Paediatric Pathology Society

Proceedings of the Eleventh Annual Meeting

The Eleventh Annual Meeting was held in Edinburgh on October 14, 15, and 16, 1965, at the Royal Hospital for Sick Children and the Pfizer Foundation Building. Drs. Agnes Macgregor and A. D. Bain took the chair. 41 members signed the attendance book. The social programme included visits to the Royal Mile, the new Forth Bridge, and the Glenkitchie Distillery.

The next meeting of the Society will be held in Sigtuna, Sweden, on June 14-16, 1966, when the president will be Dr. B. I. Ivemark. The Society will meet in London, October 21-22, 1966, under the joint presidency of Drs. L. Crome and A. E. Claireaux.

Scientific Communications

The following papers were read at Edinburgh.

PARRY, T. E., BRAY, P. T., and JACOBS, J. (Cardiff). ‘Hypersplenism in Infancy and Childhood.’ 3 cases of pancytopenia associated with splenomegaly and hyperplasia of erythroid, myeloid, and megakaryocytic elements in the marrow were described. All 3 responded dramatically to splenectomy. Neither congenital abnormalities of the red cells nor circulating red cell antibodies could be detected. They could not, therefore, be regarded as cases of congenital or acquired haemolytic anaemia. In each case the splenomegaly was a manifestation of some other disease, the course of which was not necessarily affected by the splenectomy.

Case 1: A female child, in whom hepatosplenomegaly was discovered at 9 months and pancytopenia at 17 months. The anaemia had been severe enough (Hb 26%) to necessitate 3 blood transfusions when splenectomy was carried out at the age of 21 years. The spleen weighed 175 g. and showed marked congestive splenomegaly. Liver biopsy at operation showed advanced diffuse hepatic fibrosis (portal cirrhosis). Complete relief of the pancytopenia as well as a considerable improvement in the child’s general health has occurred during the two years since the operation.

Case 2: A female child, in whom hepatosplenomegaly was discovered at 10 months and anaemia with leucopenia at 20 months. This was followed by two episodes of severe thrombocytopena (lowest platelet count 25,000/c.mm.). Small numbers of large lipoid-laden reticulum cells in a hyperplastic marrow confirmed the diagnosis of lipid storage disease. Splenectomy was performed at the age of 4½ years. The spleen weighed 490 g. with numerous large lipoid-laden cells in the pulp. She remained well with return to a normal blood picture during a 4-month follow-up period.

Case 3: A female child, with abdominal enlargement, first noticed at 3 years. There was gross splenomegaly with persistent pancytopenia. Splenectomy was performed at 5 years. The spleen weighed 4,100 g. and the pulp was packed with Gaucher’s cells. Early similar deposits were noted in the portal tracts of a liver biopsy taken at operation. Subsequently she developed progressive hepatic enlargement and multiple bone lesions, but during the 10½ years since operation her blood counts have been normal.

Pancytopenia, a hyperactive but otherwise normal, and splenomegaly are the usual triad for the diagnosis of hypersplenism. To these must be added a favourable haematological response to splenectomy. It is stressed that the splenomegaly itself is secondary to some other disease outside the erythron—such as the hepatic cirrhosis and lipidosis in the cases described.

MARSDEN, H. B., STEWARD, K. J., and WHITE, L. L. R. (Manchester). ‘Some Aspects of Lympho-reticular Tumours.’ 90 non-leukaemic reticuloendothelial tumours and 12 which became leukaemic were discussed. 6 groups were included: (1) lymphosarcomas (including reticulosaarcomas); (2) Hodgkin’s disease; (3) histiocytosis X; (4) erythraemic myelosis; (5) Brill-Symmers disease; and (6) microgliomatosis.

Lymphosarcoma was most frequent and had the worst prognosis. The distribution of lesions was widespread and the majority of fatal cases died within one year.

Hodgkin’s disease occurred in an older age-group and death occurred up to 12 years after diagnosis. The great majority showed localized cervical glands.

Differential diagnosis was discussed particularly with regard to lympho-epithelioma of the pharynx, and the distribution, complications, and treatment of histiocytosis X were considered.

