ASSOCIATION OF CLINICAL PATHOLOGISTS:
44th SCIENTIFIC MEETING

The forty-fourth scientific meeting was held at Leeds on July 20, 21, and 22 under the Presidency of Dr. Norah Schuster.

The Presidential Address

Dr. SCHUSTER'S presidential address was entitled "Nec silet mors," and it told of the increasing demands which advances in medicine and surgery made upon pathologists who undertook necropsies; to-day they must needs pay attention to parts of anatomy which 25 years ago they could safely ignore, but as a profession doctors were always willing to learn.

A full medical and occupational history was essential for the pathologist at the time of the necropsy, otherwise there might be great wastage of material.

The presidential address will be reported in full in the year book of the Association of Clinical Pathologists. The year book will be published early in 1951.

The inaugural session was devoted to a consideration of allergic diseases of blood vessels.

Polyarteritis Nodosa

Dr. G. DISCOMBE (London) reviewed 16 proved and six suspected cases of polyarteritis nodosa. Laboratory investigations did not always help in the diagnosis, for biopsy was sometimes negative. Lesions might heal and, if in the kidney, could produce an essential hypertension, the changes of which might almost completely obliterate those of polyarteritis nodosa. Eosinophilia, although common and usually demonstrable by direct counts during the active phase, was not an essential part of the syndrome. Three cases were described to illustrate the variable symptomatology.

Dr. W. PAGEL (London) discussed some unusual aspects of the histology and the question of aetiology. Subendothelial swelling due to permeation of fluid seemed to be followed by exudation of fibrinogen with subsequent necrosis, mostly eccentric, of the vessel wall, a breach in which became plugged with fibrin. Fibrin was deposited, too, both inside and outside the necrotic wall. He preferred to reserve the term "fibrinoid" for changes which failed to show the staining affinities of fibrin, and which sometimes occurred in positions which did not always favour the assumption that one was dealing with fibrin which had lost its staining affinities. In his opinion the differences between polyarteritis nodosa and the "pararheumatic" diseases, including lupus erythematosus disseminatus, dermatomyositis, and temporal arteritis, concerned the natural history of the disease and the preferential site and distribution of the basic change rather than the basic histology, which appeared to be identical. In polyarteritis nodosa extra-mural foci involved the collagen fibres and were indistinguishable from the acute infiltrative changes in rheumatic fever, lupus erythematosus disseminatus, and dermatomyositis. Preservation of the argentaffin reticulum-fibrils with loss of staining affinities of the collagen fibres could be found in the lesions of polyarteritis nodosa, while giant cell granulomas, reminiscent of
Aschoff nodules and the picture of temporal arteritis, were not uncommonly found. In some instances healed polyarteritis nodosa appeared to be the basis of an eosinophil-celled alveolitis (Loeffler's syndrome) associated with exfoliative dermatitis and asthma (in one case terminated by cerebral haemorrhage). While in these cases the arterial changes appeared to be burnt out, the eosinophilia was active, so that it was not necessarily to be interpreted as a cellular reaction to local arterial necrosis. Intradermal injections of heat-killed streptococci in healthy persons and in rheumatic and other patients who had volunteered had established the significance of bacterial antigens in the reproduction of the changes characteristic of polyarteritis nodosa. Both the histological and experimental evidence supported the view that polyarteritis nodosa and the related diseases were an expression of the hyperergic response to any aetiological factor, including bacterial (notably streptococcal) antigen.

Dr. I. Rannie (Newcastle-upon-Tyne) described the value of biopsy. A positive result was obtained in eight out of twelve cases, the four unsuccessful biopsies being explained either by the unsuitability or insufficiency of the material submitted. In five of the eight positive instances biopsy was carried out for confirmation of diagnosis; four were taken from the muscle and one from a skin nodule. The diagnosis of polyarteritis nodosa was established as a chance biopsy finding in the remaining three cases, the organs submitted being respectively appendix, liver, and cervix uteri and ovaries. Muscle was the material of choice; a tender area should be chosen for excision, and a negative report should not be issued until serial sections had been studied.

Professor T. Crawford (London), discussing the experimental production of polyarteritis nodosa, said that there were two main types which had led to the production of lesions in animals closely resembling those of polyarteritis in man. The first, introduced by German pathologists about 1930 and used extensively by Rich and Gregory in the U.S.A., consisted of the administration of foreign protein to a suitable animal such as the rabbit. The second, described in this country by Wilson and Byron, depended upon the production of hypertension by some procedure such as the clipping of a renal artery in rats. The interpretation of these experiments which the speaker favoured was that the first procedure led to a tissue-antigen-antibody reaction characterized by necrosis and fibrin deposition in the vessel walls and a cellular reaction around the injured area, whereas with the second procedure sudden elevation of blood pressure caused damage to the less well supported arteries and this again led to necrosis and fibrin deposition in the vessel wall, with a secondary cellular response as in the former lesion. When considered in conjunction with knowledge gained from clinical sources, the former of these experimental procedures seemed to constitute a closer parallel to the conditions of the human disease than did the latter. Study of these lesions might well lead to a better understanding of the human disease and of the effects of various agents upon it.

