ASSOCIATION OF CLINICAL PATHOLOGISTS:
50th GENERAL MEETING

The fiftieth general meeting of the Association of Clinical Pathologists was held in Exeter on March 26, 27, and 28, 1953.

Dr. A. Jordan was Chairman at the first session.

Effect of “Benemid” on Uric Acid Excretion

Dr. E. N. ALLOTT said that in the treatment of gout there were two problems: (1) the relief of acute gouty pain, and (2) the prevention of the accumulation of uric acid and formation of tophi. The effect of “benemid” is purely on the excretion of uric acid. Benemid, which was devised to diminish urinary penicillin output by blocking tubular excretion, increases uric acid output by blocking tubular reabsorption. The effect of 1 g. of benemid lasts for some eight hours, and urinary uric acid excretion may be increased from 0.8 mg. per min. to nearly 3 mg. per min. In a normal individual with a “miscible pool” of about 1.5 g. uric acid the increased excretion after benemid may cease after a few days, but in the gouty individual with a greatly increased “miscible pool” the rise may persist for many weeks. The increased excretion, with a prompt fall in the blood uric acid level, has no effect on acute gouty pain; one patient with advanced tophaceous gout in an acute attack had the serum uric acid level reduced from 9 mg. per 100 ml. to 4 mg. per 100 ml. in three days by 2 g. benemid daily, without any relief of pain; increase of benemid to 3 g. daily had no effect on pain, but this was promptly alleviated by A.C.T.H. without any further significant fall in the serum uric acid level. There is, however, some evidence from American experience that prolonged use of benemid may reduce frequency of gouty attacks. There is no evidence of any permanent renal change after prolonged use of the drug.

Creatine Examinations and their Value in Muscle Disorders

Dr. J. N. CUMINGS described creatine metabolic experiments in 67 cases of muscle disorder. The conditions consisted of myotonia, myasthenia, myopathy, neuronopathy, dermatomyositis, and porphyrinuria.

Daily urinary creatine, creatinine, and guanidoacetic acid were estimated, and blood levels before and after a creatine-tolerance test were also estimated. Normal results were obtained in myotonic patients and in some cases of myasthenia. A grossly diminished tolerance to ingested creatine was found in generalized myopathy, but not in any other disease except in old cases of myotonia with marked atrophy. Guanidoacetic acid was unaltered in all conditions except porphyrinuria, in which there was a considerable diminution which, on recovery from the paralysis, changed to a marked excess.

Infantile Renal Acidosis

Dr. W. W. PAYNE said that a child with infantile renal acidosis typically presents with a history of normal birth and progress until reaching 4 to 6 months of age. Then anorexia, vomiting, and constipation, with failure to gain weight, occur. The infant is irritable but hypotonic, there is wasting and dehydration, and faecal masses are felt in the abdomen. The urine is alkaline, with a trace of albumin and a few leucocytes, and often a slight growth of Bact. coli or proteus is obtained. The plasma chloride level is raised above 115 mEq and the bicarbonate level lowered below 18 mEq. With good nursing the dehydration may be corrected, but the other symptoms persist, and a further blood examination after rehydration still shows a lowered bicarbonate but not always a raised chloride level. Despite the acidosis the urine is persistently neutral or alkaline. With no treatment there is usually a steady deterioration, but a few infants after a few difficult weeks will recover without treatment. The effect of giving sufficient alkali by mouth to correct the acidosis is striking; the anorexia and vomiting cease, the temper improves, and the weight begins to increase. In 13 of our 35 cases careful radiographs of the abdomen showed shadows in the renal areas suggesting calcium deposition. The diagnosis rests on the initial clinical picture, a persistent reduction of the plasma bicarbonate level and an alkaline urine. No other condition (except forced hyperventilation) will produce an alkaline urine with acidosis. In all uncomplicated cases the final outcome has been complete return to normal after a period of treatment varying from two to 30 months.

For the second session Dr. J. N. Cumings took the chair, and two papers were read.