MARSDEN, H. B. and STEWARD, J. K. (Manchester). ‘Juvenile Sarcomas.’ In a study of 101 connective tissue tumours in childhood there were three large groups: (1) undifferentiated, rhabdomyosarcomas; (2)
osteosarcomas, and (3) fibroma, fibrosarcomas. Groups (1) and (2) provided the majority of fatal cases. Difficulties in histological diagnosis of tumours in group (1) were considered, there being a range from undifferentiated sarcomas to fully developed rhabdomyosarcomas, comparable to the appearance of Wilm's tumours. The majority of these tumours are found in the head, neck, and pelvic regions, the orbit and middle ear being worthy of special mention. With combined surgery, radiotherapy, and chemotherapy, the best results were obtained with neoplasms of the head and neck, but it is difficult to know whether prognosis depends on the natural history of individual tumours rather than on specific treatment.

HUBER, J. (Groningen, Netherlands). 'The Thymus in Children.' Recent animal experimental work has revived interest in the thymus. It is postulated to be a central lymphoid organ which, either through a humoral factor or through release of cells, influences the peripheral lymphoid system. The experimental work is not directly applicable to human pathology, and the human thymus must be studied especially in those diseases with a suspected dysfunction of the immunological apparatus.

Lympho-depletion and involution of the thymus are non-specific results of stress, and attention is called to the occurrence of so-called 'giant' Hassal bodies. They are believed to be the result of corticosteroid, either autologous or administered, and indicate an antagonism between the adrenals and the thymus. The thymus may be repopulated by clusters of new thymocytes, often around Hassal bodies. These may be considered as normal physiological reactions. By contrast, plasma cellular infiltration and the occurrence of germinal centres are regarded as abnormal. There seems to be a correlation between these pathological features and derangement of the immunological system. The concept of status thymo-lymphaticus is reintroduced and redefined as comprising those cases of sudden unexpected death, presumably due to anaphylactic shock, where an enlarged thymus with germinal centres is found. One case of absence of the thymus and the parathyroid glands (together with a tetralogy of Fallot) was demonstrated. The lymphoid system of the patient was relatively atrophic but did contain plasma cells and germinal centres. It was concluded that this observation lent support to the hypothesis put forward by Good and co-workers (1965) that there was another central lymphoid organ apart from the thymus.

REFERENCE

CLAIREAUX, A. E. (London). 'Heterologous Transplantations of Solid Tumours.' Fresh tissue from 49 tumours occurring in childhood was available for study. The material included 13 neuroblastomas, 11 nephroblastomas, and 6 embryonic sarcomas (rhabdomyosarcoma).

One rhabdomyosarcoma occurring in the cheek of a 3-year-old girl was successfully transplanted into a newborn thymectomized and irradiated mouse. A tumour was also established in the cheek pouch of a Syrian hamster. The growth in the hamster was maintained for 42 days, but retransplantation into other hamsters was unsuccessful.

For the chromosome analysis, 79 solid tumours were available, including 49 used for transplantation experiments. Satisfactory preparations were obtained in 21 cases and a detailed karyotype analysis prepared. In addition to variations in the chromosome number, numerous small fragments (double minutes) were observed in the mitotic preparations of 2 neuroblastomas and a rhabdomyosarcoma. The significance of this was discussed.

Three cases of nephroblastoma yielded diploid chromosome numbers, and this was of interest as diploid counts are rare in human tumours.

Of the tumours in the series, 9 were cultured in plasma clots and chromosome preparations were obtained. Chromosome fragments similar to those found in direct preparations were also noted following tissue culture.

Preliminary analysis of tissue obtained from the rhabdomyosarcoma indicated that there was no significant difference in the chromosome number of cells obtained by the direct method and those found on tissue culture.

LEKOW, P. (Bergen, Norway). 'Paradoxical Movement and Pulmonary Circulation in Relation to Hyaline Membranes.' In neonatal asphyxia inspiratory retraction of the lower sternum and cartilaginous part of the ribs is a frequent and striking phenomenon. Experimental paradoxical respiration, produced in rabbits by removing parts of the ribs, causes only simple atelectasis. The lung findings in neonatal asphyxia and comparable experimental conditions, such as oxygen poisoning, are of two main types: (1) hyaline membrane type (dilated ducts with hyaline membranes, atelectasis, hyperaemia and proteinaceous exudation); (2) haemorrhagic type (dilated ducts with no or few hyaline membranes, atelectasis, hyperaemia, proteinaceous exudation, and interstitial and intra-alveolar haemorrhage).