The sessions which followed provided a varied programme.

The Pathology of Measles

Dr. G. B. S. Roberts (Glasgow) reported the necropsy findings in a child who died during the prodromal stage of measles with Koplik's spots. Convalescent measles serum had been given 12 days previously. Death from a fulminating pneumococcal meningitis occurred before the appearance of the rash. The lymphoid tissue throughout the body showed hyperplasia of the germinal centres with the formation of large multinucleate giant cells of the Warthin-Finkeldy type. A second case was mentioned, in which a cervical lymph node, removed at operation, was found to show typical Warthin-Finkeldy giant cells. Although this child had been
exposed, a clinical attack of measles did not develop, so that it appeared possible that infection could produce histological changes without any clinical manifestation of the disease. Giant cells found in the lung of the fatal case contained large numbers of acidophilic intracytoplasmic inclusion bodies which showed great variation in size and shape.

An attempt to communicate the disease to rabbits with intravenous inoculation of citrated blood taken from patients on the day of appearance of the rash was unsuccessful.

The Study of Malignant Cells in the Nose and Throat

Dr. I. Friedmann (London) gave an account of his experiences with the Papanicolaou method of diagnosis as applied to laryngeal and nasal secretions collected on gauze or cotton-wool swabs attached to long straight or curved swab-holders or wooden applicators. The Papanicolaou smear was at its best in squamous-cell carcinoma, in particular of the larynx, whether intrinsic or extrinsic.

Experimental Studies on Prothrombin

Dr. T. B. Magath (Rochester, Minnesota), who conveyed to the Association greetings from the American Society of Clinical Pathologists, discussed various phases of the prothrombin problem, and described a convenient one-stage technique.

Plasma, serum, and platelet extracts possessed activity concerned with the conversion of prothrombin to thrombin. Since zymin plasma produced a conversion deficiency which differed from that produced by ageing or by ammonia, it was apparent that there was more than one conversion factor. An apparently low prothrombin value might be caused by a lack of one or more conversion factors. The thromboplastic effect of platelets was due in part to an associated prothrombin conversion factor, while complement had been shown to possess properties very like some conversion factors in plasma. Several experiments were described and critical values for dicoumarol therapy given.

"Sixth Day Disease"

Drs. R. Aidin and G. H. Tovey (Bristol) gave an account of "sixth day disease," a syndrome consisting of prematurity (which occurred in all but one instance), jaundice, and kernicterus, with death usually about the sixth day of life. In their experience, kernicterus was most commonly found in this condition, 25 examples, unassociated with haemolytic disease, having been found in a series of necropsies on 144 premature infants. While the naked eye appearance was indistinguishable from the kernicterus found in haemolytic disease, clinical, necropsy, histological, and serological studies failed to support a diagnosis of haemolytic disease; there was no evidence of sepsis or syphilis.

Clearance of Staph. pyogenes from the Nose

Dr. R. W. Fairbrother (Manchester) dealt with the problem of the clearance of Staphylococcus pyogenes from the nose. The application of penicillin cream had proved of value, but the clearance was usually only temporary, as Staphylococcus pyogenes tended to recur a few weeks after the cessation of treatment, in spite of
repeated courses of the cream. In some instances the fresh organisms were of a type different from that of the original staphylococci. Some insensitive strains were encountered.

Amoebiasis in Britain

Air Vice-Marshal T. C. St. C. MORTON (Wendover) discussed the carrier rate of amoebiasis especially in Britain. It varied considerably, not only from country to country but from town to town, and was dependent more on the state of hygiene of the community than on the geographical site. It had to be clearly separated from the incidence of actual amoebic dysentery, which in the United Kingdom was extremely low. The reason for this anomaly was probably due to the fact that in the Tropics the opportunities for the free interchange of intestinal flora were considerably greater than in the United Kingdom.

Sixteen out of 1,000 R.A.F. apprentices were found to be carrying E. histolytica cysts. Three cases of amoebic dysentery, one fatal, were encountered in R.A.F. personnel who had never left Britain, but it was significant that two of them had had contact with patients who were suffering from dysentery contracted overseas.

