undertaken the reverse migration.—I am, etc.,

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Jaundice in Severe Infections

SIR,—The recent article in the *B.M.J.*, "Jaundice in Severe Infections" by Dr. A. Eley and his colleagues (10 July, p. 75), prompts me to report a similar patient admitted to the medical wards of this hospital in March of this year.

A 44-year-old sub-postmaster, an ex-Royal Navy cook, was admitted with a history of attacks of diarrhoea and sickness for about two months, together with increased cough and purulent, brown sputum; there was also a history of fever with rigors and sweating for the week before admission.

He gave a history of dysentery in Singapore in 1958, but denied any previous respiratory symptoms apart from a "smoker's cough" for many years.

On examination the patient appeared very ill, slightly icteric, and breathless at rest: temperature 101.4° F. (38.5° C.), pulse 124/min., irregular with occasional drop beats, respirations 24/min. The sputum was purulent, copious, and very dark brown in colour, almost resembling anchovy sauce. The physical signs in the chest revealed extensive consolidation in the right lower zone, where there were coarse crepitations. The liver margin was just palpable and was tender.

Repeated microscopic and culture examinations of stool for *E. histolytica* were negative: haemoglobin 82%; total leucocyte count 14,750/c.mm., with 89% polymorphs, 8% lymphocytes, and 3% monocytes; E.S.R. (Westergren) 120 mm. in the first hour. Serum bilirubin 2.0 mg./100 ml., alkaline phosphatase 4 K.-A. units, thymol turbidity 5 units, total proteins 5.5 g.%, albumin 2.7 g.%, globulin 2.8 g.%. The urine showed a trace of albumin and contained bile salts and pigments. Blood culture and urine culture were sterile. Sputum cultures, though initially showing normal flora, were later shown to grow a coagulase-positive staphylococcus on one occasion and *Str. faecalis* on another. Radiograph of chest disclosed complete consolidation of the right lower lobe. All investigations for tuberculosis and malignancy were negative.

The patient was treated with a variety of antibiotics, including benzylpenicillin (Crystamycin), erythromycin, tetracycline, fusidic acid (Fucidin), ampicillin, and cloxacillin. His condition, clinically and radiologically, improved slowly and the liver-function tests eventually returned to normal.

Though it was initially thought, from the patient's past and present history of dysentery, enlarged liver, and very dark brown sputum, that he might have developed an amoebic abscess of liver which had ruptured into the lung, all the tests for amoebiasis were negative, and because of the extensive lung involvement it was decided to treat the patient as a case of lobar pneumonia. The patient ultimately made a good recovery, but the original clinical condition with jaundice was misleading.

I am grateful to Dr. D. H. Smith for permission to report this case and for his helpful criticism.

—I am, etc.,

Ashludie Hospital, Monifieth, Angus. M. K. TANDON.

Management of Cerebrovascular Disease

SIR,—I was a little surprised to note that Sir John McMichael in his review of my book (24 July, p. 217) should state that the average age of my patients on hypotensive therapy was 41 years, whilst for my controls it was 59 years, without also stating that the groups were standardized for age before comparison of their life expectancies was made.

I was also surprised that he should make use of the controls in the largest American series of transient ischaemic attacks treated with anticoagulants I tabulated, as these controls were selected in a manner which makes it highly likely that they carried a poorer prognosis than average, a fact I pointed out in my text. The two smaller series I tabulated were free from this defect and remain the best factual evidence we have to date about the place of anticoagulant therapy in transient ischaemic attacks. They show that anticoagulants reduce the frequency of transient ischaemic attacks but do not provide evidence that these drugs protect against a future cerebral infarction. I did not refer to the excellent work of Acheson and Hutchinson as my manuscript was with the printers before their paper appeared in October last year.

I was sorry Sir John could not find any references to transient strokes in association with disturbance of cardiac rhythm and myocardial infarction; they are on pages 121, 122, and 128.—I am, etc.,

University Department of Clinical Neurology, The National Hospital, London W.C.1. JOHN MARSHALL.

