PAEDIATRIC PATHOLOGY CLUB

Proceedings of the Ninth Annual Meeting

The ninth meeting of the Paediatric Pathology Club was held in Dublin on October 18 and 19 under the presidency of Professor D. Holland. On October 18 a meeting was held at Our Lady’s Hospital for Sick Children, Crumlin, when the chairman was Dr. E. Morrison, and on October 19 at the National Children’s Hospital, Harcourt Street, when the chairman was Dr. S. F. Cahalane. The attendance book was signed by 31 members.

Dr. F. A. Langley was elected president for 1964: this meeting will be held in Manchester. Dr. A. H. Cameron was elected secretary of the Club.

A standing Committee on Paediatric Pathology was set up with the following members:

Chairman—Dr. Agnes MacGregor
Secretary—Dr. J. L. Emery
Committee—Dr. A. H. Cameron, Dr. A. Dudgeon, Dr. E. Hall, and Professor D. Holland.

Summaries of Scientific Communications

A. H. Cameron (Birmingham). ‘Renal Biopsy in Recurrent Haematuria.’ Fifteen children with recurrent attacks of macroscopic haematuria were studied. Constitutional symptoms during the initial and subsequent attacks were mild or absent. Details of the initial attack are incomplete as hospital investigation was not usually undertaken at this stage. A minority of the patients showed some evidence of diffuse glomerulonephritis, following streptococcal upper respiratory tract infection, and of mild hypertension, oedema or azotaemia. The majority did not and showed no constant relation between haematuria and infection. The episodes of haematuria recurred for as long as four years, and in most patients the urine is still not completely clear. Percutaneous renal biopsy showed mild focal proliferative changes in the glomeruli, and electron microscopy revealed cellular proliferation and abnormally in the basement membrane. These preliminary findings indicate that periodic haematuria in children is usually due to non-surgical disease of the kidneys. The long-term prognosis is uncertain but our patients have not, so far, shown evidence of deterioration of renal function. Further detailed investigation is required, with special reference to the initial episode of haematuria, if the borderline between the two entities is to be more clearly defined.

M. Bodian (London). ‘Renal Biopsies in Focal and Diffuse Glomerulonephritis.’ (Read by B. Ockenden). Forty-six cases of recurrent macroscopic haematuria who had had needle renal biopsies were reviewed. In 36 (Group 1) there was no specific illness at, or preceding, the first episode of haematuria. The attacks lasted for a few days with subjective symptoms, i.e. vague abdominal discomfort, in 70%. The number of attacks per case varied from 2-400, often precipitated by exercise or upper respiratory tract infections. Microscopic haematuria persisted between attacks in 50%. Oedema and hypertension were never seen. 44% had proteinuria; 5% had pyuria and bacteriuria. Five boys, two now deaf, had a strong family history of renal disease.

At the onset in 10 cases (Group 2), 3 had a typical attack of acute glomerulonephritis, and 7 had anaphylactoid purpura. In the former the initial haematuria lasted three to four weeks; subsequent attacks lasted up to a week, and numbered 7 to 12. Renal function was normal. Microscopic haematuria and proteinuria persisted between attacks. One has persistent hypertension: in this case the initial haematuria lasted a few weeks or months; subsequent attacks lasted a week and varied from 4 to 40. All had persistent microscopic haematuria and proteinuria. Three have renal insufficiency and hypertension.

The glomerular pathology was classified as focal, affecting some glomeruli only; generalized, affecting all glomeruli; segmental, affecting one or more loops of the glomerular tuft; diffuse, affecting the entire glomerular tuft. In Group 1, 31 cases showed focal lesions (21 segmental, 9 diffuse, 1 segmental and diffuse); 2 cases were generalized (1 segmental, 1 segmental and diffuse); 3 showed chronic pyelonephritis. In Group 2, the 3 cases with clinical acute glomerulonephritis all showed focal segmental glomerulonephritis. Of the 7 with Henoch-Schönlein purpura 3 had focal lesions (2 segmental, 1 segmental and diffuse) and 4 had generalized lesions (2 segmental, 2 diffuse): all this latter group showed an advanced disease.

