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

Synergism and Antagonism as Displayed by Certain Antibacterial Substances.


This paper records the results of an investigation undertaken to determine the interaction of sulphathiazole, penicillin, streptomycin, chloramphenicol, boric acid, and p-aminosalicylic acid when tested in vitro in pairs against Bacterium coli. A synthetic medium was used and its pH adjusted to 7.5. The results are summarized in the following table:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Sulphathiazole</th>
<th>Penicillin</th>
<th>Streptomycin</th>
<th>Chloramphenicol</th>
<th>Boric Acid</th>
<th>p-Aminosalicylic Acid</th>
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<tr>
<td>Sulphathiazole</td>
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<td>Penicillin</td>
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<td>Streptomycin</td>
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<tr>
<td>Chloramphenicol</td>
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<td>Boric acid</td>
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<td>p-Aminosalicylic acid</td>
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</tbody>
</table>

To be read downwards, not across. S = Synergism. A = Antagonism.

Antagonism was demonstrated in five combinations, but only in the case of boric acid and sulphathiazole was each constituent antagonistic to the other. The only other marked and permanent antagonisms were those of p-aminosalicylic acid to sulphathiazole and of boric acid to penicillin. In the case of some combinations both antagonism and synergism were found at different concentrations of the antibiotics. In two cases of antagonism (chloramphenicol to sulphathiazole and p-aminosalicylic acid to streptomycin) the antagonism which was obvious for the first day or two was replaced by synergism within 3 days.

The theoretical and practical importance of these findings is discussed. The author's general conclusion is that, "as regards the six substances investigated, the synergism which, with a single exception, occurs between them might be of considerable value and the antagonism which has been demonstrated in a few cases is very unlikely ever to represent a real danger." A. W. H. Foxell.

Use of Penicillin O in Patients Hypersensitive to Penicillin G.


Several workers have reported that persons hypersensitive to penicillin G may show no reaction to some of the biosynthetic penicillins. One of these is allylmercaptomethyl penicillin, or penicillin O. The minimum inhibitory concentrations of penicillin O for Gram-positive cocci are the same as, or double, those of penicillin G. Furthermore, penicillin O was found to be less toxic and less irritating than penicillin G when injected subcutaneously into mice. The absorption and excretion curves of these two penicillins are essentially the same.

Penicillin O was administered to 57 patients who had clinical symptoms of hypersensitivity to penicillin G within a preceding period of not more than 200 days. Twenty of them had upper respiratory infections, and were given inhalations of penicillin-O dust, 100,000 units every 4 hours for 7 days.
All recovered without complications and showed no allergic phenomena. In 23 cases of tonsillitis and pharyngitis due to β-haemolytic streptococci the patient received 10 troches containing 3,000 units of penicillin O daily for 3 days. The results were excellent in 15, good in 5, and poor in 3 cases. Fourteen patients received courses of injections of penicillin O, following which penicillin G was given and was well tolerated. It appears that penicillin O had a desensitizing effect. Seven of the cases are reported in detail and a further 7 in tabular form. In every case penicillin O was as effective as penicillin G. A. W. H. Foxell.


Subcutaneous or intramuscular implantation of procaine-penicillin tablets prolongs therapeutic blood levels for several days. Tablets consisted of procaine penicillin G with 20% ox fat. Implantation of 400- to 800-mg. tablets gave a detectable level of penicillin in the blood for 14 days, and of a 1-g. tablet for 23 days. The tablets caused no local or general reactions, and the authors discuss their possible uses, especially in preventing post-operative infection and in the treatment of syphilis. René Méndez.


Previous reports on the absorption and excretion of aureomycin are reviewed and the authors’ own investigations described. The concentration of aureomycin in the blood and urine following the administration of 100- and 500-mg. doses intravenously and intramuscularly was determined in groups of 2 or 3 normal subjects, or patients convalescent from minor illnesses who had not been treated with any antibacterial agent. All had normal renal function, and the normal undiluted urine had no antibacterial action. For intravenous injection crystalline aureomycin hydrochloride was dissolved in 5% aqueous solution of dextrose; solutions for intramuscular injection contained leucine buffer and procaine in addition. Serum and urine concentrations of aureomycin were determined by a modification of the Rammelkamp method for penicillin.

