rate (90 mm./hour, Westergren). Ascitic fluid was haemorrhagic, having a specific gravity of 1016 and 2.4 g. of protein per 100 ml.; cytological examination by Papanicolaou's technique revealed class I cells. Peritoneal biopsy disclosed an anaplastic malignant growth, some cells showing evidence of mucus secretion.

Case 2.—A Hindu man aged 25 was admitted to hospital complaining of distension of the abdomen and anorexia for two months. His previous history did not reveal anything significant. Liver-function tests were slightly abnormal (T.T. 4 units, T.F. +) and the liver biopsy obtained by Vim Silverman needle confirmed the diagnosis of portal cirrhosis. Ascitic fluid had a specific gravity of 1020, 5.1 g. of protein per 100 ml., and 20 lymphocytes per c.mm. A peritoneal biopsy specimen revealed granulation tissue composed of epithelioid cells, giant cells, and caseation. Acid-fast bacilli were demonstrated in the peritoneal tissue section by Ziehl-Neelsen method of staining.

Case 3.—A Mohammedan woman aged 20 was admitted to hospital complaining of loss of appetite, low-grade pyrexia, and loss of weight for 25 days. Her previous history did not reveal anything significant. Physical examination showed glandular enlargement in the left side of the neck and minimal ascites. A skiagram of the chest was normal. A follow-up barium-meal study revealed ileal stasis, and adherent terminal ileal loops which were tender. The peritoneal biopsy showed an accumulation of epithelioid cells arranged in a follicular pattern and the presence of caseation necrosis. Acid-fast bacilli could be demonstrated in the peritoneal tissue by the Ziehl-Neelsen method of staining.

Case 4.—A Hindu woman aged 30 was admitted to hospital complaining of distension of the abdomen and weakness for two and a half months. Her previous history did not contain anything significant. Physical examination revealed ascites, hepatomegaly, and slight anaemia. Systemic examination did not show any other abnormality. Liver-function tests were normal and liver biopsy did not reveal any specific disease. Ascitic fluid was slightly haemorrhagic and probably exudative. The peritoneal biopsy revealed epithelioid cell follicles, some showing slight caseation, and acid-fast bacilli could be demonstrated by the Ziehl-Neelsen method of staining.

Comments

The procedure of obtaining punch biopsy of the peritoneum by the Harefield needle appears to be simple and safe. However, the potential dangers attending this procedure are similar to those associated with abdominal paracentesis—that is, haemorrhage, perforation of the bowel, infection, and the spread of malignancy. These should be kept in mind while performing the punch biopsy of peritoneum.

Peritoneal biopsy confirmed the diagnosis in three out of six clinically suspected cases of tuberculous abdomen, and it enabled the diagnosis of tuberculous peritonitis to be made in two unsuspected cases presenting with portal cirrhosis (Case 2) and ascites (Case 4). It is felt that peritoneal biopsy may provide an important tool for making a firm diagnosis of tuberculous peritonitis where other conventional methods usually are inadequate.

The procedure was found useful in investigation of the cases presenting with ascites. It is best exemplified in Case 4, where peritoneal biopsy clinched the diagnosis of tuberculous peritonitis when other methods—namely, clinical, ascitic fluid, liver-function, and liver biopsy examinations—failed to establish the diagnosis. The procedure was also found useful in the diagnosis of peritoneal metastases. The limitations of this procedure should, however, be borne in mind. Firstly, as in other punch biopsies, peritoneal biopsy can only reflect the

histological changes demonstrable in the focal area from which the biopsy is obtained, and hence false-negative results may be obtained. Secondly, the serous membranes often reflect no histological changes or those of a non-specific nature when involvement of membrane *per se* either does not exist or is not diffuse.

Our preliminary experience suggests that needle biopsy of the peritoneum often provides a rapid and accurate diagnosis, sometimes when other methods have failed, and in combination with other routine laboratory investigations may allow a firm diagnosis to be made in a larger number of cases presenting with ascites than would otherwise be possible.