Seventeen cases in Group 1 examined by histochemical enzyme and immunofluorescence studies showed a significant association between positive fluorescence and high glomerular enzyme activity. Fluorescence studies showed a relation with the time interval from clinical onset, being positive from the 6th to the 24th month only. Fluorescence was diffuse in cases showing segmental lesions on light microscopy, suggesting diffuse immun-
ological damage but only a segmental reaction of the glomerulus to it.

This paper by M. Bodian, J. A. Black, N. Kobayashi, B. D. Lake and S. E. Schuler is to be published in Quart. J. Med.

HJELT, L. (Helsinki). 'Congenital Nephrosis.' The most striking histological findings of microdissections were tubular dilatations in the proximal tubules and changes in the glomeruli, which are similar to those found in lipoid nephrosis.

On the basis of the study it may be concluded that congenital nephrosis is due to glomerular-bound globulin which supposedly is formed in the mother. That such an incompatibility between mother and foetus exists is suggested by the findings that skin grafts from infants born with congenital nephrosis are rejected by the mother in one to three days, and from the other children of the family in three to seven days. In addition there is a precipitation factor between the sera of patients and their mothers.

Regardless of the cause and source of antibodies in congenital nephrotic reaction, damage to the basement membranes and the glomerular capillaries result in the passing of large amounts of protein. The proteinuria and cast formation may lead to the obstructive tubular damage.

J. G. DEVLIN (Dublin). 'Vitamin D Hypersensitivity as a Cause of Renal Calculi in Twins.' Similar male twins presented with renal calculi, one at the age of 5 years with a ureteric calculus and the second at the age of 9 with a similar complaint. They are 2 of 7 sibs born to healthy parents with no family history of calculi. Urine cultures were negative, and intravenous pyelograms were normal. The stones contained calcium oxalate and phosphate. Plasma biochemistry was normal when the first boy presented. The second boy had hypercalcaemia; serum calcium was 12-0 mg./100 ml. when he presented. His brother was then re-investigated and found to have a serum calcium of 11-7 mg./100 ml. Investigation of both boys gave the following results—urine pH 5-7, falling to 5-2 after 7 g. gr. ammonium chloride: 24-hour urinary studies revealed total nitrogen 6-7 g. and 6-1 g.; amino nitrogen 291 and 338 mg. Chromatograms were normal: calcium < 100 mg. in both. Phosphorus varied between 455 and 680 mg.: oxalic acid was less than 19 mg. All these investigations were essentially normal.

A skeletal radiological survey was normal. In view of this finding, and the rapid return of the serum calcium to normal, the possibility of hyperparathyroidism was considered unlikely. A careful reappraisal of the past history revealed a high milk intake (over 2 pints daily). The possibility that they were unduly sensitive to this raised vitamin D and calcium intake was therefore considered and confirmed when it was found that the serum calcium rose to 11-9 and 12-0 mg./100 ml. respectively after one week on calciferol 0-075 mg. daily. It is suggested that the tendency to form renal calculi is due to a moderate hypersensitivity to vitamin D.

W. L. DONOHUE (Toronto). 'Juxtaglomerular Cells in Familial Electrolyte Losing Syndrome in Infants.'

J. L. EMERY (Sheffield). 'Hypertrophic Glomeruli in Dysplastic Kidneys.' Hypertrophic nodules occur in dysplastic kidneys that have been treated for a prolonged period with ureterostomies. The changes in size of glomeruli of apparently normal children of different ages had been worked out and also those from dysplastic kidneys with and without hypertrophy. The glomeruli in dysplastic kidneys of children dying around the time of birth are smaller than normal. In the dysplastic kidneys treated by ureterostomy, the glomeruli are considerably larger than normal for the age of the children at death, and this applies irrespective of whether the glomeruli are associated with hypertrophic masses of tubules or not.

H. B. MARSDEN (Manchester). 'Aneurysm of the Renal Artery.' A boy of 7 years had hypertension for 3 years. Aortogram showed small aneurysms on the renal artery. Following nephrectomy, the blood pressure fell to normal. Three aneurysms, two saccular and one fusiform, were found close to the kidney with organized thrombus and hyperplasia of some glomeruli.