Provident Association Forms

SIR,—We regret that the motion moved by Dr. B. D. Morgan Williams at the A.R.M. at Swansea ["That this Meeting deprecates the threatened action of the B.U.P.A. to remove the general-practitioner sanction clause from their claim form"] was lost (*Supplement*, 17 July, p. 45).

The majority of consultants and the majority of subscribers to provident associations are honest people whose conduct is ethical, but there are, unfortunately, some who are always prepared to take advantage of anything in the nature of insurance, thereby defeating justice being done to the general body of subscribers.

If general practitioners require a reasonable fee for completing provident association certificates, subscribers able to pay for private specialist treatment wholly or partly through insurance should not resent their general practitioner asking a fee. The Western Provident Association and the Bristol Hospitals Fund are immensely grateful to general practitioners for much unpaid, unselfish, and valuable help in the conduct of their affairs.

We have always understood that the profession adheres to the principle that specialist advice and treatment should only be given on the advice of the patient's family doctor. There are, unfortunately, members of the profession willing to ignore this principle. We therefore regret the apparent desire of the B.U.P.A. to abandon the chief safeguard they, and all provident associations, have against abuse of their rules.

The certificate is, in our view, an essential safeguard if justice is to be done to the vast majority of honest subscribers. Without this safeguard it is impossible to prevent abuse of waiting periods for benefits. To pay claims to new subscribers on account of undisclosed adverse conditions existing at the date of application for membership is unjust to the general body of subscribers, apart from its financial dangers for the associations.

Provident associations are of immense value to consultants, because without them there would be very few private patients left. It would be a retrograde step in the provident movement for general practitioners' certificates to be abandoned.—I am, etc.,

JOHN DODD,
Secretary,
Western Provident Association for Hospital and Nursing Home Services,
Bristol 1. Bristol Hospitals Fund (Inc.).

Gut-secreted Calcium

SIR,—Many workers in the field of calcium metabolism must have been as puzzled as I was by the paper of Dr. G. A. Rose and his colleagues (13 March, p. 690). The authors compared net calcium absorbed, calculated by subtracting faecal from dietary calcium, d−f, with true amount absorbed, α.d, α being the fraction of orally administered ^{47}Ca absorbed, estimated by measuring faecal excretion of isotope. The correlation coefficient for the regression of α.d on d−f was so high (+0.95), as to suggest that net secreted calcium was virtually equal to total secreted calcium and was independent of absorption.

As this conclusion contradicts much other data—e.g., Heaney,[1] Nordin *et al.*[2]—the high correlation coefficient was worrying. I attempt to show here that the contradiction is due to the way in which the authors represented their results and that the latter are in reality compatible with those of most other authors.

Before proceeding I should note one further criticism. The authors ignored ^{47}Ca resecreted into the gut, assuming that the error so introduced would not be great enough to influence their conclusions. DeGrazia and Rich[3] have shown that the underestimate introduced by this approximation is variable but seldom less than one-tenth of the value obtained by the unmodified isotope method. All the results for percentage absorption of Dr. Rose and his colleagues are therefore in error by an amount which is hardly negligible.

Two symbols are necessary to the discussion:

s = that fraction of the secreted calcium which is capable of reabsorption in the same proportion as dietary calcium, mg./day.

s′ = that fraction of the secreted calcium which cannot be reabsorbed, mg./day.

The assumption I (and most workers, I think) make about the secreted calcium is that it is all represented by s+s′.