The Physiology of Fat Metabolism

Dr. A. C. FRAZER said that, according to the partition hypothesis of fat absorption, fat is partly hydrolysed, giving rise to fatty acids and lower glycerides, which with bile salts, cause fine emulsification of the fatty material. This particulate material passes into the intestinal cell, where triglycerides are re-formed and some phospholipids are synthesized. Particulate glycerides pass in the chyle into the systemic blood, causing hyperlipaemia. Water flow and pumping of the villi may be important factors in particular
absorption. Fatty acids that can be removed from the oil into the water phase may pass into the portal blood. The basic concepts of this hypothesis have now been amply proved by studies with labelled fats (Frazer, 1952a).

Assessment of fat absorption in man is most satisfactorily carried out by the daily fatty acid balance method (Van de Kamer, Huinink, and Weyers, 1949). The intraluminal phase can be directly studied by intubation. In pancreatic enzyme deficiency intraluminal emulsification does not occur, particulate absorption is impossible, and the chylomicrograph is flat. Intraduodenal injection of finely dispersed emulsion causes a normal chylomicrographic peak (Frazer, 1952b), provided that the absorptive capacity of the upper intestine is normal. In the sprue syndrome, however, the intraluminal phase of fat absorption is normal and the defect is secondary to depression of the absorptive capacity of the upper small intestine (Frazer, 1952c). This can be demonstrated by glucose and urea absorption, using the intraduodenal drip method and by differential radiography, using flocculable and non-flocculable barium sulphate, and confirmed by the fact that fat absorption becomes normal after the removal of wheat gluten from the diet of children with coeliac disease. The subsequent administration of gluten causes a return of the absorptive defect (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952).

References

Osteomalacia in Steatorrhea

Dr. P. Fourman said that in Great Britain osteomalacia was seen most often in patients with steatorrhea. The patients complain of pain and they may suffer spontaneous fractures. Radiographs usually show generalized rarefaction of the bones; pseudo-fractures may occur. In blood taken from the fasting patient the serum phosphate level is low, the phosphatase level is raised, and the serum calcium level is usually low. The deficiency of calcium in these patients is the result of an excessive faecal loss of calcium. We have measured the effect of vitamin D and calcium on the absorption of calcium in such patients by 12-day balance studies.

Vitamin D in a dose of 10,000 units daily by mouth did not improve the absorption of calcium. Vitamin D given in the same dose parenterally or in a dose of 50,000 units by mouth improved the absorption of calcium if the intake of calcium was high. It did not improve absorption if the intake of calcium was only moderate, unless the excretion of fat in the faeces was at the same time reduced by reducing the fat in the diet. With parenteral vitamin D and large doses of calcium by mouth these patients became cured of their osteomalacia, but the amount of calcium that they retained was small and the cure was slow.

In patients with osteomalacia secondary to steatorrhea there is a failure to absorb vitamin D. The resulting deficiency of vitamin D is partly responsible for a failure to absorb calcium. In addition there is a failure to absorb calcium because calcium may combine with unabsorbed fat in the intestine to form soaps. Lastly, when these two faults are overcome it is seen that calcium is also directly involved in the absorption defect of steatorrhea.

At the third session the chair was taken by Dr. J. A. Boycott, and four papers were read.

Interference between Antibiotics

Drs. S. D. Elek and Pamela Jewell said that it had been known for some time that the bactericidal actions of pairs of antibiotics might be greater or less than that of each drug alone. Conventional methods used in studying the problem were, however, laborious. They described a simple method for investigating the lethal effects of antibiotics and for demonstrating any interaction between one antibiotic and another.

The method is an adaptation of a technique used by Lederberg and Lederberg for studies on bacterial genetics, is applied as an extension of a sensitivity test in common use, and is simple enough to be included in the work of a routine laboratory.

A sensitivity plate (Fairbrother and Martyn, 1951) is incubated overnight. A wooden block covered with sterile velvet is pressed on its surface and then pressed on a sterile plate. In this way a constant proportion of any viable organisms is transferred free of antibiotic. The number of colonies appearing after incubation of the second plate reveals the proportion of organisms surviving the action of each drug.

To detect antagonism two discs each containing a different antibiotic are superimposed on the primary plate. The lethal effect of the combination is compared with that of each drug alone. To detect synergism two discs are placed 1-2 cm apart, and in the zone where the organisms were exposed to the action of both drugs any decrease in the number of survivors is seen.

