ASSOCIATION OF CLINICAL PATHOLOGISTS:
55th GENERAL MEETING

The 55th general meeting of the Association of Clinical Pathologists was held at the Royal College of Surgeons, Lincoln's Inn Fields, London, from September 29 to October 1, 1955.

The scientific sessions included one devoted to a joint meeting of the Association of Clinical Pathologists and the Association of Clinical Biochemists.

Two formal lectures were delivered, the Panton Memorial Lecture by Professor S. P. Bedson on "Viral Multiplication and the Chemotherapy of Viral Infections," and the Foundation Lecture by Dr. J. G. Greenfield on "The Clinical Pathologist and Encephalomyelitis: Past, Present, and Future." It is hoped to publish both these lectures in full.

Demonstrations were on view for two days, and a new feature was a histopathological quiz, in which Dr. Stewart Smith, of Exeter, conducted a novel experiment by producing four well-documented cases with unusual features in their histological biopsy specimens. Members were invited to fill up a form with their diagnosis and comments. The experiment undoubtedly proved successful, and it is hoped that it will be repeated at future meetings.

The Pathology of Fatal Aircraft Accidents

J. K. MASON said that until recent years the limitations upon airframe and engine structure had been such as to confine the human factors in aviation to the sphere of the physiologist. The introduction of the jet engine had increased the hazards of flight to the extent that aviation pathology has emerged as an autonomous subject with the following objectives.

(a) To correlate the post-mortem findings in victims of fatal aircraft accidents with engineering and other evidence, thus helping to elucidate obscure causes of accidents. (b) To bring to light any recurring injuries which may suggest faults in aircraft design. (c) To apply post-mortem appearances to the assessment of new and experimental types of safety equipment. (d) To search for pre-existing disease in aircrews which might be missed on ordinary methods of medical examination and yet have a bearing on aircraft accidents. (e) To clarify some of the confusion which surrounds traumatic pathology in general and aviation pathology in particular.

Such uncertain aspects of aviation pathology include the pathology of anoxia, injuries induced by pure accelerative and decelerative forces, the aetiology and prognosis of fat embolism, and, most importantly, the pathology of explosive decompression.

The Pathology of the Comet Aircraft Disasters

D. I. FRYER (R.A.F. Institute of Aviation Medicine, Farnborough) reported that from the Comet aircraft which crashed at Elba in January, 1954, and near Naples in April, 1954, 20 bodies were recovered.

The immediate conclusion which could be drawn from the examination of the bodies was that the occupants of the aircraft had been subjected to two phases of violence: an upward and forward displacement within the cabin, and an abrupt deceleration on impact with the sea, following free-fall from altitude. The skeletal injuries received in the latter phase appeared to be post-mortem in type. However, the amount of bleeding from visceral injuries made it difficult to decide whether these had occurred during the first or second phases, and, also, their severity was such that their origins were obscure.

Experiments revealed that the abdominal and thoracic lesions could have resulted from impact with the water, and that the degree of haemorrhage was not incompatible with the theory that the first phase of the accident had already caused fatal injury. Structural, physiological, and pathological considerations excluded explosive decompression as the sole or major cause of the lung injury observed.

Two mysterious types of skin lesion observed were found to be due to scalding by the surface layer of the sea beneath a film of burning kerosene, and post-mortem melanin pigment darkening as a response to the long-wave ultra-violet fraction of sunlight.

Some Histopathology of the Skin

JOHN O. OLIVER (St. John's Hospital for Diseases of the Skin, London), after reviewing briefly the record of biopsies at St. John's Hospital for Diseases of the Skin, over a period of one year, listed those diagnoses which had been made more than 12 times during the year. After defining some of the special terms used in dermatology, Dr. Oliver considered briefly the question of the skin biopsy and its subsequent handling in the technical laboratory, urging the inclusion of normal skin in a biopsy of any skin lesion. The subjects chosen for histological description by means of colour photomicrographs were eczema (with ichthyosis simplex), intra-epidermal epithelioma of Borst-Jadassohn, granuloma annulare, histiocytomas (sclerosing haemangiomata), Lichen planus, lupus erythematosus, and molluscum sebaceous (kerato-acanthoma).
Radioactive Iron Techniques in Routine Haematological Practice

G. WETHERLEY-MEIN, M. S. R. HUTT, W. A. LANGLEY, and M. J. HILL (St. Thomas's Hospital, London) described the techniques used in iron tracer studies with radioactive iron, Fe 59.

The iron is injected intravenously either bound to β globulin or after addition to 1% sodium citrate in saline. Three methods are used to determine how the body deals with the injected dose.