Total faecal calcium is then given by

$$f=(d+s)\ (1-\alpha)+s' \quad \ldots\ldots\ldots\ldots\ldots\ (1)$$

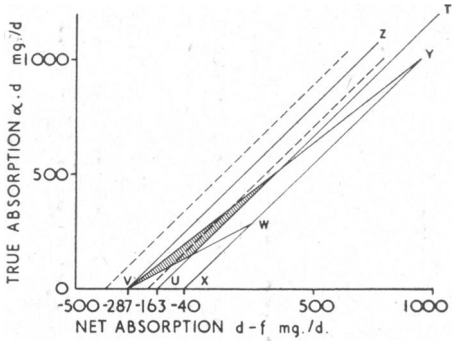
The discussion is simplified by taking $s+s'=287$ mg./day, the value found by Dr. Rose and his colleagues, and $s'=40$ mg./day, the value derived by Heaney.[1] Equation (1) then reduces to

$$f=(d+247)\ (1-\alpha)+40$$

or,

$$\alpha.d=(d-f)-247.\alpha+287 \quad \ldots\ldots\ldots\ldots\ (2)$$

Equation (2) is plotted for various values of α and d in the Figure. At constant α values $\alpha.d$ on $(d-f)$ is a family of straight lines with gradient unity. The line degenerates to a point, V, at $\alpha=0$. XY and UT represent the lines for $\alpha=1$ and $\alpha=0.5$ At constant d values $\alpha.d$ on $d-f$ is a family of straight lines radiating from V ($\alpha=0$). VW and VY represent the lines for diets of 300 and 1,000 mg./day and α values from 0 to 1.



As the figure shows, $\alpha.d$ on $d-f$, when both α and d vary, represents an area, not a single line. This area shrinks to a straight line if s is independent of α. The line then obtained is VZ, the regression line of Dr. Rose and his colleagues.

$$\alpha.d=d-f+287$$

The two interrupted lines represent the upper and lower deviations of the data of the authors.

The authors did not give the range of d studied nor the values of α found, but if d ranged from 300 to 1,000 mg. and α between 0 and 0.5, then all the results obtained would be included in the small shaded triangle, most of which falls within the lower deviation from the mean line. So, two radically different assumptions about the secreted calcium are about equally well confirmed by the data when they are presented as a regression of $\alpha.d$ on $d-f$. Therefore, it seems unjustified to accept the conclusion of Dr. Rose and his colleagues.

The danger of trusting correlation coefficients is well illustrated by the other correlation demonstrated by the authors (see their Fig. 5, line B). The correlation coefficient is again 0.95 but the correlation is spurious because it leads to an impossible conclusion. The equation of line B is

$$\alpha.d=0.82\ (d-f)+250 \text{ mg./day}$$

When $\alpha=1$—i.e., when dietary absorption is complete—the equation reduces to

$$d=0.82d-0.82f+250$$

or,

$$f=300-0.22d.$$

—i.e., f is still dependent on d. This is absurd because if all the dietary calcium is absorbed none can appear in the faeces—i.e., if $\alpha=1$, f cannot be dependent on d. This does at least suggest that the correlation in Fig. 4 which is equally good is equally spurious.

It is interesting and possibly significant that Dr. Rose and his colleagues' Fig. 5, referring to isotope given with a whole day's milk seems more compatible with my hypothetical figure than their Fig. 4. The gradient of VY is 0.80; line B in Fig. 5 (really a narrow triangle) has a gradient of 0.82. This may suggest, and I put this forward very tentatively, that absorption measured after an overnight fast is an overestimate compared with that averaged over a whole day. The authors may be able to confirm this.

I conclude that the results of Rose *et al.*, when presented differently, are likely to be quite compatible with those of the authors I quoted.—I am, etc.,

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Hookworm Infections Acquired in Britain

SIR,—The letter from Professor J. J. C. Buckley and Mr. F. R. N. Pester (10 July, p. 106) recording hookworm infection in two children acquired in this country compels a reappraisal of the possibility of its more widespread dissemination. In a consecutive series of 139 adult male immigrants applying for employment I found 49 (approximately 36%) were excreting hookworm ova.

When washed hookworm ova are placed in 5% formol saline growth and active movements of the embryos continue for five hours or more at room temperature. If the ova were protected by being embedded in a mass of faeces their survival would presumably be much longer.

It therefore seems a possibility that temporary camping sites, construction sites, or any place where the contents of pail or chemical closets are dumped or buried could be potential sources of infection under suitable climatic conditions.—I am, etc.,

London N.W.7. R. D. MACLEAN.

