

JOURNAL OF CLINICAL PATHOLOGY

EDITED FOR

THE ASSOCIATION OF CLINICAL PATHOLOGISTS

BY

A. GORDON SIGNY

EDITORIAL BOARD

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ABSTRACTS

This section of the JOURNAL is published in collaboration with the two abstracting journals, Abstracts of World Medicine, and Abstracts of World Surgery, Obstetrics and Gynaecology, published by the British Medical Association. In this JOURNAL some of the more important articles on subjects of interest to clinical pathologists are selected for abstract, and these are classified into four sections: bacteriology; biochemistry; haematology; and morbid anatomy and histology.

BACTERIOLOGY

Action of Chloromycetin on Salmonella. SELIGMANN, E., and WASSERMANN, M. (1949). *Proc. Soc. exp. Biol., N.Y.*, 71, 253.

In an effort to find an effective remedy for salmonella infections in man and animals, the authors, working at the Beth Israel Hospital, New York, have examined the effect of chloromycetin (produced by *Streptomyces venezuelae*) on 68 Gram-negative strains *in vitro*. Of 23 *Salmonella* type 19, including *S. typhi*, were sensitive to 2 μg . per ml., and 4 to 4 μg ./ml. No relation was found between streptomycin resistance and chloromycetin resistance. For experiments *in vivo*, chloromycetin was dissolved in 20% propylene glycol by heating for 10 to 20 minutes at 56° C., the final concentration being 10 mg. per ml. No toxic effects were observed when 2,000 μg . was given by mouth to mice twice daily for 4 days. In contrast to streptomycin, chloromycetin was absorbed from the intestinal tract and growth of the intestinal flora was not inhibited. In mice infected with inocula of 0.1 ml. of 18-hour broth cultures of *S. typhi-murium*, 2,000 μg . of chloromycetin by mouth twice daily for 4 days, or 2,500 μg . subcutaneously twice daily for 6 days and then once daily for 2 days, resulted in some prolongation of survival time. Parenteral treatment was superior to oral in two experiments. The action of chloromycetin was, however, bacteriostatic only and the drug had no curative effect.

Malcolm Woodbine.

Typhoid Fever Treated with Aureomycin and Chloromycetin. (Su alcuni casi di tifo trattati con aureomicina e cloromicetina). SCARZELLA, M., MIGAZZO, C., and CAPPIO, M. (1949). *Minerva med., Torino*, 1, 875.

The authors describe an outbreak of severe typhoid fever in Biella, Italy, in which 26 patients who had been treated unsuccessfully with typhoid vaccine and sulphonamides were given chloromycetin (8 cases) or aureomycin (18 cases). The patients' ages ranged from 7 to 54; 11 of them were male and 15 female. The dosage of aureomycin in adults was 125 mg. every hour for 3 hours, then 250 mg. every 2 hours until the fever subsided followed by 250 mg. every 4 hours for 48 to 72 hours.

Of the two drugs, chloromycetin gave the better results, the temperature falling within 3 to 5 days of starting treatment, headache disappearing, and the general condition improving, often in a most dramatic manner. Aureomycin was by no means as effective as chloromycetin; in one case the temperature dropped only after 10 days' treatment, while 4 patients did not improve at all, although they responded very well to chloromycetin given afterwards. In patients who responded to aureomycin the general condition improved more quickly than the fever subsided. No complications occurred during treatment with either drug, and where such complications existed before starting treatment they were quickly overcome. None of the 26 patients died.

In a control group of 62 patients the fever lasted 25 to 30 days, the mortality rate was 7%, and the incidence of complications 17%. The authors consider that the results obtained with these two drugs were excellent and beyond expectation.

Aureomycin in the Treatment of Penicillin-resistant Staphylococcic Bacteremia.

NICHOLS, D. R., and NEEDHAM, G. M. (1949). *Proc. Mayo Clin.*, **24**, 309.