First, it is possible to measure the rate at which it is cleared from the plasma. Samples of plasma are withdrawn at intervals during the first hour and a half after injection and counted in the sample counter. The plasma is cleared exponentially so that it is possible to calculate the half-clearance time. The results are usually what might be expected, in that patients with marrow hypoplasia or aplasia have prolonged half-clearance times, while in polycythaemia vera, haemolytic anaemia, and iron-deficiency anaemia the iron was removed from the plasma very rapidly. The method, however, has considerable limitations. First, it only measures clearance from the plasma and does not show whether the iron is stored or whether it is used for erythropoiesis. Secondly, because of variations in circulation and mixing rates, the normal range is very wide and therefore a clear-cut answer is only possible in extreme cases. Thirdly, it involves the patient in at least five venepunctures in just over an hour.

It is possible to get a better idea of how the body is using iron by using a surface counting technique. Following injection of iron its movement in the body can be followed by applying a directional counter and recording changes in counting rates over the heart (a measure of blood activity), the spleen, the sacrum (a measure of marrow activity), and the liver. In the normal patient there is an initial fall in the heart count associated with a rise in the marrow count as iron is taken up by the marrow. This reaches its peak at about 30 hours and then falls as red cells containing active iron are released into the circulation and this is associated with a secondary rise in the heart count. By contrast patients with aplastic anaemia show no measurable uptake of iron by the marrow, the heart count declines slowly, and a steadily increasing activity over the liver site indicates storage of iron in this organ.

Thirdly, by measuring the activity of samples of red cells on the seventh post-injection day an estimate of the percentage of the injected dose appearing in red cells can be obtained. The percentage utilization depends first on the iron stores of the body and secondly on the red cell turnover. A high percentage utilization in a patient with normal iron stores implies a rapid marrow turnover as in haemolytic anaemia. A low percentage utilization implies either increased iron stores as in haemochromatosis, or a poor red cell turnover as in aplastic and hypoplastic anaemias.

SYMPOSIUM: THE COMPLICATIONS AND Failures OF DRUG Therapy

Professor M. L. Rosenheim opened the symposium.

Bacteriological Aspects of Failures of Drug Therapy

R. KNOX (Guy's Hospital) stated that the problem in drug treatment of infections might be summed up as one of attacking at the right time and in the right place the right organism with the right drug. First, time; the organisms may not be in the right phase of growth. Dormant organisms are much less vulnerable than rapidly growing organisms. Secondly, situation; in a chronic lesion chemotherapy is much less likely to be successful than in a fulminating septicemia. Accessibility is important, and therefore knowledge of how a drug is absorbed is essential. Thirdly, the wrong drug or the wrong organism; there are several ways in which this may occur. (1) Mistakes in the laboratory—deterioration of drugs, wrong identification of organisms, etc. (2) Drug resistance which may either develop in the course of treating a particular patient or may be the result of cross-infection with resistant strains. “Super-infections” with drug-resistant fungi or bacteria must be mentioned. (3) Wrong interpretation or misleading results. There is great variability in sensitivity tests as commonly performed; perhaps the time has come for an attempt to achieve some uniformity in clinical laboratories. The tests themselves also have inherent weaknesses. They tell little about the distribution of resistant organisms in a bacterial population, whether the drug is bactericidal or bacteriostatic and little about the possible value of different combinations of drugs. A particular combination may be highly bactericidal, though the individual drugs are not.

Complications and Failures in Antibiotic Treatment

K. B. ROGERS (Birmingham Children's Hospital) said that some of the failures and complications of antibiotic therapy could be anticipated, but often one was confronted by an unpredicted reaction by an individual patient, or a failure due to a particular condition that prevented an antibiotic acting. The most common complications of antibiotic therapy are due to cross-infection by insensitive organisms such as staphylococci and moniliasis of the lungs or intestines. If there is fibrosis and loculation, as in pericarditis, empyema, or brain abscess, a theoretically effective antibiotic may not penetrate to the infecting organisms. A patient may develop a pyrexia during prolonged penicillin or streptomycin therapy. It may be difficult to prove that the temperature is solely raised because of the antibiotic, and it requires a very fine clinical judgment to discontinue therapy. Allergic manifestations to penicillin and streptomycin are relatively common, such as cutaneous hypersensitivity amongst those who handle them constantly, local irritation at the site of inoculation, and relatively rarely anaphylactoid reactions to penicillin.
Four cases of anuria, which were probably due to penicillin therapy, had been encountered. The anuria lasted from four to eight days in children between the ages of 8 months and 5 years. All recovered after treatment with Bull's regime, although one has a permanent disability after a further complication of monilial cystitis.