On intravenous administration by continuous drip infusion over \( \frac{1}{2} \) to 1 hour, a decreasing concentration of aureomycin was detectable in the serum for 12 hours after a 500-mg. dose and for 2 to 4 hours after a 100-mg. dose. No aureomycin could be detected in the blood after similar doses given intramuscularly. On intravenous injection the most rapid rate of excretion in the urine occurred within 8 to 12 hours after a 500-mg. dose, but when the same dose, which was highly irritating, was given intramuscularly it was excreted irregularly. A 100-mg. dose given intramuscularly was excreted rapidly during the first 3 hours. Appreciable amounts of aureomycin were excreted for 2 to 4 days after intravenous injection, and for 8 days after intramuscular injection. After intravenous injection 26 to 50% of the dose was recovered from the urine as active aureomycin, whereas 13 to 24% was recovered after intramuscular injection. In view of the rapid deterioration of aureomycin in neutral or alkaline solution, and particularly in view of reports that aureomycin is protected from deterioration in tissues, it is concluded that much of the loss of antibiotic occurred during manipulation of the samples. The marked irritation caused by intramuscular injection of aureomycin tends to keep the agent localized at the site of injection, and the intravenous route is therefore preferable. Rough estimations indicate that aureomycin is cleared from the plasma at the rate of 40 to 70 ml. of plasma per minute, which is similar to the clearance rate for streptomycin. It is concluded that aureomycin is excreted by glomerular filtration alone.

Clinical Observations on Terramycin.


This paper records the results of treatment with terramycin of 15 patients with various infections. Terramycin hydrochloride was given orally in all cases. Various dosage schemes were employed, but treatment usually consisted of an initial dose of 1 g. repeated 4-hourly for 3 doses, followed by 3 to 6 g. a day at 3- or 4-hourly intervals. Among the conditions for which good results were obtained were pneumococcal lobar pneumonia and infections due to staphylococci, Streptococcus viridans, Strep. faecalis, some strains of Bacterium coli, Bacillus mucosus capsulatus, Proteus vulgaris, and Vincent’s organisms. In 2 cases of subacute bacterial endocarditis the immediate response was good, but relapse occurred as soon as treatment was stopped. The only toxic effects encountered were nausea, vomiting, and diarrhoea, which occurred in 12 of the 15 cases, but were troublesome in only 3.

A. W. H. Foxell.


Harvest fever, caused by one of three species of leptospira, L. grippo-typhosa, L. sejroe, and L. australis, is unknown in Great Britain. It is rare in western Germany, and the author of this interesting paper describes in detail the clinical features of the disease as observed in 1949 during the first epidemic to be recorded in Lower Saxony, in the district of Wolfenbüttel. In July and August, 43 patients were admitted to the municipal hospital there, most of whom had been engaged in the harvesting of peas, while in the few remaining cases contact with freshly harvested peas, or in one case with the fields from which these had been harvested, could be proved. Headache and pains in the limbs and joints were typical initial symptoms, and giddiness, nausea, and vomiting were also common. The temperature was high (between 39° and 40° C.), and usually fell by lysis over a period lasting up to 14 days; after an afebrile interval of 1 to 5 days a secondary rise was frequently observed for 1 to 4 days. Injection of the conjunctiva and sclera was common. Jaundice was not observed, but rashes of varying description and intensity were frequent. Complete recovery took 10 to 12 weeks, or even longer; no fatalities were reported. The incubation period was 9 to 16 days. Positive agglutination reactions were obtained in all cases, and leptospirae were also cultured from the blood. Coincidentally with the occurrence of this epidemic a large increase of the murine population was noticed, and leptospirae were isolated from the kidneys of over 80% of mice trapped in the area. W. G. Harding.


It has been found that “benemid,” p-(di-n-propyl-sulphamyl)-benzoic acid, has the property of enhancing the concentrations of both penicillin and p-aminosalicylic acid (PAS) in plasma. Single oral doses of 1 and 2 g. were effective in doubling the plasma concentration of penicillin and PAS for periods of up to 8 hours. Most of the patients (50 were studied) received “benemid” for no longer than 2 to 3 days, but some received the compound for 40 days in an oral daily dose of 1.5 g. without toxic symptoms.

