Paediatric Pathology Society

Proceedings of the Twelfth Annual Meeting

The Twelfth Annual Meeting was held at St. Mary's Hospital, Carshalton, on Friday, October 21, and at the Institute of Child Health, Great Ormond Street, on Saturday, October 22, 1966. The Chair was taken by Dr. Leonard Crome and Dr. Albert Claireaux.

On the Friday members were entertained to lunch by the Board of Management of St. Mary's Hospital, and on Friday afternoon demonstrations were on view and a visit was made to the M.R.C. laboratories at St. Mary's Hospital. On the Friday evening the Society dined at the Livery Hall, Guildhall, London: the guests were Prof. A. W. Wilkinson, Professor of Surgery, The Hospital for Sick Children, Great Ormond Street; Dr. G. Newns, Dean of The Hospital for Sick Children, Great Ormond Street; and Professor Blacklock of the National Hospital for Nervous Diseases, Queen Square. After dinner a tour of the Guildhall was conducted by Mr. Grey.

Forty-three members signed the attendance sheet, including 3 members from Australia, N. J. Nicolaides, H. B. Hilton, and B. Gutteridge.

Minutes of the 12th Annual General Meeting
held in Carshalton on October 21, 1966

1. 43 members signed the attendance book and apologies were received from Drs. Agnes MacGregor, Henry Baar, Pitsa Kalpaktsoglou, Elwood, Brzosko, and Professor Holland.
2. The Society stood in silence in remembrance of Dr. Leslie White who had died since the Society last met.
3. The Minutes of the 11th Annual Meeting were taken as read. There were no matters arising.
4. 1967 Meeting. It was agreed to accept Dr. Kohler's kind invitation to meet in Leeds. There was considerable discussion about the date of the meeting. The consensus was that the Meeting was best held about the middle of October.
5. 1968 Meeting. The Society accepted with pleasure Dr. Daamen's invitation to hold the Meeting in Rotterdam about the same time in 1968.
6. Election of new members: The following new members proposed by the Committee were elected:
   Dr. Barbara Burke, Minnesota
   Dr. Margaret Swinburne, Leeds
   Dr. Sidney Jacobs, Manchester
   Dr. Douglas Stanley, Liverpool
   Dr. Jonathan Wigglesworth, London
   Dr. Pat Hughes, Birmingham
7. Election of officers: Dr. A. H. Cameron was re-elected Honorary Secretary for the coming year.
8. Forensic pathology and Home Office Committee. The Hon. Secretary gave a brief account of his evidence to the Home Office Committee.
9. Constitution of the Society. The constitution as proposed by the Steering Committee was discussed clause by clause.
   An amendment that rule 3 should have the phrase 'medically qualified and' inserted before 'actively' was proposed by Dr. Levin and seconded by Dr. Parry. The amendment was defeated by 24 votes to 4.
   An amendment that the second sentence of rule 4 should be deleted was proposed by Dr. Raine but not supported. An amendment that the word 'must' in the second sentence in rule 4 be replaced by the word 'should' was proposed by Dr. Emery, seconded by Dr. Kohler, and carried unanimously.
   With this single amendment the constitution was approved unanimously. See below.
10. Any other business: The Secretary gave some details of the Pediatric Pathology Club which was holding its 2nd Meeting in Columbus, Ohio, simultaneously with the current Meeting, and the Society approved the interchange of information between the two bodies.