Uncontrolled prophylactic "umbrella" therapy has produced staphylococci resistant to a wide range of antibiotics, and these have caused serious complications in surgical units, such as chest centres. This can be overcome if the surgeons and the laboratory co-operate.

Haematological Aspects of Toxic Reactions

William M. Davidson (King's College Hospital, London) said that the use of certain drugs was at present surrounded by fear of unpredictable toxic consequences. The fear was partly real and partly exaggerated, owing to emphasis on the disasters without appreciation of their frequency.

The toxic reactions extend from eosinophilia, mild anaemia, or leucopenia, through the more serious acute haemolytic anaemia, thrombocytopenic purpura, and agranulocytic angina, to the dreaded marrow destruction of aplastic anaemia.

The present method of counting the white cells at intervals or of advising the patient to stop the drug if any symptoms arise is so far from the ideal as to be really useless. The problem does not concern the very poisonous drugs which merely cause toxic reactions because of over-dosage, but those where doses recognized as safe may cause reactions in certain individuals.

Evidence has been produced that some of these drugs, such as amiodopyrine, sedormid, and phenacetin, act directly upon and destroy the circulating cells or platelets. The method of destruction of the cells is often akin to the ordinary immune reaction in the presence of complement, and it seems that the drug forms a complex with the cell protein which, being both antigenic and foreign to the individual, excites an antibody-antigen reaction. In other cases there may be an inherent defect in the cells in certain individuals which make them unduly sensitive, as has been demonstrated in "primquine" haemolysis. Again an abnormal pathway may lead to the formation of abnormal potentially toxic metabolites. Other drugs would seem to act indirectly through the precursor cells in the marrow. Either the marrow is stimulated to produce excessive numbers of leucocytes or depressed up to the point of destruction, with, after an appropriate interval, progressive disappearance of the circulating elements. In such cases there may be some mechanism whereby an abnormally high concentration of the drug or its metabolite is achieved in the marrow, and figures suggesting a 20-fold concentration, as compared with the serum, have been reported. In some cases a type of Arthus phenomenon may develop in and destroy the marrow.

These various mechanisms explain to some extent the differences in the reactions induced by various drugs, and particularly the distressing fact that bone-marrow damage may not become obvious till weeks after the treatment ceased.

Recently work on "primquine," an antimalarial drug, has turned attention to a new facet of the problem, the possibility of detecting, in vitro, red cells which will be sensitive. Further development along these lines might be helpful.

At the present stage it seems that more careful weighing of the real risk with each drug against the danger of the illness and the benefits expected, possibly the examination of the blood and marrow at critical times during the treatment, and above all the finding of less toxic but equally effective drugs offer the best chance to reduce the present, fortunately very small, but nevertheless disturbing, death rate from therapy.

Antibiotic Combinations for the Suppression of Resistant Variants in Urinary Infections

H. Stern and S. D. Elek (St. George's Hospital, London) said that combinations of streptomycin, chloramphenicol, and tetracycline had been tested, using the gradient plate technique, for their value in suppressing the emergence of resistant variants of coliform bacilli from cases of urinary infection.

Streptomycin plus chloramphenicol or tetracycline are the most effective combinations. Not only are resistant variants suppressed but these combinations possess bactericidal activity which is probably an important factor in preventing relapses in urinary infections. Chloramphenicol plus tetracycline prevent the emergence of resistant variants but have little or no bactericidal action against most strains.

Calculations of the chances of a variant arising which is simultaneously resistant to two antibiotics show that the efficacy of combined treatment is explained by the large size of the bacterial population required for such doubly resistant variants to emerge. It is unlikely that during the course of an acute urinary infection sufficiently large bacterial populations can be attained.

It is suggested that these findings have an application in clinical practice.

The Use of the Laboratory in the Diagnosis and Management of Pituitary-Adrenal Syndromes

F. T. G. Prunty, R. V. Brooks, and Ivor H. Mills (St. Thomas's Hospital Medical School, London) reported that indirect methods of assessing adrenal cortical function had recently been reviewed (Prunty, 1950). The behaviour of the gland gives the most important laboratory information in these conditions. The most recent advances concern methods of measuring adrenal cortical secretions and their metabolites and further knowledge of abnormalities of electrolyte and water metabolism. The syndromes under dis-
cussion broadly divide themselves into normal or per-
verted overfunction and decreased activity. Both of
these groups may be associated with change in pitui-
tary activity; some information in this respect has
been obtained by the difficult technique of A.C.T.H.
assay in these patients. The modern use of elective
surgery on adrenals and pituitary must not be over-
looked.

