Urinary Hydroxyproline and Thyroid Disease

SIR,—Measurement of the 24-hour urinary excretion of hydroxyproline as an index of the disturbed collagen metabolism found in thyroid disease and the use of this measurement as a test of thyroid function have been previously described.^{1,2} The changes found were increased excretion in hyperthyroidism and decreased excretion in hypothyroidism, these changes being present in some 70-90% of adults with thyrotoxicosis,^{1,2} and some 70% of adults with hypothyroidism.¹ It was concluded that these tests were useful in the diagnosis of thyroid disease in adults, particularly in thyrotoxicosis.

In view of the inconvenience and difficulty of collecting 24-hour urine samples it was decided to investigate the reliability of using random urine samples and expressing the results in terms of mg hydroxyproline per g creatinine.

The patients studied were all adults being investigated for possible thyroid disease, but excluding patients known to have other conditions which might be associated with changes in collagen metabolism. The thyroid status of the patients was assessed in all cases by history and clinical examination together with the determination of serum thyroxine iodine.³ In most cases radioiodine uptake tests and a triiodothyronine uptake test⁴ were also performed. On the basis of all the available information 50 patients were classified as euthyroid, 18 as hyperthyroid, and 6 as hypothyroid.

Random urine samples, taken on the same day as the blood samples for in-vitro thyroid function tests were analysed for total hydroxyproline⁵ and creatinine.⁶ The patients were not asked to restrict their intake of gelatin-containing foods prior to the collection of urine samples, but samples were collected between 9 a.m. and 6 p.m. to exclude early morning and nocturnal samples (see below).

Relationship between urinary hydroxyproline excretion and serum thyroxine iodine. Closed circles show values in euthyroid patients, open circles values in patients with thyroid disease. The horizontal line represents the upper limit of normal for hydroxyproline excretion and the vertical lines the normal range for thyroxine iodine. The oblique lines show the regression line $\pm$ 2S.D.

The normal and abnormal ranges for serum thyroxine iodine (corrected for 75% recovery) were as follows: euthyroid 3.5-8.0 μ g/100 ml, hypothyroid <4.0 μ g/100 ml, and hyperthyroid >7.5 μ g/100 ml. The normal range for hydroxyproline in random urine samples was taken as less than 42 mg/g creatinine. This was done because although the normal range for 24-hour urinary hydroxyproline in this laboratory is 6-42 mg/g creatinine, it was found that five of the euthyroid patients had random hydroxyproline levels below 2 mg/g creatinine. This finding is probably related to the time of

collection of the samples and the known circadian rhythm of hydroxyproline excretion,⁷ the rate being lowest at or soon after midday.

It was found that of the 18 patients classified as thyrotoxic only three had hydroxyproline values within the normal range. These normal values may have been associated with the fact that these patients had only moderately raised serum thyroxine iodine levels, all being between 8.0 and 9.0 μ g/100 ml, or may have been due to the time of day at which the urine samples were collected. The absence of a lower limit of normal for hydroxyproline values in the euthyroid patients precluded the test in this form from being of any value in the diagnosis of hypothyroidism, but the mean level in the small hypothyroid group, 8.6 mg/g creatinine, was markedly lower than the mean level for the euthyroid group, 15.0 mg/g creatinine.

A significant positive correlation between 24-hour urinary total hydroxyproline excretion and serum protein bound iodine in adults has previously been reported.² The figure shows the correlation between total hydroxyproline in random urine samples and serum thyroxine iodine levels in the 74 patients examined in this series. Analysis showed the correlation to be highly significant ($r = +0.82$, $p < 0.001$) and further analysis by the method of least squares gave a regression line of: Hydroxyproline (mg/g creatinine) = $6.04 \times$ thyroxine iodine (μ g/100 ml) - 14.6. The standard deviation (S.D.) on the line is ± 17.5 mg/g creatinine.

It is concluded that estimation of the hydroxyproline content of random urine samples is a useful ancillary test in the diagnosis of hyperthyroidism, giving as good separation of abnormal from normal as has been reported for the 24-hour test.² It is also concluded that the test in this form is, for the reasons discussed, of no value in the diagnosis of hypothyroidism. It must be stressed that this test is not a specific test of thyroid function and that consequently the results must be interpreted with caution in patients who also have other diseases which may be associated with disturbed collagen metabolism.