Three pairs of antibiotics were tested by this method against 65 strains of common pathogens, including 10 strains of enterococci from cases of endocarditis. It was found that penicillin and aureomycin together showed either antagonism or no interaction; a combination of penicillin and chloromycetin gave similar results. Streptomycin and chloromycetin, on the other hand, showed either synergism or no interaction. In this way for a newly isolated organism it may be said that the first two combinations are likely to be antagonistic, while the third is likely to be synergistic. Further work is required to assess the clinical importance of findings obtained by this simple method.
The Concentration, Microculture, and Sensitivity-testing of M. Tuberculosis

Drs. H. M. Rice and F. C. Rowan said: The recent M.R.C. Report (1953) emphasizes the need for speed in the culture and sensitivity testing of M. tuberculosis. A modification of Pryce's (1941) microculture method, applicable to concentrates of urine, pus, etc., as well as to sputum, gives a high proportion of positive cultures in 2-5 days. Sensitivity tests can in many cases be reported in five days. The method has been used with streptomycin, P.A.S., and I.N.A.H. (results demonstrated). L-J cultures are always made from the same material, so that nothing is lost if the micro method fails. If it succeeds an immense saving of time results. The method is not laborious and requires no special apparatus. Fifty per cent lysed horse blood has proved the best medium.

The use of pancreatin as a concentrating agent has led to more rapid and profuse growth on L-J medium, compared with Petroff's method. In a number of cases it has succeeded where Petroff's has failed; 8% hydrochloric acid is used to kill contaminants. Further work on the use of these methods continues.

REFERENCES

The Laboratory Testing of Tubercle Bacilli for Isoniazid Sensitivity

[This paper, by Dr. D. A. Mitchison, is published in full on page 1f8.]

The Culture of Tubercle Bacilli and Sensitivity Tests in the Routine Laboratory

Dr. W. K. Taylor began by assuming that most laboratories nowadays used the 1/7-in. fluorite objectives. Concentration methods were valuable but in watery sputa might have the reverse effect, and it was much more satisfactory to pick out purulent fragments. Oxalic acid should effect acid-fastness. Papain was a valuable liquefying agent and should be followed by 5% oxalic acid as the most useful disinfectant, having the advantage that no neutralization and only one centrifugation was necessary. Correct timing was important.

As tubercle bacilli had a relatively low specific gravity, centrifuge efficiency was important. An angle head could give 36% greater efficiency in the same centrifuge.

Flotation methods were efficient but tedious, possibly dangerous to staff, and generally unsuitable for subsequent culture. In a small series about 25% of the negative smears from tuberculous cases gave a positive result, using ligroin flotation. If a simple and safe flotation technique leaving viable bacilli could be devised there would be a considerable increase in efficiency.

The increase of sensitivity tests was making great demands on incubator capacity, but this could be overcome to some extent by using a four-bottle technique having 0, 1, 5, and 100 μg of streptomycin per ml. in Dubos medium in screw-cap bijou bottles. This gave three degrees of resistance, slight, clinical, and marked, which simplified interpretation of reports.

At the first session on March 27 the Chairman was Dr. C. E. Dukes.

Acute Haemorrhagic Leuco-encephalitis

Dr. T. Crawford said: This disease was first recognized in 1940 by Weston Hurst in Adelaide, and there are only seven recorded examples in medical literature. Three typical examples have, however, been seen at St. George's Hospital, London, in a two-year period. The condition occurs chiefly in males in the third and fourth decades. There is often a prodromal upper respiratory infection followed, perhaps after a brief recovery, by the neurological stage, which is fatal within a few days. The cerebrospinal fluid shows an increased cell count up to three or four hundreds—principally polymorphs—and there is a polymorph leucocytosis in the blood. The macroscopic lesions consist of petechial haemorrhages limited to the white matter and usually maximal in one or both cerebral hemispheres. They extend downwards a variable distance and may involve the cerebellum and the pons. The most affected parts are oedematous and discoloured.

Microscopically the white matter shows ball and ring haemorrhages, serous and cellular exudate, rich in polymorphs, fibrin impregnation in and around the vessel walls, and capillaries plugged with fibrin. Areas of demyelination and neurofibrillar destruction occur in the haemorrhagic lesions and around many venules, and there is widespread microglial proliferation.