According to current views the adrenal cortex
primarily secretes 17 hydroxycorticosterone (F), corti-
costerone B, aldosterone, and 11-β-hydroxyandro-
stenedione. Well-defined reaction patterns of corticoid
metabolism may be discerned and 14 C.21 end-
products are known in the urine.

Blood corticoid analyses have their own advantages,
but even here only a small fraction is present as free
and active hydrocortisone. As with urine metabolites
the vexed question of relative amounts of "F" and "B" secreted by the adrenal is raised and also the
problem of conjugates.

The application of these techniques to the diagnostic
problems was briefly surveyed. Predominantly
important is the diagnosis of Cushing's syndrome and
the type of adrenal lesion associated with it. Doubt
which remains may possibly perhaps be dispelled by
the use of A.C.T.H., but special care over the vari-
ability of base-line urine and steroid levels is needed.
Here eosinophil levels can be very helpful when due
precautions are taken.

The method for determining 17-ketogenic steroids is
very valuable but includes estimation of pregnanetriol,
notably present in patients with the adrenogenital syn-
drome. This substance is easily estimated by the
method of Bongiovanni and Clayton (1954). Its assay
and that of 17-ketosteroids are of value in assessing
treatment in this syndrome. The therapy of Cushing's
syndrome and patients under treatment with A.C.T.H.
can also be assessed with the methods discussed.

REFERENCES

The Determination and Significance of 17-Ketogenic
Steroids in the Urine

ARTHUR JORDAN (Sheffield) said that Norymberski
introduced the determination of the 17-ketogenic
steroids into clinical medicine as an index of adrenal
cortical activity; he showed that oxidation would con-
vert some of the metabolites of corticoids into
17-ketosteroids. Over the age of 16, 80% of people
have outputs of 17-ketogenic steroids ranging from
5.7 to 17.7 mg./day. The output increases with the
administration of cortisone or A.C.T.H. The output
tends to be low in Addison's disease and Simmonds's
disease and high in Cushing's syndrome, in virilism,
and in precocious puberty of adrenal cortical origin.
Observation of the output following A.C.T.H. ad-
ministration appears to indicate whether the adrenal
cortex can respond and is a useful diagnostic pro-
cedure in suspected Addison's disease.

Adrenal Corticoid Excretion in Cushing's Syndrome

C. L. COPE (Postgraduate School, Hammersmith,
London) said that isotope studies showed that hydro-
cortisone is rapidly metabolized into a number of
compounds of which only a small fraction remain
chloroform soluble. Chloroform extracts of urine
will thus contain only a part of the adrenal metab-
olites, and this may not be a constant fraction of the
total. Of the many chemical methods proposed for
measuring adrenal activity some suffer from chemical
unreliability, but others, though chemically valid, will
estimate an empirical fraction of the total metabolites.
Whilst most metabolites disappear almost completely
from urine when adrenal function ceases, they do
necessarily all increase proportionally when adrenal
function is stimulated.

Since hydrocortisone (F) is the natural product of
the adrenal, its concentration is likely to reflect adrenal
activity most closely. The behaviour of this steroid
has been compared with that of tetrahydrocortisone
(THE) and of tetrahydrocortisone (THF). These
have been estimated by separation on paper chromat-
grams and the use of blue tetrazoilum.

In a series of nine cases of Cushing's syndrome the
mean excretion of hydrocortisone was eight times the
mean for normals, but THE excretion was only 1.8
times and THF only 2.7 times the normal mean.

Stimulation of three normal subjects with A.C.T.H.
increased F excretion 7 times, but THE only twice and
THF 2.5 times. In three cases of Cushing's syndrome
similarly stimulated, F excretion was increased an
average of nine times but THE and THF only 1.1 and
1.3 times respectively. Similarly, if Cushing's
syndrome is inhibited by 9 fluorohydrocortisone a
much greater reduction of F output than of the metab-
olites is achieved.

Changes in urinary F excretion reflect more rapidly
and more sensitively variations in adrenal activity
than do changes in such metabolites as THE or THF,
which are comparatively rough indices.

The Significance of the Blood Acid and Alkaline
Phosphatase Values in Cancer of the Prostate

STANLEY WRAY (Middlesbrough) said that the signi-
ficance of the blood acid phosphatase value was
assessed in 500 miscellaneous patients, 407 of whom
had prostatic disease. It is shown that the formal-
dehyde-stable fraction is a better indication of the
presence of cancer of the prostate than is the more
usual investigation of the total value. It is also found
that urinary retention may be itself cause a moderate
increase in the blood acid phosphatase and that it
must be relieved before reliable results can be obtained.