Constitution of the Paediatric Pathology Society
Approved and adopted at the A.G.M.—October 21, 1966.
1. The Society shall be called the 'Paediatric Pathology Society'.
2. The aims of the Society shall be to promote paediatric pathology in its widest sense, embracing all the disciplines of pathology.
3. Ordinary members shall be actively engaged in paediatric pathology and/or have this as their main interest.
4. Any member of the Society may propose a new member and the proposal must be seconded by a member from a different centre. Applications for membership should be accompanied by a list of publications the candidate may have made.
5. All applications for membership must be scrutinized by the Committee. If approved, the names shall be included in the agenda of the Annual General Meeting and be subject to election at that meeting.
6. There shall be an annual subscription of one pound payable by Bankers Order only.
7. Honorary members may be nominated by the Committee for election at the Annual General Meeting. Such nominations shall be included in the agenda for that meeting.
8. The host at the meetings of the Society shall be the President of the Society and Chairman for the duration of the meeting.
9. The Honorary Secretary and the Honorary Treasurer shall be elected at an Annual General Meeting and may be re-elected up to a total of five years.
10. The Committee shall consist of the Hon. Secretary and the Hon. Treasurer, and 8 members elected at an Annual General Meeting. It should, as far as possible, be representative of the main branches of paediatric pathology and of the geographical membership of the Society, and shall have power to co-opt.
11. The elected members of Committee shall hold office for four years; two shall retire each year and shall not be eligible for re-election for the following year.
12. The Committee shall elect a Chairman for each meeting from among the members present. A quorum shall consist of five members, of whom only one may be a co-opted member.
13. The Committee shall have power to act on behalf of the Society and shall report its activities at each Annual General Meeting.
14. In addition to the Committee there shall be an Advisory Council which shall consist of one member from each country represented in the Society, no one member to serve more than three years when an alternative is available. The Council shall have power to co-opt and will elect its own Chairman at each meeting.
15. Voting at meetings of the Society, its Advisory Council, and its Committee will be on a simple majority basis and will be conducted by the Chairman of the meeting.
16. The Society will meet at least once a year and hold a scientific and business meeting, including reports by the Hon. Secretary and the Hon. Treasurer.
17. The Hon. Secretary shall send to each member, not less than one week before each Annual General Meeting, an agenda including the names of candidates for election as Hon. Secretary, Hon. Treasurer, or as members of Committee, along with the names of the existing and retiring officers. Nominations, with the written consent of the nominee, must be received by the Hon. Secretary four weeks before the Annual General Meeting.
18. The rules of the Society may be amended by a simple majority decision of the Annual General Meeting provided the proposed amendment has been published in the agenda circulated to members of the Society.

Scientific Communications

Leucodystrophies. L. Creme (Queen Mary's Hospital, Carshalton). Of conditions previously described as Schilder's disease (encephalitis periaxialis diffusa or diffuse sclerosis), some are now known to be instances of sclerosing leucoencephalitides (inclusion body encephalitis) and of juvenile variants of disseminated sclerosis. The term Schilder's disease is sometimes still employed for sporadic cases showing a combination of marked inflammatory changes and demyelination. The usefulness of doing so is doubtful, since inflammatory changes often accompany all other forms of leucodystrophy, while the avowedly familial forms may, of course, affect only single members of a family. The other conditions in the group formerly known as Schilder's disease are the leucodystrophies. These are characterized by extensive symmetrical demyelination of the cerebrum and cerebellum, relatively longer survival of axis cylinders, and a tendency for the subcortical fibres to be spared. Most of these cases are transmitted as Mendelian recessive traits, but the variant known as Pelizaeus-Merzbacher disease affects mainly males and could, therefore, be sex-linked. At Queen Mary's Hospital for Children leucodystrophies have about the same incidence as the lipidoses: about 16 cases in a thousand necropsies. However, in addition to cases conforming to the 'classical' pattern, others have occurred in association with such conditions as phenylketonuria, tuberous sclerosis, lipidoses, and camphor poisoning. These 'secondary' leucodystrophies cannot be distinguished pathologically from the primary ones. Still other cases presented transitional features between progressive demyelinating disease and the congenital forms of progressive gliotic encephalopathy.

The classification of leucodystrophies is not very satisfactory. The one used at this hospital distinguishes the following variants: sudanophil; globoid cell (or Krabbe's), which is the commonest form in infants; the Alexander type—with hyaline bodies (Rosenthal fibres); the Pelizaeus-Merzbacher type, with the longest survival and prevalence in males; the metachromatic type; and the Seitelberger type. Some workers have also included among the leucodystrophies the so-called Canavan's type of diffuse sclerosis or spongiform encephalopathy, characterized by rarefaction and breakdown of neural tissue. It has been stated that this condition is familial and restricted to Jewish children. We have seen this change, however, frequently in diverse and unrelated conditions and feel confident that this spongiform encephalopathy is not a separate condition. None of our cases was Jewish.

Encephalopathy following Experimental and Clinical Anoxia. J. B. Brierley (M.R.C. Laboratories, Carshalton). The neuropathological findings in a series of 17 patients with circulatory arrest or systemic hypotension were presented.

