adrenal necrosis was present, the necrotic areas appeared to merge with the tubular areas, and the necrosis was of the liquefactive variety with haematoma formation.

The changes seen in routine preparations in these cases are those of a severe and prolonged 'stress reaction' in the fetal adrenal, and are comparable to those seen in adults in the acute, active phase of such a state (Symington, 1969).

In all 4 cases the thymus showed moderate depletion of cortical lymphocytes, compatible with a stress reaction.

Discussion

The thymic and adrenal changes seen in this small series of cases suggest that the fetal adrenal cortex responded to the stress imposed by an intrauterine infection. Changes that are extremely similar are seen in the adrenal glands at necropsy in many infants dying from various causes, and Stowens (1966) described the lesion in association with prolonged infections, severe metabolic derangements, and in premature infants. He used the term 'functional exhaustion' to describe its significance. It is reasonable to suggest, therefore, that the appearances of the adrenal gland in the present series suggest an active outpouring of adrenal steroids. Since all these infants were still-born it is obvious that this reaction must have occurred *in utero*, and problems of postnatal adjustment could not have contributed to the appearances seen.

The widely known work of Liggins (1969) in inducing labour in sheep by the infusion of steroids to the fetus makes it likely that in the present series labour was initiated by an outpouring of steroids from the stressed adrenal, a finding in keeping with the hypothesis of Ho and Aterman (1970). It is unfortunate that in the reports published on chorioamnionitis the adrenal glands are not described in detail, though it should be possible to review the findings.

The adrenal changes raise certain other issues of potential interest. The relation of pseudotubular zones to the necrotic lacunar foci, described by deSa and Nicholls (1972), needs to be assessed since the lacunar lesion, believed to be the central lesion of haematoma formation in the adrenal glands of perinatal infants, may well be dependent on the coexistence of a severe stress reaction in an otherwise ischaemic gland.

The effects of such an outpouring of steroids on the development of the surfactant system of the lung (Kotas and Avery, 1971) need to be considered as well, and it appears that the infants with chorioamnionitis offer a naturally-occurring population in which this problem could be studied.

The finding of otitis media in these stillborn infants is in keeping with the findings of Benner (1940), but represents a very different pathogenesis from that described in a population of infants with otitis media, where chorioamnionitis was extremely uncommon (deSa, 1973).

Summary

Changes in the adrenal glands of 4 immature stillbirths with chorioamnionitis due to several different micro-organisms are described. These changes are interpreted as being consistent with a severe stress reaction, and it is suggested that the output of steroids *in utero* by the fetus initiated labour.

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Neonatal hypoglycaemia with congenital malformation of pancreatic islets

Neonatal hypoglycaemia is frequently associated with dysmaturity and is rarely the result of congenital abnormalities of the pancreatic islets (Grant and Barbor, 1970). These diagnoses should be considered in refractory or prolonged neonatal hypoglycaemia, and exploratory laparotomy has been suggested when symptomatic hypoglycaemia extends past the second week of life (Robinson *et al.*, 1971). We report such a case with unusual islet pathology.

Case report

A male, birthweight 2.83 kg, was a spontaneous vertex delivery at 40 weeks' gestation. No features of dysmaturity were present and the liver and spleen were impalpable. At 6 days of age the child had a cyanotic attack with generalized convulsive movements. The true blood glucose was less than 20 mg/100 ml. After an initial response to intravenous 50% dextrose his convulsions recurred but responded to 3-hourly milk feeds, reconstituted with 10% dextrose solution. Thereafter, normal milk feeds were gradually resumed with no symptomatic relapse. Normal blood glucose levels were maintained and he was allowed home, where 3 weeks later he had a further severe hypoglycaemic attack with a blood glucose of 3 mg/100 ml. After emergency treatment, a 2-hourly feeding schedule was started and dextrose, up to a total of 20 g, was added to each feed. Subsequently the frequency of feeds was reduced but fasting for longer than 4 hours was never possible. On this regimen asymptomatic hypoglycaemia was frequently observed by routine Dextrostix estimations, but hypoglycaemic convulsions occurred infrequently. Further attempts to control the hypoglycaemia with diazoxide 8 to 12 mg/kg per 24 hours and separate courses of prednisolone, chlorothiazide, and glucagon were unsuccessful. Despite these hypoglycaemic seizures, the child's psychomotor development was normal.

Laboratory investigations. Preprandial blood glucose ranged from 3 to 9 mg/100 ml with a maximum postprandial of 103 mg/100 ml (on 20 g dextrose supplements). Urea and electrolytes, liver function tests, full blood count, red cell galactose-1-phosphate uridyl transferase activity, urinary excretion of 17-ketosteroids, 17-hydroxycorticosteroids, and catecholamines were normal, and no protein or reducing substances were present in the urine.