Summary and Conclusions

Twenty-three patients with varying disease and ascites were subjected to punch biopsy of the peritoneum, using the Harefield needle.

The procedure is simple and safe. An adequate specimen of the peritoneal tissue could be obtained in 84% of cases. Failure to obtain an adequate tissue was observed in cases having minimal ascites, in which no fluid was obtained during the puncture.

No complications were encountered in any patient.

Our preliminary impressions suggest that the procedure is useful in investigation of ascites and tuberculous abdomen with peritoneal involvement, and in the diagnosis of peritoneal metastases.

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CARDIOMEGALY IN A NEWBORN DUE TO PLACENTAL CHORIOANGIOMA

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Enlargement of the heart resulting from a high cardiac output may be caused by abnormal arteriovenous communications (Holman, 1923; Cohen *et al.*, 1948; Wood, 1956). We describe the case of a newborn infant in whom cardiac enlargement was probably caused by a vascular shunt through a large placental chorioangioma.

Case Report

The mother was 33 years of age and in good health; she had had four normal full-term infants and two abortions. Routine antenatal care for the present pregnancy began at the nineteenth week of gestation. At this time she had no symptoms, physical examination was negative, the height of the fundus uteri was compatible with 18 weeks' gestation, and her blood-pressure was 100/66. Her haemoglobin was 12.6 g./100 ml. (81%), and her urine was free from albumin and sugar. Foetal movements were first noticed at 22 weeks of pregnancy. She was perfectly well when seen at the 24th and 29th weeks. At 31 weeks and again eight days later

she complained of vomiting, heartburn, and a dry cough. At this time the height of the fundus was excessive for the stage of pregnancy, and hydramnios was suspected. No other abnormality was noted, and she was advised to rest. Promethazine theoclate ("avomine"), 25 mg. eight-hourly, was prescribed. However, next day she went into labour and was admitted to hospital at the 32nd week.

The first stage of labour lasted nine hours. As the membranes were still intact after full dilatation of the cervix, artificial rupture was performed, but only a small amount of meconium-stained liquor escaped. The vertex presented, and after a second stage of 20 minutes a female infant, 3 lb. (1,360 g.) in weight, was delivered. The clinical impression of hydramnios was confirmed by the large volume of amniotic fluid which was forcibly ejected from the uterus during delivery of the infant, although it could not be collected for measurement. The umbilical cord was clamped and tied immediately after delivery, the infant being at the same horizontal level as the placenta, which was delivered 10 minutes later. Light "trilene" inhalation anaesthesia was administered to the mother only during delivery of the head.

The infant cried immediately after birth and her general condition was good. Multiple petechiae were present on the head, face, and neck, but physical examination was otherwise negative. The pharynx was aspirated with a mucus catheter, and the infant was placed in an incubator at a temperature of 90° F. (32.2° C.) and humidity of 75% with an oxygen flow of 1 to 2 litres per minute. "Synkavit" (vitamin K analogue) 1 mg. was given intramuscularly. A few minutes after birth respirations were rapid and costal recession was noted, and at about three hours grunting began. Generalized oedema was evident by the eighth hour. At 14 hours the costal recession and grunting respirations were more pronounced and the respiratory rate was 80 per minute. The percussion note over the lungs was resonant and normal breath sounds were present. There were no adventitious sounds. The liver was uniformly enlarged to 3 cm. below the right costal margin and the spleen was felt 1 cm. below the left costal margin. There were no cardiac murmurs. The tension of the anterior fontanelle was normal. The rectal temperature was 95.6° F. (35.3° C.).