J. A. DUDGEON (London). 'Laboratory Studies on Rubella.' German measles is one of the mildest infectious diseases, and the sole reason for its importance to medicine is the damage the virus can produce in the human foetus. There is now undisputed evidence that infection with rubella in the first trimester of pregnancy may result in congenital abnormalities, which are collectively known as the 'rubella syndrome'—cataracts, deafness, microcephaly, mental retardation and cardiac defects. Until recently, all attempts at isolating rubella virus have been unsuccessful, but last year several investigators in America showed by an indirect method that rubella virus would grow in kidney cell cultures from the green African vervet monkey. Throat washings taken from rubella patients in the acute phase and inoculated into primary vertc cells produced no visible change but the cells resisted challenge inoculation or superinfection with a cytopathogenic virus such as ECHO 11 or Coxsackie A9.

During the spring of 1963 patients with rubella were investigated at the Hospital for Sick Children in London. Throat washings were inoculated into primary vertc cells which were later superinfected with ECHO 11 virus. A virus-interfering agent was isolated from 13 out of 19 patients, the isolation rate being significantly higher in the first two days of the disease. These agents appeared to be identical to a strain of rubella virus received from the U.S.A. Antibody titrations were carried out by means of the interference-inhibition test. Mixtures of serum and virus were inoculated into vertc cells and later challenged. If the serum contained rubella antibody the challenge virus broke through; on the other hand if antibody was not present the challenge virus was resisted. These tests were found to be reliable provided adequate controls were included. Five patients with rubella showed a fourfold rise or greater in neutralizing antibody.
Serum from 15 patients with the rubella syndrome was also tested. Excluding three patients under 8 months of age in whom it was difficult to determine whether the antibody was maternal or acquired, 8 of the remaining 12 had antibody with levels of 8 to 256, and 4 had very low levels (1/4) or no detectable antibody. It is not known whether the antibody in the 8 children was acquired postnatally or in utero, no evidence has so far been obtained that these children suffer from immunological paralysis. These preliminary results have now been confirmed by a more direct method employing cultures prepared from a continuous line of rabbit kidney cells in which cytopathic changes can be seen. The results are comparable.

W. I. H. SEDDIN and C. W. POTT (Sheffield). 'The Comparative Susceptibility to Adenovirus Infection of Children of Blood Groups A and O.' The incidence of infection with influenza A2 virus is significantly higher in persons of blood group O than of blood group A. The present study consisted of assessing the total experience of adenovirus infection with serotypes 1, 2, 3, 5, 6 and 7 in a group of 132 children. Statistical analysis showed that significantly more infections had occurred in children of blood group O than in children of blood group A. The difference was particularly marked for serotypes 3 and 7, the so-called 'epidemic' serotypes. There was no significant difference in incidence of infections with the 'epidemic' serotypes 1, 2, 5 and 6. It is suggested that children of blood group A, as compared with children of blood group O have an innate, low grade non-specific resistance to adenovirus infection. Frequent exposure to the infecting agent (as in the case of the 'Epidemic' serotypes) increases the likelihood that this will break down, and infection ensue.

H. FOX and P. O. YATES (Manchester). 'Neurocutaneous Melanosis.' A boy aged 2 had many large pigmented cutaneous naevi since birth. During the last year of his life, he developed hydrocephalus and evidence of an intracranial tumour. Pathologically, all the skin lesions were benign intradermal pigmented naevi. The meninges of the spinal cord showed similar inactive clusters of naevoid cells. Over the surface of the brain the subarachnoid space was occupied by sheets of actively growing cells that were in many places invading the underlying brain. The right occipital lobe was replaced by a malignant melanoma. Obstruction of the subarachnoid space had caused hydrocephalic dilatation of the ventricular system. No tumours were found in any other organ. This appeared to be a case of neurocutaneous melanosis with multifocal malignant changes in the meningeal melanoblasts. Several similar cases in the literature have been reported, and there is an association of this condition with neurofibromatosis and Sturge-Weber syndrome. The condition is thought to be a congenital dysplasia of the neural crest.