An oral glucose tolerance test (1.75 g/kg) showed a 'fasting' glucose of 28 mg/100 ml rising to 60 mg/100 ml

at 90 minutes. Standard preparatory fasting was not possible. Fructose tolerance (0.5 g/kg) was normal. Oral galactose (1.75 g/kg) failed to produce a rise in total reducing substances and the true blood glucose fell from 55 mg/100 ml to 20 mg/100 ml at 90 minutes. Intravenous galactose (6.5 g) produced a similar fall in true blood glucose despite an immediate rise of total blood reducing substances to 190 mg/100 ml. A normal hyperglycaemic response followed intramuscular glucagon (0.03 mg/kg) and a hepatic biopsy showed normal glycogen content, chain length, and enzyme activity.

Plasma insulin was measured by a radioimmunoassay technique after tolbutamide, glucose, and glucagon (Table). The response was variable but the inappropriate association of high plasma insulin and low blood glucose was noted. Leucine sensitivity tests were unsuccessful, but no symptomatic improvement followed leucine restriction.

At 1 year of age, before exploratory laparotomy, coeliac axis arteriography was performed. This showed a small rounded 'blush' lateral to the gastroduodenal artery.

Operation. At laparotomy, palpation of the pancreatic head revealed a firm structure but on dissection this became less definite. The area was excised, and frozen section histology reported no evidence of neoplasm. A subtotal pancreatectomy was then performed leaving only the uncinate lobe.

After operation intravenous dextrose was continued for 48 hours until oral fluids were tolerated. By the 14th day after operation the fasting glucose was 55 mg/100 ml on a normal diet. Glucose tolerance reassessed at 5 weeks showed a fasting level of 60 mg/100 ml rising to 100 mg/100 ml at 1 hour. There was no recurrence of hypoglycaemic convulsions, and normal psychomotor development continued.

Pathology. The excised pancreas was macroscopically normal. Histopathology showed an abnormal zone in

TABLE
Plasma insulin and glucose responses to a variety of insulinotropes

Time (min)	Tolbutamide* tolerance test (20 mg/kg i.v.) aged 6 mth		Oral glucose* tolerance test (1.75 g/kg) aged 4 mth		Glucagon† tolerance test (0.03 mg/kg i.m.) aged 3 mth		Glucagon† tolerance test (0.03 mg/kg i.v.) aged 1 yr	
	Blood glucose (mg/100 ml)	Plasma insulin (μ U/ml)	Blood glucose (mg/100 ml)	Plasma insulin (μ U/ml)	Blood glucose (mg/100 ml)	Plasma insulin (μ U/ml)	Blood glucose (mg/100 ml)	Plasma insulin (μ U/ml)
0	22	8	40	44	42	46	34	22
5							46	33
10			110		72	67	63	22
15							78	21
20			130	70	45	42		
30	10	5	120	65	65	30	51	29
45			60				41	38
50					100	28		
60	29	9					36	27
90	49	6			59	26		

*Receiving treatment with diazoxide 50 mg twice daily.

†No drug therapy.

FIG.—*Abnormal islet cells in pancreatic head ($\times 71$).*

the pancreatic head confined to a lobule, where the islet cell groups greatly outnumbered the pancreatic tissue but were closely intermingled with them (Fig.). The cells of the abnormal zone were well differentiated with an attempt at rosette formation. The high degree of differentiation was confirmed by the positive staining of the cytoplasm of some of the cells by aldehyde-fuchsin, which is specific for insulin-producing β -granules. The body and tail of the pancreas showed normal histology.

Discussion

Islet cell adenoma may present in the neonatal period with refractory hypoglycaemia (Buist *et al.*, 1971). Diffuse islet cell hyperplasia is a frequent temporary observation in the infants of diabetic mothers. Hyperplasia has also been found in recurrent spontaneous hypoglycaemia but in many cases of 'idiopathic hypoglycaemia' the pancreatic islets are normal. However, using pinacyanole, an insulin-specific stain in these cases, groups of 2 to 6 islets cells have been identified throughout the pancreas (Yakovac, Baker, and Hummeler, 1971).

This abnormality, β -cell nesidioblastosis, is thought to result from disorganized development of the pancreatic islets.

Although the exact nature of the pathological lesion in our patient is uncertain, the appearances most closely resemble adenomatosis, where the islets are of varying size, shape, and cellularity and the changes diffuse (Frentz, 1959). In this case, however, the abnormal islet cells are well localized to the head of the pancreas. The functioning nature of the lesion is confirmed by differential insulin staining and it seems possible that this malformation arose during pancreatic development.