R. Wien.

BIOCHEMISTRY

Some Problems of Potassium Metabolism.


A theory of potassium metabolism is put forward, based on the following considerations and assumptions: (1) Potassium moves all the time between cells and the extracellular fluid. (2) Glucose is necessary for the cellular metabolism of potassium. (3) Potassium may be necessary for the cellular metabolism of glucose. (4) Acetylcholine increases the permeability of cells to ions, and may therefore aid
the cellular metabolism of potassium.

(5) Potassium may enhance the formation and breakdown of acetylcholine. The possible relation between these processes is expressed by the authors in the schema below, in which glucose is the only substance which must be constantly supplied.

It is concluded from this schema that disturbances of potassium metabolism may be caused by a breakdown of either the glucose metabolism or the acetylcholine cycle. This may be responsible for the low potassium levels in the cells, often seen in untreated diabetes, and for the low serum potassium levels often seen after injections of insulin or adrenaline. Another application of this schema was sought in periodic familial paralysis, in which attacks of paralysis are associated with low potassium levels in serum and can be brought about by giving insulin and adrenaline. It is possible that myasthenia gravis may be associated with a disturbance of potassium metabolism resulting from a lack of acetylcholine.


An attempt has been made to determine the extent to which iron absorption is disturbed by the presence of infection and of malignant tumours. The method used was by estimation of the serum iron concentration 1, 3, and 7 hours after an oral test dose of iron, a high rise in the serum iron level being considered indicative of a rapid absorption and so of an iron deficiency. Initial experiments showed that when iron deficiency, due to blood loss, is present, iron is readily absorbed both by febrile patients and by those with malignant disease. Cases of infective anaemia have been found which showed a rapid iron absorption and in which, therefore, iron deficiency was presumed, even when no reason for blood loss was present. Clinical improvement followed oral administration of iron in such cases. In pure infective anaemia the serum iron level is unaffected by oral iron therapy. It is considered that in these cases there is adequate iron in the tissue depots of the liver, spleen, and marrow.

[The work is based on 16 serum iron curves in cases of infection and malignant neoplasms.]

C. L. Cope.


A detailed case report is given of a patient in whom Addison's disease supervened after he had been treated for diabetes mellitus for 13 years. Usually in such cases the insulin requirement falls owing to increased sensitivity to insulin, but this patient's insulin needs did not change appreciably. In conformity with this, his urinary output of corticosteroids was normal, and it is suggested that continued formation of corticosteroids prevented the usual increase in insulin sensitivity. The clinical signs of Addison's disease were definite, the excretion of 17-ketosteroids was low, and tests showed severe impairment of the 11-oxycortico- steroid-like function of the adrenals. The possibility of suprarenal damage which did not affect the production of one group of adrenal hormones is discussed.

D. A. K. Black.

The only measure of the absorption of vitamin B₁₂ by patients with pernicious anaemia so far employed has been the haematological response. In the experiments here reported the authors made an attempt to use the vitamin-B₁₂ activity of the urine, estimated by microbiological assay, as a means of measurement of absorption. Crystalline vitamin B₁₂ was given intramuscularly and by mouth to normal subjects and to untreated patients suffering from pernicious anaemia. Urine specimens were collected for one day before, and for two days after, the dose and their vitamin-B₁₂ activity assayed. In some of these and in subsequent experiments 10 μg. of biotin was given at the same time, because this vitamin is known to appear quantitatively in both urine and stool specimens, and its addition thus served as a check on the adequacy of collection.

Up to about 50% of vitamin B₁₂ could be detected in the urine 12 hours after parenteral administration of 100 μg., there having been no appreciable vitamin-B₁₂ activity detectable in the urine previously. When doses of 100 μg. or 500 μg. of vitamin B₁₂ were given orally, no vitamin-B₁₂ activity could be detected in the urine either of normal subjects or of those with pernicious anaemia during the next 72 hours. Addition of 400 g. of beef, chicken, or pork to the diet of 3 normal subjects for four days did not lead to the appearance of any appreciable vitamin-B₁₂ activity in the urine. It had been anticipated by the authors that in normal subjects at least some vitamin-B₁₂ activity would be detectable in the urine after peroral administration of large doses of the vitamin, but that patients with pernicious anaemia would not absorb it. These experiments indicate, however, that vitamin B₁₂ may be absorbed poorly or not at all even by normal individuals.