Comparison of the lesions with polyanterioritis nodosa and post-infectious encephalitis, and with experimentally produced hypersensitivity, suggests that the disease results from acquired sensitivity of the white matter to a circulating antigen.

The Technique of Muscle Biopsy

Dr. J. G. Greenfield said: The differential diagnosis of muscular wasting has recently gained importance from the discovery that certain types of myopathy and of myositis may be benefited by treatment with wheat germ oil and cortisone. The muscle selected for biopsy should be superficial, neither extremely wasted nor pseudohypertrophic, and should not control fine movements. Great care should be taken to avoid pinching or unduly pulling on the muscle, which should be carefully dissected out after a ligature has been passed through it for traction. The piece of muscle should be gently stretched during fixation to avoid shrinkage. Zenker or formol-mercuric chloride are the fixatives of choice. Phosphotungstic acid haematoxylin is a valuable stain for cross-striation.

Recent techniques allow of methylene blue or silver staining of nerve endings in human biopsy muscle taken near the motor point of the muscle.

The indications for histological diagnosis of the different diseases of muscle were briefly described.
A Case of Congenital Toxoplasmosis Proved by Isolation of the Parasite

Drs. J. C. Valentine and W. F. Lane said that a woman of 30 years with two healthy children gave birth to a premature infant who survived only a few minutes. During her pregnancy the mother had received a severe insect bite on the leg. She also had abdominal pains, diarrhoea, and vomiting.

Necropsy on the infant showed the abdomen full of deep yellow, almost gelatinous fluid. The cerebral hemispheres were entirely replaced by similar fluid contained within a very thin membrane. The brain stem showed numerous areas of necrosis. There was haemorrhage into the posterior chambers of both eyes and there were opacities in the lenses.

Sections of the brain stem showed chronic inflammation and necrosis, and numerous Toxoplasma were found, mainly in the proliferative form. Chronic inflammation was found in the eye, but no Toxoplasma were seen.

Material from the brain stem was inoculated into mice, and repeated passages by the intraperitoneal and intracerebral route were successful, proliferative, pseudocyst, and free forms all being found.

Serological investigation of the family by Dr. Beverley showed a dye test titre of 1 in 7,000 in the mother shortly after delivery and five weeks later a titre of 1 in 2,000. Her complement fixation titre, originally 1 in 32, later rose to 1 in 80. Her two healthy children were negative both to the dye and complement fixation tests. The father had a titre of 1 in 14 to the dye test but a negative complement fixation test.

Professor T. F. Hewer then took the chair.

"Sertoli" and "Leydig" Cell Tumours of the Ovary

Dr. F. A. Langley said that Meyer separated the arrhenoblastomas from the main body of ovarian tumours. He laid stress on the morphological resemblances between these tumours and the various stages of male gonadogenesis. At least two groups of tumours are included under the term "arrhenoblastoma," viz. those derived from "Sertoli" cells and those derived from "Leydig" cells. Sometimes both types of cell may occur in the same tumour. "Sertoli" cell tumours are composed of tubules and acini and closely resemble the undescended testis. Two cases, one in a woman of 22 and another in a woman of 48, showed evidence of oestrogenic function. The second case, besides showing the usual tubular structure, also showed one area resembling a granulosa cell tumour. This combination of Sertoli and granulosa cells is not surprising in view of their common Anlage. A third "Sertoli" cell tumour was described. This was associated with uterine agenesis. "Leydig" cells were also associated with this tumour. It is suggested that many of these "Sertoli" cell tumours are essentially congenital anomalies, since many of these are associated with developmental defects of the genital tract.

Sternberg described groups of eosinophilic cells occurring at the ovarian hilum in at least 80% of women. He showed that these corresponded closely to extra-testicular Leydig cells both with regard to site near non-myelinated nerves and blood vessels, and with regard to cytoplasmic inclusions. Two cases of tumours of "Leydig" cells were described. The first in a woman of 64 showed signs of masculinization but with normal excretion of 17-ketosteroids. The ovaries were the size normally found in the childbearing period. There was an increase in the "Leydig" cells at the hilus of both ovaries and similar cells could be seen infiltrating the ovarian stroma.