Of 50 strains of *Staphylococcus pyogenes* isolated at the beginning of 1949 in the clinical laboratory at the Mayo Clinic, 34 were resistant to penicillin. Of these 34 strains, 14 were resistant to streptomycin and all were sensitive to aureomycin. Details are given of the treatment with aureomycin of 6 cases of staphylococcal bacteraemia due to penicillin-resistant strains, in which other forms of therapy had failed. Four patients recovered

Increase in Resistance of Tubercle Bacilli to Sodium *p*-Aminosalicylic Acid: Observations on Cultures Isolated from Patients During Chemotherapy.

DELAUDE, A., KARLSON, A. G., CARR, D. T., FELDMAN, W. H., and PFUETZE, K. H. (1949). *Proc. Mayo Clin.*, **24**, 341.

Cultures of tubercle bacilli obtained from 73 patients were tested for *in vitro* resistance to sodium *p*-aminosalicylate (NaPAS). The patients were divided into 4 groups: (A) received no PAS (46); (B) received PAS (total 70 to 900 g.) for 94 days or less (18); (C) received PAS (total 850 to 1,684 g.), "promin," and streptomycin for 144 to 180 days (4); (D) received PAS (total 950 to 2,250 g.) for 157 to 251 days (5). Egg-yolk agar medium, to which solutions of NaPAS, sterilized by filtration, were added in graded concentrations, was used for resistance tests. The inoculum was 0.1 ml. of a ground suspension of the original culture at about 1 mg. per ml., and the highest concentration of the drug permitting growth after 30 days of incubation was taken as the end-point. The resistances of cultures isolated from groups (B), (C), and (D) before the start of PAS treatment were 0.006 to 0.012 mg. per 100 ml. of medium; as would be expected, the resistances in group (A) (no PAS treatment) were the same. At the end of treatment, the resistances of cultures from groups (B) and (C) had not increased, but those from 4 of the 5 patients in group (D) (receiving approximately the same amount of PAS as group (C)) were now resistant to 1.6 mg. to 6.4 mg. NaPAS per 100 ml. of medium, representing a 200- to 500-fold increase. The main difference between groups (C) and (D), in which the increases of resistance of cultures after treatment were so different, was the fact that PAS was combined with streptomycin and promin in the former group. [The development of strains of tubercle bacilli resistant to PAS by *in vitro* exposure to graded concentrations of the drug has not, so far as the abstracter is aware, yet been reported.]

P. D'Arcy Hart.

Roseola (Exanthem Subitum). HILL, L. F. (1949). *J. Iowa St. med. Soc.*, **39**, 283.

The author summarizes 38 cases, which show the classical features of an infection of sudden onset in children under the age of 3. The fever lasted for 3 to 5 days, without abnormal physical findings, then fell suddenly with the appearance of a morbilliform rash which lasted for 24 to 48 hours. The important laboratory finding was of a leucopenia and lymphocytosis. The cause was probably a virus of low infectivity, as the disease rarely spread from child to child. The differential diagnosis from measles and rubella is easily made from a study of the temperature chart and of the day on which the rash appears. In measles the exanthem appears at the height of the fever, in rubella at the start of the illness, and in roseola infantum as the temperature falls.

N. M. Jacoby.

BIOCHEMISTRY

Dextran as a Plasma Substitute. THORSEN, G. (1949). *Lancet*, 1, 132.

Dextran is now produced commercially—"dextran Ph"—and is a polydispersoid glucose polymer whose average molecular weight is similar to that of albumin. It has been given to 5,000 patients in quantities up to 4 litres per infusion. It is non-toxic, non-antigenic, and virus free, and in Sweden to-day the hospitals rely on it largely for the prevention and treatment of all forms of shock.