(i) Circulatory arrest—14 patients. The age range was 16 months to 74 years, and four were children under the age of 5. The range of survival was 12 hours to 9 months. All were unconscious up to death, a few grand mal seizures occurred in one child and one adult. Moderate brain swelling was seen in one child.
In the cerebral cortex, damage was generalized and most severe in pre- and post-central and parieto-occipital regions. Necrosis in the hippocampi, particularly the Sommer sector, H.1, was seen in all, and was severe in the striatum but less in the pallidum. The anterior complex in the thalamus and the mamillary bodies in the hypothalamus were often damaged, the mamillary bodies being affected in all four children. There was a generalized loss of Purkinje cells in the cerebellum of most cases.

In the four children, as distinct from the adults, there were lesions in the brain-stem (IIIrd nerve complex, Vth nerve nuclei, vestibular complex, N. gracilis and cuneatus). These correspond to the lesions in the brain-stem of the asphyxiated infant Macacus rhesus (Ranck and Windle, 1959).

(ii) Systemic hypotension—13 patients. These were divided on a neuropathological basis into three groups. (a) 3 patients: age 22-40 years; survival 3-28 days. Two were conscious at the time of a sudden and severe hypotensive episode and one was under dental anaesthesia. In all, cortical necrosis was confined to the 'boundary zones' between the territories of the major cerebral and/or cerebellar arteries. There were patches of necrosis in the thalamus and striatum and only minor lesions in the hippocampi. (b) 5 patients: age 71-74 years; survival 2 days to 23 months. All were under anaesthesia at the time of a moderate and prolonged hypotensive episode. 4 were unconscious until death and 1 was demented until death at 23 months. All showed generalized loss of neurones in the cerebral (particularly parieto-occipital) and cerebellar cortex, severe cell loss in the thalamus (particularly the anterior complex), and minor changes in the hippocampi. There were multiple lesions in the brain-stem of the child aged 71/2 years. (c) 5 patients: age 5-35 years; survival 4-14 days. A hypotensive episode of severity intermediate between (a) and (b) occurred in the conscious state in 4 and during recovery from anaesthesia in 1. 4 remained unconscious until death. One became unconscious after 6 days and died 8 days later. Boundary zone lesions were seen in the cerebrum of 3 and the cerebellum of 2, and there was neuronal loss in the intervening areas. Recent alterations were seen in the hippocampi of 2. Necrosis was present in the striatum of 3 and in the thalamus of 5. Multiple lesions were seen in the brain-stem of the child aged 5 years.

In the rhesus monkey Brierley and Excell (1966) produced necrosis in arterial 'boundary zones', and also generalized neuronal damage in the cerebral and cerebellar cortex by drug-induced arterial hypotension, combined with head-up tilt of the table and, in some instances, bleeding.

## REFERENCES


**Fifteen Cases of Arrhinencephaly. K. M. Laurence** (Llandough Hospital, Cardiff). Arrhinencephaly (absent first nerve structures), usually regarded as a rare malformation of the brain, has aroused interest because of its association with 13-15 (D) trisomy. In the extreme form, alobar holoprosencephaly, a single fused cerebral mantle encloses a single cerebral ventricle, while in the mildest, the brain is nearly normal apart from the absent olfactory bulbs, tracts, and trigmone. Between these extremes intermediate forms are found, usually with abnormalities of the corpus callosum (Laurence, 1966).

Fifteen cases of arrhinencephaly have been examined in Cardiff since 1960. 6 were associated with 13-15 trisomy; 1 had 13/21 translocation, 1 had a partial 13-15 trisomy (Ishmael and Laurence, 1965), and 3 had the usual 13-15 trisomy. Five had a normal karyotype. Analysis failed in 3 and was not carried out in 1; the clinical and pathological features suggested that 2 of those with failed cultures may also have been trisomic.

Although the facies in the trisomic cases tended to be more abnormal than those with a normal karyotype, 3 of the trisomic cases showed the mild form of arrhinencephaly, while 2 of those with a normal karyotype had holoprosencephaly. Furthermore, the association of the severe facial abnormality with holoprosencephaly was not invariable. Extracranial malformations were, however, more common and more severe in the trisomic cases.