The second patient was 18 years of age, with marked signs of masculinization, but with a "high normal excretion of 17-ketosteroids. A small tumour was removed from one ovary; it contained numerous eosinophilic cells which were identified as of "Leydig" cell type.

Obstruction at the Bladder Neck*

Dr. G. S. Andrews said that squamous metaplasia had been produced in the prostates of man and animals by the injection of oestrogens (Parkes and Zuckerman, 1935; Moore and McLellan, 1938; Sharpey Schafer and Zuckerman, 1941; Lisco and Biskind, 1941; Nanson, 1930), and Zuckerman (1938) had observed large collections of lymphocytes beneath the urethral epithelium of monkeys receiving daily injections of oestrin. Whatever the cause of the condition, this work emphasized that persistent enuresis in children should not be regarded lightly because some of the cases of bladder-neck obstruction, and although the condition tended to clear up at puberty for a short time, usually recurred later.

References


The Persistence of Foetal Structures in the Pyelonephritic Kidney†

Dr. A. G. Marshall said that the initial lesion in pyelonephritis was almost always bacterial embolism of glomeruli, and the question arose whether all glomeruli were equally vulnerable in this respect. Renal infection being common in childhood, and the structural abnormality of the nephron might be associated with imperfect development. He claimed these structures found in the inflammatory foci of infections.
kidneys showed a marked resemblance to foetal nephrons and that they had been regarded without proof as the result of the inflammation on normal tissue. Such structures are more easily recognizable in children's kidneys, where the effects of infection, vascular disease, hydrenephrosis and normal or abnormal maturation have had less time to alter the microscopic appearance. The appearances of rudimentary glomeruli, primitive tubules, partially differentiated connective tissue, and persistent cavernous capillaries were illustrated in nine slides of photomicrographs from children's kidneys. He suggested that failure of reduction of the early generations of the divisions of the Wolffian duct might be the cause of hydrocalyx. It was stressed that all these appearances could be found in kidneys in which infection, vascular disease, and hydrenephrosis were absent, and they could not, therefore, be the consequence of any of these conditions. Dr. Marshall suggested that a patchy dysplasia of the renal cortex was the fundamental underlying condition of pyelonephritis.

Transfusion Siderosis
Professor D. F. Cappell described the post-mortem findings in three cases of aregenerative anaemia which had received repeated blood transfusions, amounting to 48 pints of blood over eight years, 187 pints over three years, and 827 pints over 12 years respectively. In all three pronounced haemosiderosis of the organs was present, the liver, pancreas, stomach and small intestine, spleen, bone marrow, thyroid, and adrenals being notably affected, but the kidneys were relatively free from iron. Chemical analysis of the organs in the third case, which had received about 200 g. iron in transfused blood, revealed over 55 g. of iron in the liver and approximately a further 50 g. in the other principal organs. The amount of iron was thus fully equal to that found in haemochromatosis.

Microscopically, in all three cases stainable iron was found abundantly in the hepatic parenchyma and Kupffer cells, the bile duct epithelium, and the stroma of the portal tracts, in the pancreatic acini and islet tissue and in the cells of the ducts, in the reticulo-endothelial cells and free macrophages of spleen, bone marrow, and lymph nodes, and abundantly in the macrophages of the connective tissues and stroma of organs. The thyroid epithelium was rich in iron, but the colloid was free. The glomerular zone of the adrenal cortex was heavily laden, but the other zones and the medulla all contained small amounts. The anterior pituitary contained a little iron, but there was more in the posterior pituitary, a reversal of the normal finding in haemochromatosis. The kidneys contained iron only in the cells lining the ascending limb of Henle's loop and the distal convoluted tubule as in haemochromatosis but in contrast to the findings in haemolytic states. Pigment having the character of haemofuscin was totally absent, and there was a noteworthy absence of gross fibrosis in the liver and pancreas, indicating that even such large amounts of iron are relatively non-irritating to the tissues. In the third case a noteworthy finding was the presence of amyloid in the intestine, kidney, and especially in the adrenal, a feature perhaps attributable to the transfused globulin.