We would like to thank the physicians in the Bristol clinical area who have been kind enough to allow us to study patients under their care.—We are, etc.,

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C. A. PENNOCK

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- 1 Uitto, J., Laitinen, O., Lamberg, B.-A., and Kivirikko, K. I., *Clinica Chimica Acta*, 1968, 22, 583.
- 2 Lamberg, B.-A., et al., *Acta Endocrinologica (København)*, 1970, Suppl. No. 146, p. 23.
- 3 Murphy, B. P., *Journal of Laboratory and Clinical Medicine*, 1965, 66, 161.
- 4 Herbert, V., Gottlieb, C. W., Lau, K. S., Gilbert, P., and Silver, S., *Journal of Laboratory and Clinical Medicine*, 1965, 66, 814.
- 5 Pennock, C. A., Moore, G. R., and Hoyle, M. D., *Journal of Medical Laboratory Technology*, 1970, 27, 302.
- 6 Technicon Method File N-11.
- 7 Mautalen, C. A., *Journal of Laboratory and Clinical Medicine*, 1970, 75, 11.

G.M.C. Finances

SIR,—The General Medical Council has recently reminded us sharply of its lack of funds and proposes further financial levies.

In the past, many of us have felt that lack of business acumen and prudent

housekeeping had much to do with the parlous financial state in which the General Medical Council finds itself. We all hoped it would have remedied this, after the recent scrutiny of its financial arrangements. But alas, this is not so.

Following the policy of the British Medical Association agreed at the Special Representative Meeting last spring (*Supplement*, 21 February), I paid my donation this year on 25 October to the General Medical Council. Despite its vast overdraft it took a month to pay my £2 into the bank. I have enquired among my friends and it appears that the same dilatory attitude applies to the cheques of others. I would have thought that any properly run organization with an overdraft such as the General Medical Council runs would be along to the bank every day to pay in the money received as soon as it comes in.—I am, etc.,

J. S. ROSS

Welwyn Garden City,
Herts

Platelet Transfusions

SIR,—Is it the climate? Or is it the angle from which we view things in the Antipodes? Your excellent succinct leading article on platelet transfusions (2 January, p. 2) states that the dose for the treatment of thrombocytopenia comprises the platelet concentrates from ten donors twice weekly, but makes no mention of the technical work involved in preparing these concentrates. Our good friend Dr. R. A. Cumming and others (2 January, p. 50) in the correspondence columns of the same issue laments the ignorance of clinicians (their Antipodean counterparts are similarly uninformed) concerning the logistics of blood banking, but unfortunately omitted the details of the technical load. Yet if one starts with ten donations of blood collected without any interruption to the flow rate, as even microclots consume platelets, and provided a special centrifuge is available, it takes the equivalent of three accident-free technologist man-hours to carry out the necessary centrifugings and transfers of plasma to produce ten platelet concentrates.

However, two donations of blood less than 36 hours old, or the platelet rich plasma from five donations, if administered within 1-1½ hours, will produce the same therapeutic result as that obtained from the use of ten platelet concentrates in partial correction of thrombocytopenia, with the added bonus of partial correction of the severe leucopenia which often results from the use of "ablative" chemotherapy in the treatment of leukaemia. Circulatory overload can be avoided if a half litre of blood is removed from the patient before use of the citrated blood or platelet-rich plasma.

This technique, reported¹ in 1969 (and subsequently the subject of an annotation in the *Lancet*²) has been used successfully in Queensland and elsewhere for the past three years. It has a particular advantage in avoiding iron overload in the patient requiring prolonged treatment with twice-weekly withdrawals of half a litre of blood and alternate administration of a litre of blood or five platelet-rich plasma units. Currently the saving in our service—which caters for the needs of a population of nearly 2,000,000—

is in the vicinity of 5,000 blood donations annually, apart from the cost of the associated equipment for the preparation of platelet concentrates and the salary of a technologist over and above the salaries of the blood collection staff necessary.