By intravital intravenous injection of Indian ink in animals with experimental hyaline membranes, the capillary circulation is demonstrated. This shows only a few dye-filled patent capillaries, while the remaining capillaries contain columns of erythrocytes which must be stagnant. As low molecular proteins are lost through a capillary wall, local haemoconcentration occurs, causing conglutination of erythrocytes and capillary erythrostasis which must be distinguished from ordinary thrombosis and coagulation. When capillary erythrostasis is extreme and long-lasting the animals develop acute cor pulmonale, comparable to the heart findings in neonatal asphyxia. The paradoxical retraction of the chest wall is mainly attributed to blood being trapped in the pulmonary capillaries causing increased rigidity of the parenchyma. The rigidity of the engorged capillaries may both prevent the inspiratory expansion of the lung and the final collapse of the alveolar ducts. Death is not caused by insufficient respiration due to weakness of the chest wall, nor by hyaline membranes preventing the gaseous exchange, but by increasing pulmonary...
capillary erythrostasis gradually reducing the functioning vascular bed of the lungs.

Lauweryns, J. M. (Louvain). ‘Hyaline Membrane Disease: A Pathological Study of 55 Infants.’ (Published in full in Archives of Disease in Childhood (1965), 40, 618.)

Faint, Sheila (Bristol). ‘Cerebellar Histology in the Immature Infant.’ A study of 52 infants dying in the neonatal period correlated gestational age with the appearance of recognizable Purkinje cells in the cerebellar hemispheres. The appearance of these cells was shown to be a marker of the 30th week of gestation, but neuronal degeneration was frequently seen. Further investigation showed that the degree of neuronal damage was associated with hypoxia or other metabolic disturbance. For this purpose, 4 groups of cases were defined: (1) those with secondary atelectasis of the lungs, with or without hyaline membrane; (2) those with primary atelectasis of the lungs; (3) other cases of hypoxia such as congenital heart disease, or metabolic disturbance, e.g. uraemia and hypoglycaemia; and, finally, (4) infants who had suffered from intrauterine hypoxia. The degree of degeneration in Purkinje cells was shown to be associated with the duration and severity of hypoxia rather than with any particular underlying pathological process.

Guli, E. (Siena, Italy) and Cameron, A. H. (Birmingham). ‘The Dandy-Walker Syndrome.’ The pathological features of 4 infants with the Dandy-Walker syndrome were described. In all, a large thin-walled extension of the fourth ventricle filled the posterior fossa, and 2 showed hydrocephalic enlargement of the upper ventricles. The cerebellar hemispheres in one case were separated by a complete mid-line cleft, and in the others the cerebellar vermis showed minor clefts or simple atrophy due to compression. In one, there was complete absence of the corpus callosum.

It was stressed that the characteristic cystic malformation was liable to collapse during removal of the brain at necropsy and might not be recognized; such cases might be wrongly interpreted as isolated lesions of the cerebellar vermis. The Dandy-Walker syndrome should be considered in all infants with hydrocephalus not associated with myelocoele.

Sullivan, Margaret (Pathology Department, Dartmouth, USA). ‘Abnormalities of the Chromosomes in Fanconi’s Anaemia.’ 2 young boys with Fanconi’s hypoplastic anaemia were found to have structural anomalies of the chromosomes; the patients were cousins. Clinical, haematological, and genetic studies of the patients and their families were reported, and the significance of these findings for an understanding of the hereditary pattern of Fanconi’s anaemia was discussed.

Berry, C. L. (London). ‘The Post-mortem Assessment of Myocardial Ischaemia.’ A simple technique of differential staining of formalin-fixed tissues with acid fuchsins was used to investigate the incidence of early myocardial ischaemic change in infancy and childhood.

135 unselected cases were studied. In 40 cases whole heart sections were examined; in the remainder, blocks were taken from each ventricle and the septum. 96 of those examined showed evidence of ischaemia. In 81 terminal events may have produced the changes seen. In the remaining 15 this was not so. It was apparent that haemoglobin levels of 4 g./100 ml. or less, prolonged hypotension, prolonged convulsions, and respiratory difficulty without assisted respiration, were all conditions in which myocardial ischaemia might occur in childhood.

Conen, P. E. (Toronto, Canada). ‘Granular (Nemaline) Myopathy.’ A 4-year-old boy with a peculiar granular myopathy was previously described (Conen, Murphy, and Donohue, 1963). This paper gives a follow-up report of the original patient and describes the same condition in a 3-year-old boy.