Analysis of Causes of Transfusion Errors
Dr. G. H. Tovey said: This analysis is based on 24 transfusion accidents reported from hospitals receiving blood from the South-west Regional Transfusion Centre over a three-year period, during which it is estimated that 40,000 transfusions were administered. The accident rate was therefore 1 per 1,660 transfusions. Five of the accidents (21%) were fatal.

In five cases (21%) the cause was ABO incompatibility from a misgrouping of the recipient and a failure or omission of the direct-matching test. Such errors arose mainly because of short cuts in technique. Three of the accidents (12%) occurred because Rh-negative recipients were incorrectly typed as Rh-positive. In two of the cases anti-I-D was present in the recipient's serum, but D-positive blood appeared to be compatible in one case in a capillary matching test, and in the other because the antibody showed a marked prozone effect with albumin-suspended red cells. Failure to detect incompatibility from irregular agglutinins other than anti-D caused five of the accidents (21%), the antibodies being anti-Kell, anti-c (two cases), anti-e, and anti-M. The commonest mistake was the use of a saline-slide technique in direct-matching. Two cases, both fatal, resulted from faulty storage. The largest single cause of error, accounting for nine of the 24 cases, was the transfusion of blood intended for another patient through failure to check carefully the labelling on the blood bottle. It is concluded that accidents from this cause might be fewer if a coloured group report were attached to the patient's case history sheet and each bottle carefully checked against this report before transfusion.

On March 28 the Chairman was Professor R. J. V. Pulvertaft for the first session of four papers.

Phase Contrast Appearances of Cells of Normal Human Blood and Bone Marrow
Dr. A. P. Waterston discussed the advantages and difficulties in the use of phase-contrast microscopy in haematology, and the appearances of normal blood and marrow cells were described and illustrated by photomicrographs. The technique of observation is simple, and gives a renewed stimulus to descriptive morphology. At present the practical applications in routine haematology are few, and it is as a research tool that the phase-contrast microscope is of greatest value, allowing unfixed, unstained living cells to be observed.
The Behaviour of Normal Human Bone Marrow Cultured in Vitro in Fluid Media

Dr. F. G. J. Hayhoe discussed the behaviour of cells of the myeloid series. The technique of culture in a simple fluid medium, consisting of equal parts of Tyrode solution and the patient's own serum, was described, and graphs were shown depicting the quantitative changes in the total nucleated cell count and in the various myeloid cells at different stages of maturity. The findings, based on 26 cultures from 12 normal marrow aspirates, showed that maturation and proliferation of cells took place in vitro in the medium used, but the wide range of normal quantitative responses in the more mature cells was particularly emphasized.

Bone Marrow Changes in Acholuric Jaundice

Drs. J. L. Emery and D. W. Lemmon reported four crises in three children with spherocytic haemolytic anaemia. All crises were associated with reticulocytopenia and with hypoplasia of the erythron in the bone marrow. Recovery was associated with the reformation of the usual hypertrophic marrow. No evidence of increased haemolysis was seen in the crises.

It is suggested that the marrow aplasia is the primary cause of the anaemic crisis and that the aplasia is due to conditional deficiency states induced by the presence in the body of infection on a marrow undergoing prolonged compensation hypertrophy.

Myelocytes in the Peripheral Blood of Women in Pregnancy and the Puerperium

Dr. G. A. C. Summers said that 482 blood films from 343 women in all stages of pregnancy and the puerperium were scanned for myelocytes, which were found in 43% of the films. The factors which appeared to influence the production are those which may be considered responsible for the well-known leucocytosis of pregnancy: a quite moderate degree of anaemia, or practically any disturbance of balanced function in pregnancy or the puerperium, however slight. The case-notes were studied to assess these factors. Graphs were drawn which indicated clear linear relationships between the degrees of leucocytosis and of anaemia and of other disturbances, and that age and parity had no influence.

Control series were run on 100 unsellected hospital patients with leucocytosis, where the incidence, heavily weighted by severe infections and children in the series, was only 9% ; of 100 nurses, where the incidence was nil, and of patients with anaemia of moderate degree, where the incidence was very low. Bias had been avoided in every possible way in making the observation, which was thus seen to be confirmed.

It was concluded that the bone marrow of women in pregnancy and the puerperium is in a sensitive state, and that it does not take much to produce the appearance of a shift to the left in the polymorphonuclear leucocytes, even without the usual leucocytosis of pregnancy and the puerperium.