In this country we have available a "mini-exchange" set,³ comprising a needle and tubing connected to one limb of a Y-piece which has a free length of tubing from another limb, and the third limb fits the needle adaptor on the standard giving set. This enables the whole manoeuvre of mini-exchange and transfusion to be carried out with a single venepuncture.—I am, etc.,

A. E. SHAW

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Red Cross Blood Transfusion Service,
Brisbane, Queensland, Australia

¹ Shaw, A. E., *Medical Journal of Australia*, 1969, 2, 529.

² *Lancet*, 1969, 2, 1176.

³ Obtainable from Tuta Laboratories, Lane Cove, Sydney, N.S.W., Australia.

Tuberculous Meningitis in Children

SIR,—May I comment on one point in your recent leading article on this subject (2 January, p. 1)? "An intradermal tuberculin test (Mantoux 1:1,000) should be carried out at once, but in advanced cases a negative result does not rule out tuberculous meningitis." Surely a negative result does not rule out an early case either? This warning is particularly needed in view of the higher incidence of the disease in underdeveloped countries where tuberculin reactions are often suppressed.^{1,2}—I am, etc.,

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London S.W.1

¹ Lloyd, A. V. C., *British Medical Journal*, 1968, 3, 529.

² Bhattacharyya, A. K., *British Medical Journal*, 1968, 4, 580.

Low Molecular Weight Dextran in Systemic Sclerosis

SIR,—Dr. Peter Lane's paper (12 December, p. 657) calls for comments on at least two major points. He implies in his introduction that he attempted to repeat my findings by using identical methods and treatments but my paper¹, as its title indicates, dealt with the "effect of intermittent low molecular weight dextran infusions upon the digital circulation in systemic sclerosis." In fairness, Dr. Lane states at the end of his paper that final conclusions cannot be drawn from his own series of patients since each patient received only one infusion of low molecular weight dextran. I have more recently² emphasized that patients who have not previously been treated with this regimen may require infusions of 2 litres of low molecular weight dextran, given over 48 hours, initially at intervals of three to four weeks on three or four occasions, before the peripheral blood-flow is improved. Subsequently intervals between infusions have been extended and my first 3 patients, treated since 1964, have not required dextran infusions for the past 14 months because of their maintained satisfactory digital bloodflow. Each has

received 15 infusions so far. Others have confirmed the efficacy of this regimen.^{3,6}

It is important to ensure that the kidneys are protected against unduly high concentrations of dextran. Our nursing staff has instructions to slow down the rate of infusions (normally 2 l. over 48 hours) if the specific gravity of urine exceeds 1045. During the past 6 years I have treated 35 patients suffering from systemic sclerosis and 98 affected by other disorders associated with obliterative disorders of small blood vessels with a total of 1,121 dextran infusions without adverse renal side effects in a single patient. Dr. Lane rightly states that systemic sclerosis is an intractable condition for which there is no specific treatment. Ischaemic digital changes, with or without intractable ulceration, can make the life of these patients utterly miserable. I hope that Dr. Lane's paper will not dissuade any physician from using a treatment which, in my experience, is beneficial as well as safe provided simple precautions are observed.—I am, etc.,

G. HOLTI

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Royal Victoria Infirmary,
Newcastle upon Tyne

¹ Holti, G., *British Journal of Dermatology*, 1965, 77, 560.

² Holti, G., *Practitioner*, 1970, 204, 644.

³ *Year Book of Dermatology*, 1966-67, p. 94. Year Book Medical Publishers, Chicago.

⁴ Korting, G. W., and Holzmänn, H., *Die Sklerodermie und ihre nahestehenden Bindegewebsprobleme*, p. 293. Stuttgart, Thieme.

⁵ Alani, M. D., 1970, *Acta Dermato-Venerologica*, 50, 137.

⁶ Burrows, D., Shanks, R. G., and Stevenson, C. J., *British Journal of Dermatology*, 1968, 80, 767.

Problems in Quebec

SIR,—"No man is an Island, entire of itself."