Both were slow to walk and had generalized muscular weakness affecting especially the proximal parts of the lower limbs: they had a waddling gait and got up from the prone position in the typical Gower fashion. Muscle biopsies showed fatty replacement of muscle fibres, and the small fibres particularly contained many irregularly ranged granular bodies of somewhat basilar shape. They were best seen in paraffin sections stained with PTAH and could be missed in H and E preparations. Electron microscope studies showed that myofibrils had a periodicity similar to that of crystallized muscle protein paranynosin.

The original patient is now 7 1/2 years old. The muscular weakness remains unchanged but co-ordination has improved so that he is less disabled, and he is doing very well at school.

The precise nature of this disease is unknown but there is some indication of a genetic element. A review of more than 100 muscle biopsies taken over the past 10 years in the Hospital for Sick Children, Toronto, has revealed no further cases. The ultimate prognosis is unknown but appears to be more favourable than the Duchenne type of muscular dystrophy from which it must be distinguished.

REFERENCE


Raine, D. N. and Hughes, Pat A. M. (Birmingham). ‘Factors Affecting the Interpretation of a Tryptophan Load Test.’ Pyridoxal phosphate acts as a co-enzyme at several stages in the metabolism of tryptophan. On this basis a test for pyridoxal deficiency, the tryptophan load test; after an oral dose of tryptophan the urine is examined for various metabolites, notably xanthurenic acid, formed in the kynurenine pathway. The interpretation is affected by variations introduced by different workers. Some have expressed the excretion of one or more metabolites over a timed period after the tryptophan load, whereas others have compared the excretion before and after. The latter is recommended and a collection 24 hours before and after tryptophan should be made.
The amount of tryptophan given has varied from as little as 30 mg./kg. of the L-isomer to 540 mg./kg. of the racemic (DL) mixture. For children, many authors have graded the dose according to the age, and a dose of 100 mg./kg. of the L-isomer has been recommended. There is some evidence that higher doses over 5 years increases the excretion of xanthurenic acid. Below 5 years, normal children excrete less than 3 mg. xanthurenic acid in 24 hours.

Four young adults were given doses of tryptophan increasing from 30 to 100 mg./kg. at weekly intervals. The excretion of xanthurenic acid increased from just over 3 mg. in 24 hours to 60 mg. One of the subjects then repeated one of the 30 mg. doses at weekly intervals, and the xanthurenic acid excretion was 8·8, 12·6, 10·6, 9·8, 5·1, and 10·7 mg. The experiment was then repeated taking daily supplements of pyridoxine, and the levels fell to 3·6, 1·2, 2·0, and 2·4 mg.

It is known that any amino acid can combine non-enzymatically with pyridoxal phosphate to form a Schiff’s base. It is suggested that the administration of large doses of tryptophan, designed to test pyridoxine status, may in fact render the body temporarily deficient by combining with pyridoxal phosphate and making it unavailable as a co-enzyme.

The interpretation of tryptophan load tests will be facilitated by standardization of the procedure. We suggest that urine is collected for 24 hours before and after the tryptophan, that the amino acid should be given in the form of the L-isomer only, and that the dose in children should be given on the basis of 100 mg./kg. body weight up to a maximum of 2 g. This level does not produce unpleasant symptoms in an adult. It has yet to be established that a maximum of 2 g. tryptophan will show up a defect in a subject deficient in vitamin B6.

ROGERS, K. B. (Birmingham). 'Urinary Typhoid Carriage in a Child.' Gram-negative bacilli of the Enterobacteriaceae group should be examined to ensure that they are not Salmonellae or Shigellae, so that carriers of dangerous intestinal pathogens are excluded from ordinary wards. A few 'coli-forms' were grown from the urine of a 12-year-old Pakistani girl. These proved to be Salmonella typhi: direct questioning established that she had had typhoid fever 7 years previously. Investigations showed that she had a non-excreting pyonephrotic kidney which was excised, but she continued to excrete S. typhi. On intensive chemotherapy she ceased to excrete S. typhi and her Vi antibodies disappeared, but both reappeared after chemotherapy had been stopped. Further investigations and surgical treatment showed that in the ureteric stump there was an abscess containing a pure uric acid calculus. When this was removed the carrier state was cured and her Vi antibodies disappeared.