After an infusion of 1 to 2 litres the dextran level in plasma rises to 1 to 2.5 g. per 100 ml. The fraction of molecular weight less than 25,000 is soon excreted in the urine, and the dextran level in the latter may rise to 7 g. per 100 ml. without any sign of renal damage. The fraction with higher molecular weight is presumably metabolized. Dextran slowly disappears from the circulating plasma. "In animals to which dextran has been given in repeated infusions, so that the total amount of dried substance corresponds to a third of the body weight, no dextran has been discovered in the brain, lungs, heart, muscle, liver, spleen, kidney or bone marrow . . ." [Further evidence of this is highly desirable.]

The dextran exerts a colloid osmotic pressure and its infusion has corrected states of lowered plasma colloid osmotic pressure, notably in paralytic ileus with oedema of the intestinal wall. In the presence of dextran in the plasma, the plasma protein level may fall as low as 2 g. per 100 ml. without signs of disturbance of the mechanisms of coagulation of the blood or of the formation of antibodies. *John F. Loutit.*

Diagnostic Significance of Urinary Hormonal Assays: Report of Experience with Measurements of 17-Ketosteroids and Follicle Stimulating Hormone in the Urine. ESCAMILLA, R. F. (1949). *Ann. intern. Med.*, 30, 249.

In this paper the results of a study of the daily urinary excretion of 17-ketosteroids and follicle stimulating hormone (FSH) in a number of endocrine and other disorders are recorded. The 17-ketosteroids have recently been subdivided into ketonic and non-ketonic fractions, of which the former has been further separated, by the action of digitonin, into alpha and beta fractions. It is suggested that further fractionation will enhance the diagnostic importance of the 17-ketosteroids, as certain of the compounds seem only to be present in particular clinical states.

High levels of excretion of the 17-ketosteroids were found in carcinoma or hyperplasia of the adrenal cortex, the excretion of the beta fraction being particularly increased in patients with carcinoma. Diminished excretion of the 17-ketosteroids was found in hypophysial infantilism, Simmonds's disease, anorexia nervosa, and Addison's disease. Daily variations in 17-ketosteroid excretion in normal subjects makes the finding of slightly high or slightly low values in a number of conditions of limited clinical value. FSH excretion was measured by bioassay and was found to be consistently high in ovarian aplasia (when the patient was not receiving oestrogen therapy) and occasionally at the male and female climacteric. A low level of FSH excretion was found in hypophysial infantilism, anorexia nervosa, and Simmonds's disease. A long list is given of disorders in which 17-ketosteroid and FSH excretion was normal.

Studies in Diabetic Acidosis and Coma, with Particular Emphasis on the Retention of Administered Potassium. DANOWSKI, T. S., PETERS, J. H., RATHBUN, J. C., QUASHNOCK, J. M., and GREENMAN, L. (1949). *J. clin. Invest.*, 28, 1.

It is becoming well recognized that the hazards of recovery from diabetic coma include a risk of significant deficiency in serum potassium and total body potassium. This paper supplies a detailed quantitative description of the changes in electrolyte

and nitrogen metabolism in 7 patients who recovered from diabetic coma, one patient being observed on two separate occasions. The chief points brought out by the authors are as follows: (1) The serum potassium level was below normal on admission in about half the patients; even when this was not so it fell during the initial period of treatment of the coma with insulin, glucose, and isotonic saline. (2) When potassium chloride was given, either by mouth or intravenously, large amounts of potassium were retained; during a subsequent period without added potassium there was no excretion of the potassium retained in the previous period. The obvious conclusion is that a gross deficit of potassium had developed during coma—since potassium deficiency was present on admission—and also during the usual treatment, potassium balance being negative on the ordinary treatment. (3) As would be expected, large amounts of sodium, chloride, and carbohydrate were retained during recovery from coma. (4) Nitrogen was lost from the body during the early stage of observation and treatment, but was retained during recovery.

Discussing their results, the authors attribute the loss of potassium mainly to extracellular dehydration, with its transfer of water and potassium from the cells, and to the loss of potassium in the diuresis associated with diabetic coma. Subsidiary factors may be the loss of potassium normally associated with glycogen in the liver and with protein in the tissues, and the effect of interrupted carbohydrate metabolism in causing potassium to leave the cells.