For the last session on March 28 Dr. G. Stewart-Smith was the Chairman.

Observations on a Case of Cyclical Thrombocytopenia Treated with A.C.T.H. and Cortisone

Drs. B. Creamer and G. Weatherley-Mein presented investigations on a woman aged 44 suffering from thrombocytopenic purpura. The course of the disease was unusual in that nine months after splenectomy it was observed that there was a cyclical variation in the platelet count with purpura and fever in the thrombocytopenic phase. These episodes of thrombocytopenia recurred every fourth day for over one year. The possibility of drug sensitivity—indeed elimination was observed, and it was considered that the probable hormonal disturbance, possibly associated with the menopause, might be responsible. This hypothesis was not established, but the patient was treated with A.C.T.H., cortisone, oestrogens, and testosterone. A.C.T.H. and cortisone produced only a temporary and incomplete modification.

The cyclical variation in bleeding time and platelet count was not inhibited, but the fall in platelets was less marked and the bleeding time was reduced for as long as the patient received either drug. Complete relapse occurred when treatment was stopped.

It did not appear that in this patient the limited action of A.C.T.H. and cortisone could be explained solely on the basis of a reduction in capillary permeability, and the mode of action of these drugs remains obscure.

Similarly the mechanism of the cyclical changes itself is difficult to explain, but the nature of the process suggests an underlying endocrine abnormality.

The Mode of Action of the Circulating Anticoagulant in Acquired Haemophilia-like Disease

Dr. R. M. Hardisty presented a case of a haemorrhagic diathesis occurring in a woman of 71 with chronic rheumatic heart disease and resulting in a fatal intestinal haemorrhage. Clinical and routine laboratory findings suggested that the most likely cause of the disorder was the presence in the patient's circulating blood of an anticoagulant which inhibited thromboplastin formation. Further investigations confirmed this diagnosis, and provided evidence that the anticoagulant was an inhibitor of antithaemophilic globulin. It is suggested that this condition may be due to auto-immunization to antithaemophilic globulin and thus analogous to the acquired haemolytic anaemias and thrombocytopenias.
ASSOCIATION OF CLINICAL PATHOLOGISTS MEETING

A Clinico-pathological Trial of Phthalylsulphacetamide

Drs. W. P. Foster and K. B. Rogers said that phthalylsulphacetamide had been described as an ideal sulphonamide for treating intestinal infections and for reducing the bacterial content of the gut before operation.

The drug was taken by two ambulant healthy adults in a dosage of 0.3 g. per kg. per day for five days. Within two days both were suffering from diarrhoea and abdominal discomfort due to excessive bowel movements. By the fifth day both had severe tenesmus and proctitis. The faecal organisms did not apparently diminish, nor did any organisms disappear during this trial.

A carefully conducted blind trial on student volunteers produced the same set of unpleasant reactions, which were so severe that the students’ work and social activities were interrupted, while there was no evidence of any reduction or alteration in their faecal bacteria. Blood levels were low in the students, but when the first two subjects took the same course, except for an initial dose of 10 instead of 3 g., there was an average blood level of 10.9 mg.% on the fourth day.

A very few cases of Bact. coli type O 111 B 4 infantile gastro-enteritis were treated with the drug without clinical improvement or loss of the organisms. One carrier of Shig. sonnei and one of Salm. paratyphi B were treated without success.

A Fertility Index Derived from Seminological Analysis*

Clare Harvey, B.Sc., said that by a simple calculation based on the observed density, morphology, and motility of the sperm the quality of a given semen specimen could be expressed in a single figure known as the fertility index. The mean value of the fertility index of two or more semen specimens from the same donor is a measure of his fertility. In subfertile marriages the husband may be the principal or sole cause of childlessness if his mean fertility index is below 30, while if it is over 70 the wife’s subfertility is mainly responsible for her failure to conceive. There is a correlation between the fertility index of semen and the ability of sperm from a given specimen to invade and penetrate through cervical mucus in vitro. The index provides a useful method of classifying semen for experimental studies, and has been used in this way in biochemical investigations on semen plasma. Its chief clinical application is in assessing the effects of therapy in subfertile men.

[*This paper will appear in full in the next issue.]