In 1960-62 and 1965 and 1966, only 4 cases, 1 with trisomy, were seen, while in 1963 there were 8, including 4 with trisomy, and in 1964 there were 3. So far, no likely common causative factor has been identified nor has there been an explanation for the concentration of cases. 8 of them were drawn from one large maternity unit with 3000 deliveries annually, suggesting an incidence of 1 in 2500 births for arrhinencephaly, and 1 in 3500 for 13-15 trisomy, with a peak incidence of 1 in 750 and 1 in 1000, respectively, in 1963. It was concluded that: (1) Probably every case of 13-15 trisomy has some degree of arrhinencephaly. The converse is not true, and probably half of this series had normal karyotypes. (2) The degree and type of facial abnormality does not always predict the degree of brain abnormality. (3) 13-15 trisomy tends to have severe extracranial malformations associated with the arrhinencephaly (4) Hitherto unexplained concentrations in the incidence of arrhinencephaly seem to occur, up to 1 in 750 births.

## REFERENCES


**Determination of Sodium in Saliva by the Electrode Method. D. Lawson and B. Saggeres** (Queen Mary's Hospital, Carshalton). (To be published in full.)

**Hyperprolinaemia. F. Emery, L. Goldie, and J. Stern** (Queen Mary's Hospital, Carshalton). In man the degradation of proline takes place in two steps: in the first, proline is oxidized to pyrroline-5-carboxylic acid (PC) by the enzyme proline oxidase, and in the second PC to glutamic acid by PC dehydrogenase.
Hyperprolinaemia is a very rare inborn error of metabolism. Efron (1965) showed that it could be due either to proline oxidase deficiency, hyperprolinaemia type I, or to PC dehydrogenase deficiency, type II. He studied 4 affected families, 2 with type I and 2 with type II. Both types have hyperprolinaemia and an excess of proline, hydroxyproline, and glycine in the urine. Type I is associated with mild mental retardation, photogenic epilepsy, and renal disease, and PC cannot be detected in the body fluids, or in vitro after incubation of a liver biopsy with proline. Type II is characterized by epilepsy, mild mental retardation, and the absence of renal disease, and excessive amounts of PC can be detected in the body fluids.

Hyperprolinaemia type II has recently been diagnosed in a girl aged 18 years, and appears to be the third case so far reported. She is the fourth child of parents who are first cousins. The parents and 3 surviving sisters are of above average intelligence. A fourth sister was mentally retarded and died in 1953 of what was thought to be measles encephalitis. However, histological examination of the brain (Dr. Brierley) produced no evidence of inflammation.

The patient is mildly mentally retarded (IQ 74) and has petit mal epilepsy, controlled by ethosuximide. EEG shows a spike and wave pattern; renal function is normal. She excretes several grams of proline per day, and the urinary excretion of hydroxyproline and glycine is also increased, but to a lesser extent. The serum proline level was twice found to be between 20 and 30 mg./100 ml. Excess of pyrroline carboxylic acid could be detected in the body fluids by its reaction with o-aminobenzaldehyde, and by chromatography.

As in Efron's cases, no excess of proline was found in the blood and urine of the parents and of two sisters. Prolin, a non-essential amino acid, is readily synthesized in vivo from glutamic acid. Therapy with a diet low in proline is, therefore, unlikely to be effective.

**Reference**


**Pulmonary Sequestration.** D. I. Rushton and A. H. Cameron (The Children's Hospital, Birmingham). The wide range of malformations of the tracheobronchial tree and its vascular supply was discussed and illustrated by a description of the findings in five cases. Attention was drawn to the confusion in the present terminology, and a revised classification, which takes into consideration the relevant features of normal embryology and their pathological deviations, was suggested. (To be published in full.)

**Laboratory Diagnosis of Rubella.** J. A. Dudgeon (The Hospital for Sick Children, Great Ormond Street). Accurate diagnosis of rubella is of paramount importance because of the risk of foetal malformations following maternal rubella in the first trimester of pregnancy. Diagnosis on clinical grounds can be extremely difficult because rubella lacks a pathognomonic sign, simulates other exanthetic disorders such as measles and enteroviral infections, and because of the marked clinical variations that occur. The need for accurate diagnosis is enhanced by the fact that rubella is the only virus known to have teratogenic action.