HAEMATOLOGY

Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. XXXVIII. Serum Iron Transport. Measurement of Iron-binding Capacity of Serum in Man. RATH, C. E., and FINCH, C. A. (1949). *J. clin. Invest.*, **28**, 79.

In cases of iron deficiency the serum iron level was found to be low, but the total iron-binding capacity was above normal; saturation was below 10%. In cases of chronic infection both the serum iron and total iron-binding capacity were reduced and the saturation was above 10%. The results in pregnancy and in other anaemias and the effects of injections of human globulin are also discussed.

Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. XXXIX. The Anemia of Infection. Studies on the Iron-binding Capacity of Serum. CARTWRIGHT, G. E., and WINTROBE, M. M. (1949). *J. clin. Invest.*, **28**, 86.

The total iron-binding capacity of serum is the sum of the serum iron content and the "unsaturated iron-binding capacity." The "percentage saturation" is calculated by dividing the observed serum iron content by the total iron-binding capacity. In patients with chronic infections the serum iron and total iron-binding capacity were found to be reduced and the percentage saturation lowered. The values rose in patients recovering from infections.

In two patients intravenous injection of metal-combining globulin raised the total iron-binding capacity to normal, but did not diminish the rate of disappearance of iron from the serum. Experimental work in dogs is also referred to.

Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer. FARBER, S. (1949). *Blood*, **4**, 160.

In this important paper are summarized the results of the treatment of children with acute leukaemia by means of aminopterin and related compounds (amethopterin and amino-an-fol). Of 60 children, rather more than 50% showed temporary clinical

and haematological improvement. Two children were still alive 23 and 16 months after the onset of the disease.

The Use of Folic Acid Antagonists in the Treatment of Acute and Subacute Leukemia. A Preliminary Statement. DAMESHEK, W. (1949). *Blood*, 4, 168.

The results are given of treatment with aminopterin and related compounds of 35 patients with acute or subacute leukaemia (31 adults). It is considered necessary to give doses large enough to cause general toxic effects. When remissions have occurred attempts have been made to continue treatment by smaller maintenance doses given orally. Amethopterin, amino-an-fol, and a-ninopterin are less toxic drugs, but less active therapeutically. A-ninopterin may, however, be slightly less toxic in effective doses than is aminopterin. Remissions occurred in nine of the 35 patients.

The Distribution Curve of Erythrocyte Fragility. A Different Method of Presentation of Fragility of Erythrocytes to Hypotonic Saline, with Preliminary Remarks on the Function of Reticulocytes. BOLTON, J. H. (1949). *Blood*, 4, 172.

The author describes a method for recording erythrocyte fragilities (increment haemolysis curves) which demonstrate the distribution of fragility in much the same way as a Price-Jones curve gives the distribution of cell diameters amongst a cell population. Curves drawn in this way have demonstrated that the distribution of cell fragility may be bimodal or even trimodal in certain cases.

Haemolytic Disease of the Newborn: Criteria of Severity. MOLLISON, P. L., and CUTBUSH, M. (1949). *Brit. med. J.*, 1, 123.

This paper contains much valuable factual information, and is based upon a study of 74 cases, mostly treated by exchange transfusion. Five infants were born dead and 19 died later. The haemoglobin level of the cord blood was found to be of prognostic significance; no infant with a value of 14 g.% or over died. Taken in conjunction with the haemoglobin level the bilirubin content of the cord plasma also afforded some indication of the severity of the disease. The strength of the direct Coombs reaction performed on the infant's corpuscles and the amount of free antibody in the infant's serum were, however, not found to be a reliable criteria of severity.

MORBID ANATOMY AND HISTOLOGY

The Effect of Total Thyroidectomy on the Function of Metastatic Thyroid Cancer. RAWSON, R. W., MARINELLI, L. D., SKANSE, B. N., TRUNNELL, J., and FLUHARTY, R. G. (1948). *J. clin. Endocrinol.*, 8, 826.