Summary

Symptomatic neonatal hypoglycaemia in a male infant was associated with an islet cell abnormality of uncertain aetiology. Before operation localization of the lesion by coeliac axis arteriography was attempted. A successful outcome followed subtotal pancreatectomy at age 1 year.

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Pulmonary candidiasis treated with 5-fluorocytosine

Infection with *Candida albicans* occurs only when there is impaired host defence, such as in debilitating disease, after prolonged treatment with antibiotics or central venous catheters (Goldstein and Hoeprich, 1972), in immunological deficiencies (Kirkpatrick, Rich, and Bennett, 1971), or after treatment with prednisone and immunosuppressives (Folb and Trounce, 1970). 4 patients with pulmonary candidiasis without such predisposing factors, one of whom died, have been reported (Arthur, 1969; Stevens, Jameson, and Philpott, 1972). We report the development of severe pulmonary infection in a previously healthy girl who was cured with 5-fluorocytosine (Isacson *et al.*, 1972).

Case report

A 10-year-old girl was admitted to hospital on 11 January 1972 because of tonsillitis and pneumonia. She had previously been in good health. At the age of 6 she had been vaccinated with BCG and subsequently became tuberculin positive. In December 1971, she had rhinitis and cough for a few days. On 5 January 1972 she developed a fever and a sore throat. 3 days later her physician took a throat swab which was positive for *Candida albicans*, gave two injections of penicillin, and referred her to hospital.

On admission the girl was acutely ill and dyspnoeic. She had conjunctivitis, rhinitis, and pharyngitis. The tonsils were covered with thick white membranes, a Gram-stained preparation of which showed abundant fungal hyphae, cultures being positive for *C. albicans*. Cervical lymph nodes were massively enlarged. An

initial chest x-ray showed enlarged hilar nodes and bilateral hilar infiltrations. No pathogen was detected except for massive growth of *C. albicans* from throat, sputum, and stools. The sedimentation rate was 25 mm in the first hour. Leucocytes were 9100/mm³ with 47% band forms. Peripheral lymphocytes and bone marrow studies were unremarkable.

During the next days, dyspnoea worsened in spite of administration of several broad-spectrum antibiotics. Fever up to 40 °C, severe respiratory distress, cyanosis, and liver enlargement developed. The chest x-ray (Fig.) suggested miliary tuberculosis. Para-aminosalicylic acid and isoniazid were given with no improvement. During this critical stage, *C. albicans* was also cultured from urine. Nystatin (1,000,000 units/day orally) did not suppress the growth of *C. albicans*.

Ten days after admission, treatment with 100 mg 5-fluorocytosine/kg body weight per day* was started for a total of 6 weeks. Because of diarrhoea and high serum transaminase levels the dosage was not increased. After 2 weeks of this treatment, fever and dyspnoea disappeared. A 3-week course of prednisone (1 mg/kg body weight per day) was started. On March 29, 10 weeks after admission, the girl had recovered and was discharged. Chest x-rays still showed large hilar nodes and minor interstitial changes of the lungs. *C. albicans* continued to be grown from the throat and stools after recovery, but hyphae were no longer visible and the fungus had become resistant to 5-fluorocytosine *in vitro*.

The girl was followed-up for one year, during which time she regained excellent health and showed normalization of chest x-rays and pulmonary function tests.

Immunological observations. Granulocyte function was assessed by the nitro blue tetrazolium test (Rubinstein and Pelet, 1973). 7% of cells spontaneously reduced the dye (normal values 0–4%), and 96% did so after stimulation with bacterial antigens (normal values 84–100%). These results indicate normally functioning granulocytes which react to infection.

The serum IgM level was raised initially to 1000 mg/100 ml (normal values 38–135). Blood levels of IgA and IgG, IgA secreted in tears and saliva, and electrophoretic and immunoelectrophoretic patterns of serum proteins were all normal. There were positive titres of complement fixing antibodies against influenza and parainfluenza virus, adenovirus, and mycoplasma, of haemagglutinating antibodies against influenza virus, and of isoagglutinins anti-A1 and anti-A2. No antibodies were detectable against toxoplasmosis, ornithosis, herpes, Q fever, brucellosis, or *C. albicans*. These titres did not rise during the disease. Titres of haemagglutinating antibodies against *C. albicans* (Müller, 1972) stayed negative until 28 April and subsequently rose to 1:20.

Skin tests with *C. albicans* antigen (Candidine, Institut Pasteur, Paris) and Tuberculin Purified Protein Derivative (Serum- und Impfinstitut, Berne) were negative during the acute phase of the disease, but

*Supplied as 'Ro 2-9915' tablets by Hoffmann-La Roche, Basle, Switzerland.