Virological tests can now produce useful information to confirm or refute the diagnosis in a suspected case of rubella. First, attempts should be made to recover virus from the patient during the acute phase of the illness. Swabs should be collected from the nasopharynx preferably during the first four days after the onset of the rash and should be inoculated either into the primary green African monkey kidney cultures or into RK13 cells. The RK13 cell line, in which rubella virus produces cytopathic changes, is equally good as a cell system for virus isolation as for estimation of neutralizing antibody. Secondly, serological tests should be carried out on paired specimens of sera to determine the patient's immune status to rubella. Preferably both neutralization and complement-fixation tests should be carried out in parallel. Neutralizing antibody develops rapidly and persists indefinitely, whereas complement-fixing antibody develops more slowly and does not persist for longer than a few years. By carrying out both tests together it is frequently possible to determine whether a patient was immune at the time of exposure or whether recent infection was likely to have occurred. Serological diagnosis of congenital rubella is also possible on account of the persistence of neutralizing antibody and the raised IgM values in infancy.

**Intrauterine Cardiac Failure Associated with Premature Closure of the Ductus Arteriosus.** H. G. Kohler (Maternity Hospital, Leeds). Intrapartum death, with signs of foetal distress, in the 42nd week of gestation. Necropsy showed moderate placental hydrops, mild cutaneous oedema, bilateral pleural effusions, and some ascites. The heart was significantly enlarged and was twice the normal weight for body size. There was no lesion to account for this apart from an occluded ductus arteriosus. Histological examination with serial sections revealed a minute lumen.

The relation of the obstruction to the cardiac failure and foetal death, and the possible significance of prolonged gestation were briefly discussed.

**Enterocolitis with Hirschsprung's Disease.** C. L. Berry (The Hospital for Sick Children, Great Ormond Street, London). In a review of 64 cases of neonatal Hirschsprung's disease, it was found that 21 of these infants failed to survive their first admission to hospital. In this respect, delay in the diagnosis and treatment appeared to be significant.

At necropsy it was found that 11 cases showed the changes associated with ulcerative enterocolitis. Histological findings resembled those seen in the localized Schwartzman reaction. It was possible to produce the disease experimentally in the rabbit colon, using an experimental system resembling this reaction. The therapeutic implications of this finding were discussed.

**Fetal Granulomatous Disease of Childhood.** J. Huber (Pathologisch-Anatomisch Laboratorium,
Groningen, Netherlands). The necropsy findings in a boy of 3½ years were presented. For two years he had suffered from recurrent supplicative lymphadenitis of the neck and pericarditis. The liver and spleen were enlarged. There was hyperglobulinaemia but otherwise serum immunoelectrophoresis was normal. Leucocytosis was present during active infection and Staphylococcus aureus was cultured repeatedly from the draining abscesses in the neck. He died with generalized sepsis.

There were miliary abscesses and granulomatous foci in spleen, liver, lymph nodes, and lung. In the lung, small 'tubercles' were found with giant cells, and epithelioid cells surrounded by a rim of lymphoid cells. There were old quiescent abscesses in the pericardium extending through the diaphragm to the liver capsule. The reticuloendothelial system in the liver, spleen, lymph nodes, and thymus was full of pigmented lipid histiocytes. The yellow brown pigment had the staining properties of lipofuscin.

This syndrome, called *fatal granulomatous disease of childhood*, was first described by Landing and Shirkey (1957). So far, 19 cases have been reported, all in the U.S.A. The disease occurs only in boys, inheritance being sex-linked recessive. The aetiology of the disease was unknown until recently when Holmes, Quie, Windhorst, and Good (1966) described a defect in the granulocytes. Phagocytosis of bacteria occurred normally but there was failure to digest and kill ingested bacteria.

Further work needs to be done to clarify the defect which might be a disorder of lysosomal enzymes in the granulocyte. Although the disease is rare and this is the first case to be described in Europe, more cases are likely to be discovered once attention has been drawn to the syndrome. Study of the families might then be possible to define the defect further.