Dr. T. B. MAGATH believed that the incidence of carriers in the United States was of a similar order—namely, about 1.6 to 2.0%, although textbooks often quoted a carrier rate of 10%. It took many years of experience to become proficient in recognizing pathogenic amoebae, and he believed that iron haematoxylin was the best stain for identifying them. Epidemics, in his experience, were almost always water-borne.

The Distribution and Frequency of Non-pulmonary Tuberculosis

Dr. G. S. WILSON (London) gave an account of the survey that was carried out in England and Wales during 1943-5 into the distribution and frequency of non-pulmonary tuberculosis caused by the bovine type of bacillus. The survey was an excellent example of what could be achieved by co-operation between different laboratories making use of ordinary routine material, and Dr. Wilson took the opportunity of thanking the 149 pathologists who had gone to the trouble of collecting specimens for examination by the bacteriologists. In England strains from 994 patients had been examined; of these, 26.3% belonged to the bovine type. The percentage distribution according to site of disease was: meninges 27.1%; cervical glands 46.5%; bones and joints 10.8%; genito-urinary system 12.8%; miscellaneous 10.6.

The proportion of bovine-type strains was highest in the second quinquennium of life, and higher among females than males. It was calculated that in England and Wales during 1944 about 24% of all cases of non-pulmonary tuberculosis were of bovine origin and that 1,300 to 1,400 persons died of milk-borne tuberculosis. In conclusion Dr. Wilson drew attention to the high proportion of mistaken diagnoses in cervical adenitis and suggested that further work was required to distinguish the tuberculous from other forms of the disease.

Dr. G. STEWART SMITH (Exeter) spoke on the problem of non-pulmonary tuberculosis as seen in an urban and rural community in the south-west.

The Epidemiology of the Coxsackie Virus

Dr. A. J. RHODES (Toronto) gave an account of the epidemiology of the Coxsackie virus and of a recent epidemic in Dufferin county, in which both the viruses of poliomyelitis and of the Coxsackie infection appeared to take part; it appeared that the two viruses possessed a similar epidemiology. Difficulties in diagnosis of virus infections were dealt with and many valuable practical hints given.

Dr. F. O. MACCALLUM (Colindale)
described briefly the results of recent investigations made on material sent in to the Virus Reference Laboratory, and the problems of diagnosis to-day.

The Interpretation of Blood Cholesterol Estimations

Dr. J. B. Foote (London) discussed the interpretation of blood cholesterol estimations, favouring the method of Bloor because of its simplicity, reproducibility, and speed. However, in a series of 33 male and 17 female medical students, he and Dr. Merivale had found the normal range to be 150 to 350 mg.%. The method had the disadvantage of not separating free cholesterol from its esters, and rate of colour production and intensity of colour were not the same for free and ester cholesterol. Nevertheless, by careful attention to technique, the errors tended to cancel out. Despite the wide normal range they found that the estimation was of limited value in the diagnosis and control of treatment in 22 cases of myxoedema, but that in 49 examples of thyrotoxicosis the overlap with the normal was so great (68.8%) that the use of serum cholesterol estimations in its diagnosis was precluded. Thirty cases of hepatitis investigated at the Westminster Hospital showed a wide scatter and 90% within the normal range.

Polarographic Serum Waves in Prostatic Disease

Dr. P. G. Wilkins and Mr. R. D. Wilkins (London) compared the polarographic serum waves with the total and formol-stable serum acid phosphatases in a series of cases diagnosed clinically as malignant disease of the prostate: 55% had abnormal polarographic waves and 52% abnormal phosphatase values. However, these did not necessarily coincide, for, while in 25% both values were high and in 25% both values were within the normal range, in the remaining cases one or other determination was above the normal.

Acute Porphyria

Professor C. H. Gray (London) made observations on acute porphyria, eight examples of which had illustrated the great variation in the clinical picture and had supported the view that this condition was wholly different from congenital, light-sensitive porphyria. In all probability congenital porphyria is a genetically determined enzyme abnormality, probably localized in the bone marrow leading to production of Type 1 porphyrins in excess during erythropoiesis. In acute porphyria there might be an excessive production of mono-pyrrolic porphyrin precursors, possibly in sites of porphyrin synthesis other than the bone marrow. The clinical condition might be brought about by direct action of the porphyrins on the central nervous system, by primary changes in the central nervous system resulting in the excessive production of porphyrin precursors, or by the direct action of the porphyrin precursors themselves on the central nervous system.