Twenty-one patients with metastatic thyroid cancer were studied at the Massachusetts General Hospital, and the Memorial Hospital, New York. These patients had metastatic carcinomata which were considered relatively or absolutely non-functional because tracer experiments showed little or no ability to metabolize radio-iodine. In seven cases total thyroidectomy was carried out surgically: in the remainder the thyroid was destroyed by means of a large dose of radio-iodine (I^{131}). Tracer experiments were carried out before and after thyroidectomy to determine whether or not thyroidectomy altered the ability of the metastases to metabolize iodine.

Of these patients, 13 had solid and/or follicular adenocarcinomata, and eight of these metastatic tumours became able to concentrate radio-iodine after removal of the normal gland. This change occurred after periods varying between 1 month and 32 months. Four papillary adenocarcinomata failed to concentrate iodine after thyroidectomy. Three patients with giant-cell carcinoma died within six months after thyroid-

ectomy; in these there was no change in the function of the metastases. In one case of metastatic Hürthle-cell adenocarcinoma no change in the function of the metastases has been observed up to the time of reporting.

Thyroid-stimulating hormone was given to one patient with a solid adenocarcinoma; the metastases in this case did not collect radio-iodine after thyroidectomy and the patient became myxoedematous. After administration of thyroid-stimulating hormone, the metastases were found to collect significant amounts of radio-iodine.

[This paper is of great significance to those interested in the clinical application of radio-iodine and to oncologists in general. This is one of the few instances, if not the only instance, in which interference with normal physiology produces a definite and measurable alteration in the metabolism of neoplastic cells.] *Douglas Findlay.*

Pulmonary Adenomatosis. A Report of Three Cases. DRYMALSKI, G. W., THOMPSON, J. R., and SWEANY, H. C. (1948). *Amer. J. Path.*, **24**, 1083.

Pulmonary adenomatosis accounts for about 5% of all pulmonary tumours and probably results from non-specific irritation. Occurring in the sixth decade, and more commonly in women than in men, the disease runs a course varying from weeks to two years and is without distinctive clinical or radiological features, although it may simulate tuberculosis, carcinoma, or pneumonia. Macroscopically the lung resembles that of grey hepatization, while microscopically the alveolar walls are lined by uniform nonciliated cubical or columnar cells, which may assume papillary formations and which are probably of bronchiolar origin. Mitoses are infrequent. The disease is considered to be a benign variant of the so-called alveolar-cell carcinoma, and has many features in common with pulmonary adenomatosis in sheep (Jaagsiekte).

Of the cases reported here, one shows a small focus of malignant change in the adenomatous cells and another is the second surgical specimen of the condition to be recorded. *R. C. B. Pugh.*

Mast Cells. Their Distribution in Various Human Tissues. JANES, J., and McDONALD, J. R. (1948). *Arch. Path.*, **45**, 622.

Mast cells were proved to be present in the subendothelial layer of synovial membranes, and their number to be increased in cases of chronic inflammation and tuberculosis. They were absent from cartilage, thyroid, kidneys, endometrium, umbilical cord, placenta, and scar tissue. They were more numerous in normal or acutely inflamed organs than in those affected by neoplastic growths. The authors regard it as likely that mast cells secrete heparin, and that this substance is the anticoagulant in synovial fluid. They indirectly confirm this assumption by recording that coagulation occurred in fluid from a haemarthrosis immediately after addition of protamine, a substance which is known to annul the action of heparin. *R. Salm.*

Congenital Pneumonitis in Newborn Infants. ADAMS, J. M. (1948). *Amer. J. Dis. Child.*, **75**, 544.