**REFERENCES**


**Ovarian Tumours in Children.** R. A. Langley and J. K. Steward (St. Mary's Hospital, Manchester).

43 ovarian tumours occurring in children were reviewed. These were drawn from the Manchester Children's Tumour Registry and from the Regional Ovarian Tumour Register. 29 of the tumours were of germ cell type, 1 serosal, 5 sex-cord mesenchymomas, 1 rhabdomyosarcoma, 1 ovarian tumour associated with Burkitt's disease, and 1 broad ligament teratoma. 5 tumours were undiagnosed. Particular attention was drawn to the characteristic features of 2 recently recognized types of germ cell tumour, viz. the gonadoblastoma and endodermal sinus tumour.

**Vasculature of the Lung in the Neonatal Respiratory Distress Syndrome.** J. Lauweryns, T. Lerut, and Cl. de Corinck (University of Louvain, Belgium).

A radiological, microradiological, histological, and histometrical study of the pulmonary arterial vasculature after injection with barium sulphate solution at pressures of 10, 20, 30, 40, 60, and 80 mm. Hg was undertaken in 10 infants who died of histologically proven hyaline membrane disease. The same technique was used with a control group of lungs from 12 4-day-old normal Texel lambs.

In hyaline membrane disease the filling of the arterial network was incomplete. Histometry of the diameters of all injected and non-injected vessels revealed that the barium solution had filled nearly all main pulmonary arteries, and almost no pulmonary arterioles. In the control group there was filling of practically all main pulmonary arteries and small muscular pulmonary arteries, as well as the majority of the pulmonary arterioles.

These observations argue strongly in favour of a disturbance of pulmonary perfusion, localized mainly at the level of the small muscular pulmonary arteries (50 to 30μm) and even more at the level of the pulmonary arterioles (30μm) in hyaline membrane disease. This is in accordance with previous morphological findings (Lauweryns, Bonte, and Van der Schueren, 1961; Lauweryns, 1966) and with the recent findings of Chu, Clements, Cotton, Klaus, Sweet, Thomas, and Tooley (1965), which have shown that pulmonary hypoperfusion is the prominent characteristic of the respiratory distress syndrome of the newborn.

**REFERENCES**


Within the broad spectrum of refractory anaemia those cases associated with thymoma form a distinct group, with features that suggest the likelihood of some failure of the immune mechanism. The female is particularly susceptible, and there may be myasthenia gravis and hypo-γ-globulinaemia. The direct Coombs test is frequently positive and in two cases the coating was a non-γ-globulin. LE cells have been found and there is frequently an antinuclear factor associated with the IgM fraction.

We have examined the effect of sera from such cases upon erythropoiesis and myelopoiesis using short-term bone-marrow from cultures from a normal donor. Incorporation of 3H-tritiated thymidine and 56Fe uptake was examined, using autoradiographic techniques. Marrow cells were examined after varying times in either normal serum or serum from one of four cases of the thymoma-refractory anaemia syndrome. With the test serum, both red and white cell precursors showed a diminished uptake of 3H-tritiated thymidine and 56Fe uptake into the red cell precursors was diminished.

Cells from the marrow cultures were investigated for the presence of bound auto-antibody using a 'sandwich' immuno-fluorescent technique. In the two cases so far examined we have noted that IgM and IgA were both...
present, while cells from the control culture showed no immunoglobulin coating. Controlled ‘blocking’ experiments suggest that this result is specific.

Although these findings are confined to the examination of elderly cases with this syndrome, refractory anaemia in childhood may have a similar pathogenesis. To date the examination of the thymus from 12 such cases has revealed no neoplasm or changes characteristic of myasthenia gravis. Sera from 4 children with aplastic anaemia, including 3 with erythrogenesis imperfecta, have shown no inhibiting effect upon the bone-marrow and no coating of the cells in culture.

However, investigations for bone-marrow grafting in one case of idiopathic refractory anaemia suggested indirectly a possible causal auto-immune mechanism. Viable lymphocytes from the patient and from control subjects were injected into the skin of potential donors who were direct relatives. The reaction induced by the patient’s lymphocytes was 6-10 times greater, suggesting that the lymphocytes from the patient were reacting against antigens present in the relatives. As certain of these skin antigens are likely to be present in the relatives and the patient, it might be considered that these hyperactive lymphocytes were directly involved in an auto-immune process.

Demonstrations

The following demonstrations were given.