Central cyanosis became evident after the first 24 hours, the respiratory distress increased, and the general condition steadily deteriorated. The size of the liver and spleen remained unaltered. There was a small vomit at 39 hours. Small amounts of sterile water were offered by mouth. Streptomycin, 40 mg. 12-hourly, and crystalline penicillin, 100,000 units six-hourly, were given intramuscularly. Because of the severe respiratory distress a mixture of 79% helium and 21% oxygen was supplied to the incubator, but no improvement resulted, and death occurred at 69 hours.

Six hours before death the urine was free of sugar and albumin, though it contained many epithelial cells and scanty leucocytes, but no casts; culture gave a growth of coagulase-negative *Staphylococcus albus*. A chest x-ray film taken five minutes before death showed marked cardiac enlargement and mottled opacities in both lung fields.

Post-mortem Findings

At necropsy (Dr. G. A. K. Missen) the weight was 1,600 g., length 41.3 cm., and head circumference 28.8 cm.

The placenta measured 172 by 145 by 50 mm. and weighed 635 g. after formol fixation. The cotyledons were large and appeared pale. A chorioangioma measuring 166 by 100 by 60 mm. and weighing 542 g. after formol fixation was adherent to the maternal aspect of the placenta; a fusiform vessel (3 by 1 cm.) connected the chorioangioma to the umbilical vein (Fig. 1). The chorioangioma was a dark-brown reniform mass, with a smooth lobulated surface. The concave aspect was firmly attached to the maternal surface of the placenta. The cut surface of the chorioangioma showed spherical nodules of varying sizes, separated by a framework of many branching fibrous trabeculae. Microscopically the nodules were seen to be made up of densely packed capillary channels filled with blood and separated

from each other by less vascular connective-tissue septa (Figs. 2 and 3). A number of venous channels were also present. In one nodule a focus of necrosis was seen, and in another an area of calcification was present. The umbilical cord appeared normal apart from moderate dilatation of the distal 2.4 cm. of the umbilical vein. It is probable that blood entered the angioma from vascular channels supplied by the placental arteries through its

FIG. 1.—Chorioangioma and placenta. 1, Chorioangioma. 2, Outline of chorioangioma, showing original relationship to placenta. 3, Placental arteries feeding tumour. 4, Fusiform dilatation of umbilical vein, draining the chorioangioma. 5, Umbilical cord. 6, Edge of amnion.

surface attached to the maternal aspect of the placenta and returned to the foetus by the large fusiform vessel connecting it to the umbilical vein.

Heart and Great Vessels.—The only abnormality was generalized cardiac enlargement, the heart weighing 21 g.—normal for weight of infant, 10.8 g. (Potter, 1952). This cardiomegaly was due to hypertrophy of all chambers. There was no endocardial fibro-elastosis. The foramen ovale showed a normal valvular aperture. The pericardium, valves, coronary arteries, and main blood-vessels were all normal. The ductus arteriosus was patent and normal in size. Histologically the heart showed hypertrophied muscle fibres as the only abnormality. No excess of glycogen was demonstrated either in periodic-acid-Schiff preparations or by Best's method.

Respiratory System.—The bronchial tree and pleurae were normal. Both lungs appeared well aerated and floated in water, but there were a few foci of haemorrhage up to 3 mm. in diameter, especially in the lingula. Histology showed

changes typical of pulmonary syndrome of the newborn (Bound *et al.*, 1956), consisting of areas of intra-alveolar haemorrhage, atelectasis, and scanty hyaline membrane formation.

The liver was uniformly enlarged, weighing 96 g.—average for weight of infant, 66.3 g. (Potter, 1952)—and of a tawny brown changing to deep green with formol fixation. Microscopy showed the canaliculi to contain large numbers of bile

FIG. 2.—Tumour with branch of a large blood-vessel running between two nodules of angiomatous tissue. (H. and E. $\times 17$.)

FIG. 3.—Tumour with numerous large channels of capillary structure. (van Gieson, $\times 375$.)

thrombi. Only small amounts of glycogen were demonstrated. The bile ducts were not dissected, but the meconium was of normal colour. The spleen was uniformly enlarged, weighing 19 g.—normal for weight of infant, 4 g. (Potter, 1952).