Oliguria and Anuria

Drs. E. M. Darmady, J. Harkness, and A. Richardson Jones (Portsmouth) drew attention to the fact that oliguria and anuria might follow a large number of precipitating causes, over 60 of which had already been described. The course of the majority of cases could be divided into three phases. The phase of onset, frequently taking the form of shock, showed oliguria and haemoconcentration. This was followed by the anuric or oliguric phase, in which there was a rapid rise in blood urea, a fall in serum sodium and chlorides, and a rise in serum potassium, with its danger of acute
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cardiac failure. It was important to restrict fluids in this second stage. The two methods of controlling accumulation of metabolites, either by dialysis, as a temporary measure, or by a high fat and carbohydrate diet, were reviewed.

In the third, or diuretic, phase, the authors drew attention to the rise in urinary output, which might be extremely sudden in onset and often accompanied by a serious loss of potassium. They had had difficulty at times in keeping pace with the diuresis and with the potassium deficiency. Faulty hydration was the important aspect of the disease.

Agranulocytosis of Glandular Fever

Dr. C. J. Young (Bradford), in considering the agranulocytosis of glandular fever, expressed the opinion that this was a diagnosis which was commonly missed. When looked for, three examples were seen in a period of just over two years, one of which yielded new information on the nature of the condition. In this case the marrow was found to be normal, but the granulopenia persisted in the blood and was still present two and a half years later. The condition was liable to be confused with drug agranulocytosis, but there were four features which helped to distinguish it, although none were specific; these were the Paul–Bunnell test, the constant presence of a few polymorphs in the blood, the normal bone marrow, and the absence of fatalities.

Dr. Young suggested that the mode of production of the agranulocytosis was different from that caused by drugs, being due to the unduly rapid removal of polymorphs from the blood, and not to a failure to produce them in the marrow. It was recommended that glandular fever should be looked for in agranulocytosis which might be due to other causes. When due to this condition the prognosis was good, and the patient need not be deprived of a suspected drug, if this would be to his disadvantage. Bacterial invasion could, however, occur.

The Relationship between Carcinoma in Situ of the Cervix and Invasive Carcinoma

Dr. Oscar B. Hunter, jun. (Washington, D.C.) referred to reports that carcinoma in situ in the cervix developed into invasive carcinoma. However, proof that carcinoma in situ was actually the precursor of invasive carcinoma was presumptive, because of the nature of the lesion. Biopsies might miss an invasive carcinoma, whereas in attempting to examine the cervix adequately conization sections might completely destroy the lesion. Other evidence of the relationships existed in that the statistical incidence of cases of the two lesions were approximately the same. Age incidence statistics, however, revealed that carcinoma in situ averaged round 35 years of age, whereas invasive carcinoma was 45 years. From experience of 20 cases of clinically occult cervical lesions discovered by positive cytological examination, he had discovered extremely early evidence of invasion in what was otherwise carcinoma in situ. This evidence had been found after serial sectioning of the cervixes. More clear-cut proof that carcinoma in situ ultimately developed into invasive carcinoma could probably be made by further study of very early cases of carcinoma in situ. The sheer weight of evidence might then force the proper conclusion.

Laboratory Investigation of Haemophilia

Dr. C. Merskey (Oxford) described laboratory findings in cases of haemophilia.
In Vitro Tests for Haemolysins in Cases of Cold Haemoglobinuria

Dr. J. V. Dacie (London) referred to a number of discrepancies concerning the behaviour in vitro of cold haemolysins in cases of cold haemoglobinuria, as revealed in a survey of the literature. Particularly was this true of the effects of carbon dioxide, the role of complement in the cold sensitizing phase, the thermostability of the haemolysins, and the optimum time for sensitization. There were also suggestions that the patient's serum might sometimes be deficient in complement. He had studied the sera of three patients; in two of them cold haemolysins were associated with cold haemagglutinins at high titres. The pH ranges for the three sera differed; in one case haemolysis did not take place unless the serum was acidified to within the pH range 7.5–6.5. It could be demonstrated that pH affected the adsorption of the haemolysins in the cold sensitizing phase. In two out of the three sera the presence of fresh serum in the cold phase was found to be necessary for the adsorption of the haemolysin. The serum of one patient was deficient in complement.

Dr. Dacie concluded that as real differences existed between the behaviour in vitro of cold haemolysins no test should be regarded as negative unless it had been carried out with serum acidified within the pH range 6.5–7.5 with a further tube set up in which an equal volume of fresh normal serum had been added to the patient's serum, so as to provide an adequate concentration of complement. The patient's serum should never be heated, and fresh serum must be present in both the cold and the warm phases.

Speakers at the dinner of the Association, which was held on July 21, included Professor Matthew Stewart and Dr. Robert A. Moore, Professor of Pathology at the Washington University of St. Louis, Missouri, and Secretary of the American Board of Pathology.