H. B. MARSSEN (Manchester). 'Prenatal Closure of the Foramen Ovale.' A case of prenatal obliteration of the interatrial foramen. The main lesions were paraventricular cavitation in the cerebral hemispheres and sclerosis of the liver with deposition of haemosiderin.

K. GAJ-Peczalska (Warsaw). 'The Analysis of the Hyaline Membranes in Newborn Infants by Means of Immunofluorescence.' The lungs of six newborn infants with well-defined hyaline membrane disease were studied by means of immunofluorescence. It was found that the hyaline membranes were composed of fibrin, y-globulin and albumin, which also focally impregnated the alveolar septa. Moreover cell nuclei were found within the membranes by means of fluorescent antibody procedure.

It was concluded that the hyaline membrane might be formed in the plasma-clotting process resulting from capillary wall damage and increase of capillary permeability.

F. A. LANGLEY (Manchester). 'Changes in the Brain Associated with Pulmonary Hyaline Membrane.' In 5 years, 67 cases of intraventricular cerebral haemorrhage were encountered in a group of 408 premature infants who were neither macerated nor anencephalic. Of these, 27 also had hyaline membranes in the lungs. By comparison with a group of balanced controls, it is shown that this association of intraventricular cerebral haemorrhage and pulmonary hyaline membranes is statistically significant. It is suggested that both lesions have a common underlying pathogenesis which may be cardiovascular; in the less mature infant, this expresses itself as intraventricular cerebral haemorrhage, and in the more mature, but still premature infant, as the pulmonary hyaline membrane syndrome. The role of antecedent conditions, such as ante-partum haemorrhage tending to cause foetal anoxia is uncertain; the evidence of association with intraventricular cerebral haemorrhage is suggestive but not statistically significant.

P. KALPAKTSoglOU, S. DOKIADIS and P. MATTHEW (Athens). 'Macroscopic study of the Placenta in 357 Normal and 135 Hypoxic Live Newborn Babies.' This study is an attempt to find some gross features of the placenta of hypoxic live newborn babies.

We studied the placentas with their membranes and the umbilical cords of 357 normal and 135 hypoxic newborn babies. The gross development of placentas does not seem to be largely altered in cases of live newborn babies with perinatal hypoxia. The proportion of stained membranes is higher in hypoxic full-term babies. There is a higher proportion of hard vessels on the placental foetal surface and a higher occurrence of peripheral infarcts and calcified infiltration in the maternal surface in hypoxic than in healthy newborns.

J. M. SCOTT (Glasgow). 'Glycogen Reserves of the Foetus and Neonate with Histological Observations.' Sections of liver and heart from stillborn babies and babies who died soon after birth were examined for glycogen and fat using a lead tetra-acetate Schiff method after picric alcohol fixation for the former and frozen
sections stained with Sudan IV for the latter. It was found that the glycogen content in mature stillbirths varied considerably depending on the degree of stress to the foetus, whereas in premature stillbirths, stainable glycogen was invariably low or absent. Fatty change was uncommon in stillbirths and was confined mainly to gross cases of placental insufficiency or Rhesus incompatibility.

In neonatal deaths these changes were more obvious especially in babies dying with respiratory distress syndrome (Scott, 1961). Biochemical control and treatment of these babies with bicarbonate and fructose has recently altered this picture (Hutchinson, 1964). Apart from the very immature babies (under 1,000 g) who seem to have a reduced ability to lay down glycogen, it was obvious from those who did come to necropsy that glycogen stores were being replenished. Generally the amount deposited was proportional to the amount of fructose administered except in a few mature babies where the initial wide variations in glycogen levels probably masked this effect. At the same time, the onset of fatty change appeared to be delayed.

With this form of therapy the mortality rate has fallen from 65 to 46%, or 11.5% if cases of intraventricular haemorrhage are excluded (Hutchinson, 1964). Occasional umbilical vein complications were noted. Most veins show evidence of some local reaction near the umbilicus, but this is of no apparent significance. Sepsis with pyaemic abscesses developed in one case. In 10 other cases, endothelial necrosis was seen in portal veins: nine of these developed an aseptic portal vein thrombosis and five of these pulmonary emboli. Two cases showed liver necrosis: in one where the right portal branch was thrombosed, the greater part of the right lobe was involved.