[Some haematopoietic response has been claimed after peroral ingestion of the vitamin if given in very large doses. It has also been shown that administration by mouth of only 5 to 10 μg. of vitamin B₁₂ together with 100 to 150 ml. of normal gastric juice, or with extract of hog's stomach or duodenum, seems to produce a haematopoietic response in patients with pernicious anaemia which is comparable to that obtained by parenteral administration of a similarly small dose of the vitamin. The intrinsic factor may thus protect the vitamin from destruction by the gastrointestinal secretions or the microorganisms of the upper small intestine, or, on the other hand, facilitate its passage through the intestinal wall.]

Z. A. Leitner.

HAEMATOLOGY


At the Royal Victoria Infirmary, Newcastle-upon-Tyne, bone marrow cells, obtained by aspiration from cases of pernicious anaemia in relapse, were cultured in media containing varying proportions of normal plasma or serum derived from normal subjects and from patients with pernicious anaemia. The method of culture used was that of Osgood and Brownlee, and erythroblasts were classified according to the method of Davidson et al. (Quart. J. Med., 1942, 11, 19).

Cultures in various dilutions of normal plasma ranging from 10 to 100% showed no significant difference in the degree of maturation. But in cultures made in media containing plasma from cases of pernicious anaemia the number of immature cells present increased with the concentration of plasma present, though this effect varied with different samples of plasma. Moreover, the addition of pernicious
anaemia plasma to normal plasma produced an inhibition of the maturing effect of the latter. These findings agree with those of Rusznay et al. (Hungarica Acta med., 1948, 1, 1), who suggested that such an inhibitory factor was present in the serum of patients suffering from pernicious anaemia, and that the disease was not simply due to the absence of a specific maturation element. A. T. Macqueen.


The test for paroxysmal nocturnal haemoglobinuria (PNH) described here has been developed from observations previously reported in detail. It depends on the activation by thrombin of an inert plasma factor which when active becomes specifically haemolytic against erythrocytes in PNH. The test is simple and rapidly performed; it has been carried out over a hundred times in patients with PNH. In these it was invariably positive. Erythrocytes from normal subjects and from a variety of patients with haemolytic anaemia of types other than PNH always gave negative results. [Readers are referred to the original paper for details of the test.] A. Brown.


A farm labourer of 57 complained of blood spots in his skin and swellings over the bones of his legs, pains in his leg bones, and occasional small haemoptyses. Later he noticed mistiness of vision, whose disappearance was followed by transient enlargement of his salivary glands. Radiographic examination showed increased density and coarse trabeculation of the whole skeleton, with marked thickening of the cortex of the long bones. The general picture was much like that in Paget's disease, but the alkaline phosphatase level in serum was only slightly raised; the alternative diagnosis was sarcoidosis. No evidence of myelomatosus could be obtained.

The patient's serum formed a gel on cooling; it passed from fluid at 27° C. through cloudiness at 25° C. and increased viscosity at 24° C. to the formation of a solid gel at 23° C.; the whole process was reversible. The active component was a substance migrating electrophoretically with the β-globulin, but it cross-reacted with anti-γ-globulin sera. It contained 0.5% cholesterol, less than 0.03% liquid phosphorus, 7% or less total lipid, and about 5.8% carbohydrates (as galactose-mannose). Its sedimentation constant was 17.2 x 10⁻¹³, corresponding to a molecular weight between 400,000 and 1,000,000. The tyrosine: tryptophan ratio (1.63:1) was lower than that found in β or γ globulin, or in fibrinogen. The protein is compared with that obtained from cases previously described, and the symptoms shown by the patients are contrasted. C. L. Oakley.