It is also shown that, when the blood alkaline phos-
phatase is estimated and graphically recorded in cases
of cancer of the prostate with bone secondaries on stilboestrol therapy, a definite pattern of response is obtained. This response pattern or alkaline phosphatase "kick" may be used in cases of prostatic cancer to (1) confirm diagnosis, (2) aid in doubtful cases, (3) help to assess the presence of osseous spread, (4) help in the choice of a therapeutic agent, and (5) act as "end-point" when assessing the value of therapy in other forms of cancer which give rise to bone secondaries.

The Effect of the Ingestion of Potassium Salts on the Excretion of Salt-retaining Corticoids in the Human Subject

H. Ellis C. Wilson (Glasgow) reported that it had been shown in the normal subject that the plasma K falls after the ingestion of acid or alkaline K salts. It was suggested that tissue saturation and not plasma level controls the rate of K excretion (Wilson, 1948). The present investigations show an increase in the amount of salt-retaining corticoid in the urine (rat assay) after taking potassium salts. As the plasma K does not rise any direct effect on the pituitary or adrenal would be excluded. It is suggested that the K coming to the liver from the alimentary canal inhibits the breakdown of the corticoid. The increase in corticoid in the blood causes K excretion and a tendency to fall in plasma K which is made up by release of the ingested K from the liver. The hypothesis is put forward that the liver is one of the main factors controlling the amount of salt corticoid in circulation, adjusting the breakdown according to the amount of K exogenous or endogenous coming to it. The scheme suggested, along with the experimental results, shows that there is a quickly responsive mechanism for keeping the plasma K constant. This effect of K on the output of salt corticoid may be of significance in conditions where there is frequently a loss of K from the muscles associated with an increase in salt corticoid in the urine, such as congestive heart failure and nephrosis (Fox and Slobody, 1951). It is suggested that the release of K from the tissues may initiate its excretion by the mechanism proposed above.

References

Aspects of Hyphysectomy

D. N. Baron (Royal Free Hospital, London) described the use of hypophysectomy and of radiation destruction of the hypophysis in the treatment of malignant disease, and the experience gained by the study of patients on whom the operation had been performed by Mr. E. J. Radley-Smith. Of 13 female patients with carcinoma of the breast who had been operated on within the past year, five had had a good result, with complete relief of pain and variable regression of the metastases. The rationale of the operation is the removal of somatotropin and lutetropin, as well as of A.C.T.H. and gonadotropins, for certain tumours of breast and prostate are dependent on hormones for their continued spread. It is too early to state whether hypophysectomy will replace adrenalectomy plus oophorectomy in the treatment of carcinoma of the breast.

The tasks of the chemical pathologist in the pre-operative assessment of patients (with particular regard to their adrenal function), in the biochemical control of the disturbances of metabolism, and in the difficult problem of assessing whether hypophysectomy has been complete, were discussed. Much further research is required on the latter problem, and on the aetiology of the different phases of water diuresis that follow the operation.

Blood Aceto-acetate Levels in the Immediate Post-operative Period

L. Naftalin (Lincoln) said that it had been shown by other workers that in the first post-operative days endogenous fat is burned at the rate of (approximately) 2,250 cal./day, i.e., many times the rate observed in semi-starvation. On the assumption that increased aceto-acetate is formed only when 2-C fragments are being produced in excess of immediate tissue needs serial examinations were made of blood acetoacetate by the method of Walker (1954) in the hope of timing the switch-over to fat utilization.

Evaluating the results account has to be taken of starvation ketosis and certain other variables: nevertheless, a sharp rise in the blood acetoacetate level appears to occur regularly at an early stage after operative trauma, and sometimes after an anaesthetic (intravenous pentothal) only. The immediate rise is probably an adenalfen effect: the first high peak at four to five hours post-operatively may also be due to adrenaline, since A.C.T.H. and cortisone have been shown to depress blood acetoacetate levels (Kinsell et al., 1951). The curve of blood acetoacetate against time may therefore show a dip before rising to a further peak, in excess, sometimes far in excess, of the level produced by simple starvation at a comparable time.

Also the effect of post-operative transfusion of blood or glucose at or immediately after operation was studied: the results suggest that, after the immediate calorie value of the material transfused has been made use of, the post-operative pattern of a high blood acetoacetate level returns. In three well-defined cases of post-operative ileus no rise in blood acetoacetate was found. The reason for this may lie in it, is suggested, in the temporary ion poisoning of the aceto-CA-kinase enzyme system.

References