Nervous System.—The meninges and cerebral vessels were normal. The cerebrospinal fluid was slightly xanthochromic. The brain was not swollen, but numerous petechial haemorrhages were scattered throughout the white matter of both cerebral hemispheres. There was no kernicterus.

The remaining systems all appeared normal both to the naked eye and microscopically.

Discussion

The clinical picture and pathological findings at necropsy left little doubt that the cause of death was pulmonary syndrome of the newborn with prematurity. We believe that the cardiac hypertrophy did not contribute to death, since the cause of the hypertrophy—namely, the shunt through the placental angioma—was no longer operative.

Benign tumours of the placenta have been recognized for many years, and John Clarke (1798) reported one of the earliest cases. Since then there have been numerous reports of similar tumours, which, from the description of Beneke (1900), have been classified as chorioangiomas. There have been several reviews, notably those by Siddall (1924), Marchetti (1939), and DeCosta *et al.* (1956). The incidence of chorioangiomas has been variously assessed as 1 in 9,000 (Kühnel, 1933) and 1 in 3,500 (Marchetti, 1939). Hydramnios and prematurity, both of which were present in our patient, have been associated with about one-third of the cases reported. Hydramnios is more often associated with large tumours (Siddall, 1924), and the size of the chorioangioma described in this paper is greater than most of those previously reported. Most authors have considered that the high foetal mortality rate was due to prematurity. However, Siddall (1924) has reported 17 deaths among 73 probably mature infants, and this seems a remarkably high death rate.

Various congenital abnormalities in the infant have been described in association with chorioangiomas, and these have included hydrocephalus (Steinbüchel, 1892), anomalies of the aortic arches (Barry *et al.*, 1951), haemangiomas of the liver (Barry *et al.*, 1951; DeCosta *et al.*, 1956), haemangiomas of the skin (Bret *et al.*, 1953), and multiple congenital anomalies (Burger *et al.*, 1952).

The size of the heart has only occasionally been mentioned in reported cases, and we have found no report of cardiac hypertrophy. Cardiomegaly in newborn infants may be due to congenital heart disease, endocardial fibro-elastosis (Potter, 1952), or glycogen disease of the heart (Di Sant'Agnese *et al.*, 1950), and has been seen in newborn infants with cerebral arteriovenous aneurysm (Corrin, 1959; A. E. Claireaux, 1960, personal communication). However, there remain a small number of cases of cardiac enlargement in which no cause is evident (Green and Apley, 1950). We suggest that large placental chorioangiomas may be a further and hitherto unrecognized cause of cardiomegaly in the newborn.

Summary

The case of a premature infant with cardiac hypertrophy is reported. A large chorioangioma was attached to the placenta.

Death from pulmonary syndrome of the newborn occurred on the third day.

The heart was normal except for hypertrophy of the muscle fibres.

It is suggested that the cardiac hypertrophy was caused by high cardiac output due to the shunt through the chorioangioma.

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Preliminary Communications

Optimal Dose of Streptomycin in Pulmonary Tuberculosis

Stradling and Pool (1958) have advocated long-term streptomycin and isoniazid as the most efficient drug combination in tuberculosis. Whether patients will accept this over a long period has yet to be shown, and the question of how to overcome vertigo in elderly patients receiving streptomycin is still unanswered.