Several cases of the syndrome of fever, progressive anaemia, mild icterus, thrombopenia, and changes in the central nervous system have now been reported in the literature. The case reported in this paper was unusual because the onset took the form of a confusional state, for which the patient was admitted to a mental hospital. The usual manifestations of haemorrhage, especially from the vagina, severe anaemia, and constant pyrexia appeared very soon. As in other cases, there was no response to transfusion and the patient died about three weeks after the onset. Post-mortem examination showed numerous thrombi in
the blood vessels of almost every organ, including the brain. These thrombi were made up of masses of platelets, and none of the usual fibrin was present. This finding also agrees with previous descriptions. The literature and theories of aetiology are fully discussed. M. C. G. Israëls.


These three communications all deal with the same subject and show conclusively that exposure of plasma to ultraviolet light does not inactivate the hepatitis virus. Altogether 16 cases of hepatitis are described, two of them fatal, following the injection of irradiated plasma. There is thus no reliable method as yet for inactivating hepatitis viruses in plasma, serum, or whole blood. G. M. Findlay.


The authors describe two severe cases of purpura fulminans following scarlet fever in a 7-year-old girl and a 6-year-old boy. The clinical picture, the pathogenesis, and the treatment of purpura fulminans are discussed and the following points are emphasized:

In these two cases a severe disturbance of coagulation existed which was due to an acute insufficiency of Owren’s factor V, which was combined in one case with an excess of antithrombin of the heparin-antithrombin type. The great increase in plasma cells of the reticulum and of eosinophils in bone marrow, as well as the increase in γ globulins in the blood electrophoresis—findings which, too, were made for the first time—point to an increased production of antibodies and to an allergic diathesis. The second patient could be saved when moribund by a complete blood-exchange transfusion, while repeated smaller transfusions in the first case were unsuccessful. The exchange transfusion alone assures complete removal of abnormal products and a sufficient supply of those products which were absent in the blood. Exchange transfusion appears to be the method of choice for the treatment of purpura fulminans.—[From the authors’ summary.]

MORBID ANATOMY AND HISTOLOGY


This study was prompted by the observation that, in male patients with cirrhosis of the liver, gynaecomastia, testicular atrophy, and other signs of endocrine imbalance frequently develop. It is believed that endogenous oestrogen is inactivated by the healthy liver, and that this function is impaired when the organ is grossly diseased.

The necropsy findings in 50 patients with portal cirrhosis of long standing and 50 subjects with no history of, or necropsy evidence of, liver dysfunction were compared. Special attention was paid to the histological changes in testis, breast, and prostate in both groups.

The testes of all but 3 of the patients with cirrhosis showed atrophy of a mild to severe degree. Advanced atrophy was observed in half of the cases of cirrhosis, and this was associated with marked thickening and hyalinization of the seminiferous tubules in most cases. Gross atrophy was found in only 6.1% of the controls, and tubular thickening was not greatly in evidence.
The only noteworthy change in the prostate of patients with hepatic disease was a metaplasia of the columnar-cell acinar epithelium to epithelium of a transitional type. This change was observed in 7 patients with cirrhosis and in 2 controls.

The breasts of 20 patients with hepatic cirrhosis were available for study. In 7 there was marked hyperplasia, and a definite correlation between hypertrophy of the breast and atrophy of the testis was noted. Minor degrees of hyperplasia were found in 10 out of the 50 controls.

The authors conclude that the lesions complicating cirrhosis of the liver are probably caused by an excess of endogenous oestrogen.

G. B. Forbes.


Necropsy findings, histological and chemical, are described in 8 patients with refractory anaemias treated by multiple blood transfusions. In all cases the liver had the highest haemosiderin concentration. It contained more iron than the total amount found in the normal body.

Three livers, specially assayed, contained more iron than the total contribution of transfused iron. The source of this extra iron is uncertain, but may be the intestine. Five livers were diffusely fibroesed. The cause of this fibrosis was not the presence of the haemosiderin, and it is possible that a local nutritional factor was involved.

A. Wynn Williams.


From a study of 9 cases of testicular tumour the author concludes that seminoma is a "teratoid" tumour, and that all malignant tumours of the testis are related "teratoblastoma." Chorionepitheliomatous tissue is more often present in malignant teratomas than has been supposed. A case of rupture of the spleen due to metastases of a testicular chorionepithelioma in a man of 42, and another of disseminated chorionepithelioma with retrogression of the primary testicular tumour (like those reported by Prym, Michel, and others) and accompanied by gynaecomastia, are described, and the hormonal effects of testicular tumours are reviewed and discussed. In the latter case the patient had also had diabetes insipidus, which necropsy showed to be due to a coincidental chronic inflammatory lesion of the pituitary.