Absence of Carcinogenic Properties of Propranolol in Mice

SIR,—Alderlin (pronethalol) has been shown to produce thymic lymphosarcomata and reticuloses in mice,[1] and it has been suggested that this may be related to the production of a reactive ethyleneimine as a transient breakdown product.[2] Inderal (propranolol) is probably broken down in much the same way, but the resulting intermediate product would be expected to be much less reactive and therefore might not produce tumours. This hypothesis is supported by an experiment on similar lines to those of Alcock and Bond[1]; there is no significant difference between mice treated with propranolol and a control group.

Specific pathogen-free mice of the Alderley Park strain were used. The drug was given by stomach tube for ten months and for a further nine months was administered in the diet as follows: 30 male, 29 female mice given 150 mg./kg. by tube for 10 months and 0.2% in diet for nine months; 28 male, 28 female mice given excipient only by tube for 10 months and control diet for nine months.

During the 19-month period of treatment there was no significant difference between the animals given propranolol and the control group. The incidence of tumours was equal and fitted into the pattern with which we are familiar in this strain of mice. In the series reported by Alcock and Bond[1] thymic tumours began to appear 75 days after the start of treatment with pronethalol and by the end of the experiment 11.1% of the animals had died with thymic tumours.

With the observation that pronethalol caused tumours in mice its use in man was necessarily restricted, although there is no evidence that any species other than mice are susceptible. No tumour attributable to it was seen in rats dosed with the drug (0.2% in the diet) for 18 months. Apart from giving reassurance that propranolol is free from this hazard, these experiments highlight how relatively minor structural changes can alter toxicity as well as pharmacological activity.—We are, etc.,

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Scared to Death?

SIR,—We would like to report a case of an apparently healthy middle-aged woman dying with massive adrenal haemorrhage, following a relatively minor operation, who was subsequently found to have had forebodings of death.

Mrs. A. B., aged 43, mother of five children, was admitted to North West River Hospital, Labrador, on 18 March 1965. She had been complaining of severe stress incontinence for several months. She had been treated during the past three years for anxiety which responded well to reassurance and mild sedation with phenobarbitone, 30 mg., three times daily. There was no relevant past medical history. On examination she was found to be in good health. Vaginal examination revealed a moderately large cystocele and urethrocele. On 19 March anterior colporrhaphy was performed under general anaesthesia. The premedication was pethidine, 100 mg., and atropine, 0.65 mg.; induction with intravenous thiopentone, 400 mg., and Flaxedil (gallamine triethiodide), 40 mg.; maintenance with nitrous oxide, oxygen, and a trace of trilene, accompanied by intermittent intravenous pethidine to a total of 80 mg. The operation, which lasted less than one hour, was straightforward with minimal blood loss. Her blood-pressure remained around 120/70 throughout the operation, and pulse and respiration were normal. She regained consciousness before leaving the theatre. One hour later she became shocked and her systolic blood-pressure fell to 70 mm. Hg. She remained conscious, but shortly afterwards complained of severe pain in the left hypochondrium. Methedrine (methylamphetamine) was immediately given, 15 mg. intravenously, and 15 mg. intramuscularly, and the foot of the bed was raised. As the blood-pressure showed no response Aramine (metaraminol), 10 mg., was given intramuscularly. An infusion of dextran, 500 ml., with hydrocortisone, 100 mg., was started. Despite continuous infusion with metaraminol and hydrocortisone no improvement was obtained and intranasal oxygen was required as the patient became cyanosed. The pain was partly controlled by injections of morphine, 16 mg., given on three occasions. The E.C.G. was normal. Her condition deteriorated and her temperature rose to 103.6° F. (39.8° C.) by midnight, when she became comatose. She died at 5 a.m. on 20 March.

At post-mortem examination the adrenal glands showed extensive haemorrhage. Petechial haemorrhages were found in the stomach, ileum, liver, and in the skin of the nose. There was no other pathology.