GAJ,-PECZALSKA, K. (Warsaw), 'Cytomegalic Inclusion Disease.' 21 cases of generalized cytomegalic inclusion disease in infants 2–6 months of age were discussed. On the basis of clinical manifestations and necropsy findings, the author has tried to establish criteria for differentiation of the neonatal and postnatal form of the condition. Generalized cytomegalic inclusion disease was found in 5% of unselected necropsies from the pathology laboratory of a Warsaw Children’s Hospital. This high percentage seems to be connected with a rather detailed pathological examination, since the cytomegalic cells in the investigated organs were most frequently single, and in 17 of the 20 cases other changes (which might have been the cause of death) were found. The problem is discussed whether during a symptomless, so-called localized, salivary gland infection, single cytomegalic cells can be formed in other organs, and be associated with persistent viruria and viraemia.

LAURENCE, K. M. and GRAY, O. P. (Cardiff). 'Generalized Moniliasis.' A female child, 1·9 kg., was born at the 42nd week to a mother who had lost 4 previous infants—3 stillbirths and one anencephalic abortion. She had little antenatal care and was admitted in labour. Time of rupture of membranes was uncertain. The child was born after a normal labour, but was pale and shocked with a full fontanelle. There were crepitations in the lungs on the first day soon after birth and the respiratory rate was raised. Throughout the 19 days of her life she remained pale, difficult to rouse, and generally hypotonic, but there were periods of increased tone with fits and occasional cyanotic attacks. Two days before death the left kidney became enlarged and a subcutaneous abscess over the scalp was incised. Oral thrush was noted from the seventh to tenth day.

The CSF, examined on the fourth and tenth days, was normal. A subdural tap on the fourth day grew Candida albicans, as did a blood culture on the seventh day. These results did not become available until just before the infant’s death.

Necropsy showed severe brain softening with extensive monilial invasion of the cerebrum, cerebellum, brainstem, and spinal cord, large mycelium-containing abscesses in the medulla of the kidneys, and small myocardial and skin abscesses. There was a terminal pneumonia but no evidence of intestinal invasion.

It is believed that the illness was acquired in utero, as there were signs of infection at birth and as the clinical status did not change. Very few such cases are on record.

BROZKO, W. J. and NOWOSLAWSKI, A. (Warsaw). 'Immunopathology of Pneumocystis Pneumonia.' The characteristic plasma cell infiltration of the lungs in the epidemic type of pneumocystis pneumonia led us to investigate the possible role of Pneumocystis carinii antigens. Our studies were based on necropsy material of infants. Highly purified, immunoelectrophoretically monospecific fluorescein isothiocyanate (FITC) and Lissamin-rhodamine B200-labelled anti-human fractions were used directly according to the Coons' method.

The most striking feature was the presence of large quantities of y-globulin in the bronchiolar and alveolar lumina. This was closely bound to the honeycombed conglomerates of parasites. Further analysis revealed that y-globulin represented specific components of the antigen-antibody complex. It was shown that the
globulins bound to the *Pneumocystis carinii* conglomerates were a mixture of IgM and IgG globulins. Contrary to this, the immunoglobulins in plasma cells were mainly, if not exclusively, of 19 S type. On some occasions fluorescent cells contained both IgM and IgG globulins.

The use of sera of infants suffering from *Pneumocystis carinii* pneumonia as an intermediate layer resulted in brilliant specific fluorescence of parasite structures after subsequent staining with anti-human globulin reagent. This 'staining' was further routinely used for specific identification of *Pneumocystis carinii* antigens in tissues, and has been found in many aspects superior to all known histological methods. The indirect staining procedure could also be employed for the evaluation of *Pneumocystis carinii* antibodies in sera of infants suffering from pneumocystis pneumonia.

RAINE, D. N. (Birmingham). 'Intrauterine Chickenpox.' A review of 38 published and 2 unpublished cases of neonatal chickenpox occurring before the 14th day of life has revealed that, (1) the 6 infants that died were all female; (2) of 34 infants in whom the sex was known there were 9 boys and 25 girls, a sex ratio of 1 to 2.8; (3) the age of onset of the rash in the infants showed a bimodal distribution, the main peak occurring at birth and being complete at 5 days, and a second peak occurring between the 5th and 12th day; (4) in all the fatal cases the onset of the rash was between the 5th and 20th day of life.

It is suggested that the second group of cases were infected at birth and that under these circumstances the usual incubation period of 14 days was reduced to about 8 days. The more serious prognosis in the later group of patients may be due to their infection occurring after their separation from maternal defence mechanisms and before their own were fully established.

DR. J. L. EMERY (Sheffield) showed his film 'Post-mortem Technique in the Newborn', which had already been awarded prizes for its artistic merit.