Six cases of primary virus pneumonitis are described. Characteristic shadows are seen in the radiographs of the lung. Pharyngeal smears contain large numbers of epithelial cells, and almost no bacteria or polymorphonuclear leucocytes. Cytoplasm inclusion bodies in the epithelial cells have diagnostic significance if present in large numbers. In some babies during an epidemic, sneezing and coughing occur without pneumonitis. The mortality rate is in direct relation to the severity of symptoms and signs. In all, pharyngeal smears from both the mother and the infant showed many inclusion bodies.

Ultra-violet Microscopy of Living Malignant Cells. LUDFORD, R. J., SMILES, J., and WELCH, F. V. (1948). *Nature, Lond.*, **162**, 650.

Cells of several kinds of transplantable malignant tumours, fibroblasts from subcutaneous connective tissues, and mesothelial cells were studied. To avoid unnecessary exposure to ultra-violet irradiation suitable preparations were selected by dark-ground illumination. Preliminary studies of the cells were made by phase-contrast microscopy in order to detect signs of injury to cells exposed to ultra-violet irradiation. With objectives computed to wavelengths of 2,570 Å and 2,750 Å, photomicrographs of living cells were obtained without causing appreciable injury to cell structure. It was assumed, since living cells were irreversibly injured by a series of exposures to irradiations of varying wavelengths, that structures showing strong absorption with wavelengths of 2,570 Å and 2,750 Å contained nucleotides.

Mitochondria exposed to ultra-violet irradiation become distorted, then disintegrated, and finally replaced by vacuoles. The cytoplasm of rapidly growing malignant cells contains much absorbing substance. During cell division a regular sequence of changes in the distribution of nucleotides was observed. When the nuclear membrane breaks down at prophase the previously filamentous mitochondria become rounded and carry peripheral deposits of nucleotides. "Ground cytoplasm" is almost devoid of absorbing substance. Chromosomes show strong absorption throughout mitosis. The mitochondria resume their filamentous shape during the last stages of cell division, parallel with the reappearance of nucleotides in the cytoplasm. At this time the chromosomes are clearly distinguishable in the reconstituting nuclei, and nucleoli have not reformed. The nucleus is often surrounded by a relatively clear zone, and no indications were found of a higher concentration of absorbing material immediately bordering the nuclear membrane. Mitochondria rather than nucleoli appear to be implicated in the synthesis of cytoplasmic nucleoprotein. Under suitable conditions nuclei can be seen to contain fine double threads bearing parallel pairs of minute granules which are presumably chromosomes or possibly gene loci. A definite correlation exists between the amount of nucleotides and the rate of cell growth.

A. K. Powell.

Carcinoma Developing in Sebaceous Cysts. PEDEN, J. C. (1948). *Ann. Surg.*, **128**, 1136.

Evidence of carcinoma was present in 14 of 832 sebaceous cysts subjected to microscopy—an incidence of 1.7%. Of the 14, 7 were removed from the scalp, 2 from the face, and one each from the ear, shoulder, arm, forearm, and thigh. Though the incidence does not justify the view that sebaceous cysts are pre-cancerous, it points to the need for their routine histological examination after removal. The growth is usually a highly differentiated squamous-cell carcinoma of low malignancy, and the lymph nodes are not commonly involved. Suspicion of the complication may be aroused if in older people an increase in the size of the cyst has been noted, or pain develops, and under such circumstances treatment should be by wide local excision.

Harold C. Edwards.

A Reorientation on the Histogenesis and Clinical Significance of Cutaneous Nevi and Melanomas. ALLEN, A. C. (1949). *Cancer*, **2**, 28.

This is a careful and well-illustrated study of the histogenesis of pigmented moles and melanomata. The author concludes that these arise, not from any specialized neural cells, but from the ordinary cells of the epidermis. He distinguishes between "junctional naevi," in which the naevus cells are still within or connected with the epidermis, and intradermal naevi, in which the naevus cells have migrated from the epidermis; the former is the usual type in children, the latter in adults. Transitional or combined naevi are frequent. The blue naevus and Mongolian spot, however, are not epidermal in origin but probably neurogenic.

R. A. Willis.