In 1958 we began a study which, among other aims, was designed to assess methods of diminishing streptomycin vestibular damage either by using a smaller daily dose of streptomycin or by the addition of pantothenic acid to streptomycin in the normal dose. The following were excluded—non-Europeans, diabetics, expectant mothers, those with evidence of pneumoconiosis, and those who had previous chemotherapy. So far, 135 new patients over the age of 15 suffering from active pulmonary tuberculosis have been accepted. When a patient was admitted to the trial the name was forwarded to a central secretary, who chose a card at random from a series specifying one of the following three regimes:

- (1) S.I.=Streptomycin sulphate 1 g. daily+isoniazid 1,000 mg. given in two divided doses with pyridoxine 50 mg. b.d. (After leaving hospital, isoniazid reduced to 600 mg. once daily+pyridoxine 100 mg. once daily.)
- (2) S.P.=Streptomycin sulphate 1 g. daily with pantothenic acid 150 mg. daily at the same time+isoniazid 100 mg. b.d.
- (3) S.½=Streptomycin sulphate 0.75 g.+isoniazid 100 mg. b.d.

Each patient received initially sodium *para*-aminosalicylate (P.A.S.) 12 g. daily for six weeks, and after leaving hospital streptomycin and isoniazid were given daily except Sundays.

Subsequent testing of our random selection confirmed that the patients were matched in terms of age, weight on admission, E.S.R., and extent of disease. Positive pretreatment cultures for *Mycobacterium tuberculosis* were obtained in 97 patients. The allocation of the sputum-positive patients showed a slight bias in favour of the S.½ group—namely, S.I., 32; S.P., 37; S.½, 28.

RESULTS

The clinical improvement of all patients has been satisfactory. The rate of sputum conversion after one month's and three months' treatment is similar in all three groups, and by six months all patients were

culture-negative and have remained so. To date, 56 patients have completed 18 months' chemotherapy. A preliminary analysis of the radiological results on the first 88 patients who had completed nine months' treatment shows similar degrees of improvement. This was based on independent dual reading of films where the identity of the treatment was unknown to the reader.

Thus the accepted criteria of response to treatment of active pulmonary tuberculosis have so far shown no evidence that a daily dose of 0.75 g. of streptomycin is inadequate. This trial is still in progress, and the final results will be submitted later.

When patients complained of persistent dizziness or unsteadiness of gait, treatment with streptomycin was stopped. Objective ataxia was observed in most of these patients, but the Romberg test, presence of nystagmus, and caloric tests were only of limited value.

Incidence of Vertigo

	S.I.	S.P.	S.½	Total
No. of patients	44	46	45	135
„ developing vertigo	14	12	2	28 (21%)

Vertigo of a degree to require cessation of streptomycin developed in 28 (21%) patients (see Table). The incidence of vertigo in the S.I. group was 32%, while that in the S.½ was 4%. The observed difference (28%) is 3.7 times the standard error. Pantothenic acid is in our experience of no value in preventing or diminishing the development of vestibular damage due to streptomycin. Reduction of the daily dose of streptomycin to 0.75 g. has nearly abolished this serious complication.

We are indebted to Dr. Peter T. Main and to Boots Pure Drug Company, who have generously supplied all the 0.75-g. streptomycin viules used in this trial.

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“The work of the Nuffield Institute of Comparative Medicine, Zoological Society of London, will be a development of one of the society's traditional activities. For 130 years it has been providing material to medical research workers for the study of isolated problems in comparative anatomy, pathology, haematology, and parasitology. In the past, however, the laboratory facilities were never sufficient to permit exhaustive studies to be made, and the society was not able to employ a research staff of its own to take advantage of the ever-present opportunities for studies in comparative medicine. The variety of material that is available is remarkable. Recently, for example, there was a case of cardio-renal failure in a Malay wild dog; one of coronary thrombosis in an Indian wild ass; and one of cardiovascular degeneration in a hornbill. But once these diagnoses had been made in the post-mortem room by microscopic study of tissues, there was little opportunity of doing further work. . . . In the society's zoological gardens the research workers will have at their disposal pathological material from vertebrates living on almost every conceivable diet. There can be systematic investigation of specific conditions in the living animal, and eventually it will be possible to compare the findings with those of the post-mortem examination.” (*Nuffield Foundation Fifteenth Report*, 1960.)