I am writing to draw your attention to recent events affecting our medical colleagues in the Province of Quebec. The source of my information is friends and colleagues working there, and also the *Canadian Medical Journal*.^{1,2} In June last, the Quebec Government passed Bill 8 creating a compulsory Medicare Scheme with a very low fee schedule for specialists, at the same time denying to the latter or to the public the right to opt out of the scheme. The specialists refused to take part and limited their services to a hospital emergency cover scheme. In response the Government, in October, passed the notorious Bill 41; the salient features of this were:

(1) All doctors were ordered back to work under threat of imprisonment or heavy fine.

(2) Similarly it disallowed their freedom to move their practice or place of work and equally forbade them "even to speak against the order."

(3) It made it an offence, liable to a gigantic fine, for any association or group to encourage a medical specialist to defy the order, and allowed for the imprisonment of its individual officers "without even prosecution or conviction."

The equivalent in this country of this selective withdrawal of civil rights would be if you sir, in speaking against the government order, were liable to imprisonment without trial or conviction. As the president of the C.M.A. rightly stated, the medical specialists have been "conscripted, muzzled and threatened with gaol terms." This

vicious deprivation of civil rights and threat to our colleagues, however far removed geographically, must be our own direct concern.

"Any man's death diminishes me, because I am involved in Mankind; And therefore never send to know for whom the bell tolls; it tolls for thee."—I am, etc.,

GEOFFREY STEEL

London S.W.15

¹ *Canadian Medical Journal*, 1970, 103, 1106.

² *Canadian Medical Journal*, 1970, 103, 1308.

Prostatic Acid Phosphatase

SIR,—I have read with interest the report of Mr. D. Dow and Mr. R. H. Whitaker (21 November, p. 470) with regard to the prostate and level of acid phosphatase. In this study, the authors state that "there is no justification for referring to the tartrate-labile serum acid phosphatase as 'prostatic acid phosphatase.'" With reference to the prostate gland in man, I should like to point out that in our immunological studies of normal human prostatic tissue¹ we have identified two tissue- and species-specific antigens, one of which, through the specific immunochemical staining of the gel-precipitation pattern by a modification of the Gomori histochemical procedure, was identified as prostatic acid phosphatase. Furthermore, we have recently concluded an investigation in which specifically absorbed heteroimmune sera to saline extracts of benign and malignant human prostatic tissue were employed in an attempt to compare the antigenic composition of these tissues with that of normal human prostatic tissue through the utilization of the adjunct specificity of antigen-antibody interaction in gel diffusion precipitation and enzymatic analysis.² Results suggest that benign and malignant prostatic tissue are, in comparison with normal prostatic tissue, antigenically deficient. The possible deficiency of normal prostate-specific antigens, particularly prostatic tissue-specific acid phosphatase antigens, in extract preparations of malignant prostatic tissue has been particularly interesting in view of previous chemical and histochemical reports of diminished quantities of acid phosphatase in patients with advanced carcinoma of the prostate.^{3,6}

The possible prognostic and therapeutic utilization of the detection of the antigenic deficiency of specific prostatic tissue-specific acid phosphatase antigens looms as a possibility pending the demonstration of a definitive correlation between the presence or absence of specific prostatic tissue-specific acid phosphatase antigens and the histological confirmation of the stage of prostatic carcinoma.—I am, etc.,

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Immunology Section, Renal Unit,
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Springfield, Ill., U.S.A.

¹ Ablin, R. J., Bronson, P., Soanes, W. A., and Witelsky, E., *Journal of Immunology*, 1970, 104, 1329.

² Ablin, R. J., Witelsky, E., Bronson, P., and Soanes, W. A., in press.

³ Woodard, H. Q., and Dean, A. L., *Journal of Urology*, 1947, 57, 158.

⁴ Kirchheim, D., Györkey, F., Brandes, D., and Scott, W. W., *Investigative Urology*, 1964, 1, 403.

⁵ Parkin, L., Bylsma, G., Torre, A. V., Drew, D., and Madden R. J., *Journal of Histochemistry and Cytochemistry*, 1964, 12, 288.

⁶ Kent, J. R., Hill, M., and Bischoff, A., *Cancer (Philadelphia)*, 1970, 25, 858.