**REFERENCES**


R. De Rom (Ghent). 'Intrauterine Hypoxia in Twin Deliveries.' A study had been carried out on groups of 237 and of 223 abnormal deliveries in which lactate and pyruvate determinations were done using highly specific enzymatic methods.

The determination of the lactate-pyruvate ratio in umbilical cord blood is a reliable and sensitive method that makes a rational study of intrauterine hypoxia possible. The simple determination of the L/P ratio in umbilical vein blood may sometimes be sufficient when a group of complicated deliveries is compared with a normal group and the results are submitted to statistical analysis.

To study particular cases, however, a comparative investigation of the blood of both the artery and the vein of the umbilical cord is necessary.


T. E. Parry (Cardiff). 'Histiocytosis with Extensive Pulmonary Involvement.' A boy aged 9 presented with a month's history of epigastric pain, dyspnoea on exertion and lower lumbar and chest pain. He had had intermittent abdominal pain for two years, severe enough to warrant his admission to hospital as an abdominal emergency on two occasions. On the second admission, the abdominal pain was accompanied by enlarged tender glands in the left groin. A biopsy was taken of one. The glands subsequently subsided. Chest radiograph, the Mantoux test, and Paul Bunnel reaction and virus agglutinations were all negative at the time.

Four months later, the child was very ill with obvious respiratory distress. There was dullness over both bases and moist sounds all over the lungs fields. Chest radiograph showed extensive bilateral pulmonary infiltration. Small glands were palpable in the right groin. There was no anaemia. The white blood cell count was 26,800 with 84% polymorphs. He died 14 days after admission.

At necropsy there was extensive infiltration of both lungs with innumerable white nodules measuring about 5 mm. in diameter presenting both under the pleurae and on the cut surface. Enlarged glands were present in the neck, the portal fissure and in the para-aortic region. Two small tumour nodules (5 mm. in diameter) were present both in the right lobe of the liver and in the wall of the left ventricle. The spleen was only slightly enlarged (120 g.).

Histology of the gland biopsied during life showed loss of architecture, with extensive infiltration with large histiocytic cells and moderate numbers of lymphocytes and plasma cells. The picture was typical of histiocytosis. Lungs and lymph glands at necropsy showed striking histological differences. Although histiocytes were present, the predominating cell had reverted to a more primitive type resembling small reticulized cells, many of which were in mitosis. Small multinucleated giant cells of the Sternberg Reed type were fairly numerous. The splenic pulp was infiltrated by histiocytes, some of which showed erythropagocytosis together with lymphocytes and plasma cells with numerous polymorphs and eosinophils. The splenic picture was essentially granulomatous and akin to eosinophilic granuloma.

K. M. Laurence (Cardiff). 'Arrhinencephaly and Trisomy of the 13-15 Chromosomes.' Three cases that had absent first nerve tracts and trigones and vestigial or absent olfactory bulbs and three cases that had the classical arrhinencephaly with more or less fusion of the cerebral hemispheres, a single cerebral ventricle and abnormalities of the hippocampus and corpus-callosum as well as the first nerve abnormality, but with relatively normal hind-brain, were described. All the cases also had a cleft palate as well as other less constant malformations including hare-lip, microphthalmia, renal tract abnormalities, extra digits, hypoplastic lungs, congenital heart disease and a bicornuate uterus or cryptorchism.
All had a peculiar facies and were either stillborn or died during the first week. The three cases that have so far had chromosome analyses performed (one with only the first nerve abnormality and two of arrhinencephaly) showed trisomy of one of the 13-15 chromosomes. One showed a translocation in this chromosome group as well.

It was suggested that as the cases with gross and the less severe central nervous system malformations described showed that same chromosome anomaly they were both variants of the same basic abnormality as had been previously hinted. Because three of the six infants, including all those with chromosome analyses, were born in one maternity unit this year, amongst just over 2,000 deliveries during that time (incidence 1:700 births), the incidence of the condition is probably higher than is generally believed.

All infants with peculiar facies, especially if cleft palate and other malformations are also present, should have chromosome analyses performed.