R. A. Willis.


An unusual type of epididymal tumour was described in 1941, and the case records of two additional specimens of similar tumours are now given. These tumours have been variously regarded as of endothelial, mesothelial, epithelial, and mesonephric origin. They are attached to, though not always part of, the epididymis. They are white or light brown, glistening, and whorled, like small fibromata. The histological appearances vary somewhat in different cases, and it is in the interpretation of these variations that the difficulties in diagnosis have arisen in reports of cases. The indefinite term "tumour of adenomatoid nature" should be retained until such time as the precise pathology is determined by the accumulation of evidence from succeeding cases. The tumours are not malignant. Simple local excision sufficed in all cases reported for complete recovery.

[Photographs of the tumours in the cases reported are reproduced.] James Kemble.


An excellent account is given of 4 cases of tumours of the carotid-body type in unusual situations. In the first case the growth arose
from the ganglion nodosum of the vagus nerve; in the second there were two separate tumours, one arising in the vagus nerve and the other in the carotid body of the opposite side; the third patient had an upper anterior mediastinal tumour; and in the fourth case there were three independent tumours, involving respectively the ganglion nodosum, carotid body, and adventitia of the aortic arch. Microscopically, these tumours all resembled those of the carotid bodies and those of the glomus jugulare. The carotid body, the glomus jugulare, the paraganglion intravagale, and the aortic-arch bodies all have a similar structure and are probably similar chemoreceptors; they form a "paraganglionic system" which is quite distinct from the chromaffin tissues. The development of similar, and not infrequently multiple, tumours from these several structures is thus readily understandable. This is the first report of tumours of the aortic bodies in man, though Bloom has described such tumours in the dog (Arch. Path., 1943, 36, 1). The present paper contains a full bibliography, and also includes some excellent photomicrographs of the aortic and vagal paraganglia.

R. A. Willis.

Prognosis in Carcinoma of the Breast


A series of 470 cases of carcinoma of the breast treated at the Middlesex Hospital were graded according to the degree of tubule formation, uniformity in size, shape, and staining of the nuclei, and the number of hyperchromatic nuclei and mitoses.

By combining this method with the Manchester system of classification, a more accurate prognosis can be given than by classification alone. Certain tumours, if they are of a low histological grade, may be associated with a better prognosis even if they have reached Stage III than other more malignant grades still confined to the breast in Stage I; this finding is a strong argument in favour of the author's system of grading.

Possible fallacies in grading and staging are discussed.

Errors in staging arise from involvement of lymph nodes (as in the internal mammary chain) not revealed clinically or post-operatively; and from the fact that lymph nodes clinically enlarged may not be actually involved in tumour, and conversely that nodes involved may not be palpable clinically. Supraclavicular lymph-node involvement, undetectable either clinically or after operation, is another factor which might vitiate the accuracy of staging. Nevertheless, the author concludes that the system which he proposes is the best possible means of classification available, and he makes out a well-argued case that the universal adoption of this combined clinico-pathological method will lead to more accurate assessment of different methods of treatment.

H. J. B. Atkins.


The case is described of a man of 52 who complained of cough, fever, headache, and loss of weight. At necropsy the left kidney showed the changes of benign and malignant hypertension and gross cortical necrosis. The right kidney was normal. The renal artery on the right side was grossly sclerotic, with marked reduction of the lumen, which was terminally thrombosed. There were old and recent infarcts in the heart, a non-tuberculous cavity in the lung, and [2] viral hepatitis. The pituitary gland was normal.

It is thought that the hypertension was due to ischaemia of the right kidney, and that this was unaffected by the cortical necrosis because its functional activity was low and its nutritional demands adequately supplied by the capsular anastomotic vessels.

D. M. Pryce.

Correction.—Dr. Callender writes that in her paper "The Effect of Citrovorum Factor (Folic Acid) on Megaloblasts in vitro" (J. clin. Path., 4, 204) the abbreviation μg. was used for millimicrograms instead of mg.