the Institute of Urology, London, for photograph and drawings.

REFERENCES

- Barrett, N. R., and Thomas, D. (1952). *Brit. J. Surg.*, **40**, 222.
 Dew, H. R. (1928). *Hydatid Disease*. Australasian Med. Publishing Co., Sydney.
 — (1930). *Brit. J. Surg.*, **18**, 275.
 Howell, N. (1938). *On the State of the Public Health*, p. 192. Annual Report of the Chief Medical Officer of the Ministry of Health. 1938. H.M.S.O., London.
 Jenkins, J. A. (1949). *Postgrad. med. J.*, **25**, 107.
 Kneebone, J. Le M. (1937). *Med. J. Aust.*, **1**, 201.
 Meltzer, H., Kovacs, L., Orford, T., and Matas, M. (1956). *Canad. med. Ass. J.*, **75**, 121.
 Oulié G (1934). *Bull. Soc. nat. Chir.*, **60**, 88.
 Wilson, W. W. (1950). *Brit. J. Surg.*, **37**, 453.
 Wolfe, H. R. I. (1943). *Lancet*, **1**, 795.

INFLUENCE OF THYROXINE ON THE INCIDENCE OF HARELIP IN THE "STRONG A" LINE OF MICE

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The incidence of congenital malformations produced in the laboratory animal both by hypervitaminosis-A and by x-irradiation may be modified by the use of hormones and hormone antagonists. Cortisone augments the teratogenic activity of both vitamin A (Millen and Woollam, 1957; Woollam and Millen, 1957), and x-radiation (Woollam, Millen, and Fozzard, 1959). Methylthiouracil also increases the teratogenic action of vitamin A (Woollam and Millen, 1958), whereas insulin (Millen and Woollam, 1958a), thyroxine (Millen and Woollam, 1959), and vitamins of the B group (Millen and Woollam, 1958b) afford protection against this activity of the vitamin. Attempts have also been made to elucidate whether the modifying action of vitamins, hormones, and hormone antagonists extended to those deformities which were genetically determined rather than produced by a teratogenic agent. This paper records the findings of one such series of experiments.

Present Experiments

Methods.—Female mice of the Strong A line were used in these experiments. Only brother-sister matings were employed throughout, and the onset of pregnancy was determined by the presence of a vaginal plug, the day on which the plug was detected being taken as Day 1 of the pregnancy. The animals were divided into two groups. Animals in group 1, the control group, received no treatment. Each animal in group 2 received 0.1 mg. of thyroxine by subcutaneous injection on both Day 11 and Day 12 of pregnancy. On Day 18 all the animals were killed. The young were removed from the uterus and examined for the presence of harelip.

Findings.—The incidence of harelip in the two groups is shown in the Table. Statistical analysis of the results of these experiments indicates a highly significant

Incidence of Harelip

Group	A No. of Litters	B No. of Litters with at Least One Foetus with Harelip	C Total No. of Young	D Total No. of Young with Harelip
1. Control ...	28	17	207	25 (12.1%)
2. Thyroxine 0.1 mg. on days 11 and 12 of pregnancy	19	5	138	6 (4.4%)

Statistical analysis:
 Comparison based on columns C and D, $\chi^2 = 6.05$ on 1 d.f.
 " " " " " A " B, $\chi^2 = 5.36$ "

difference in incidence between the two groups, and justifies the conclusion that the administration of thyroxine to the pregnant dam has the effect of reducing the incidence of harelip in the Strong A line of mice.