Duration of Council Membership

SIR,—I was interested, but dismayed, to see the short shrift given to Dr. G. D. H. McQuitty's proposal (*Supplement*, 1 August, p. 92) concerning the long stay of various members of the Council—that they should give way to younger men, perhaps more in tune with the present-day practitioners.

It is the natural reaction of those in power to protect the establishment, and while this applies to the practitioners it applies perhaps just as much to the consultants and their representative committees. Many of the members have been giving judgments and making decisions ever since the inception of the National Health Service, and I feel that it is perhaps time that those who are more in touch with the opinions of the present-day consultants should have their chance.

I have had experience of this; it is amazing how once a representative committee is formed they perpetually vote each other on to the more senior committees, and any proposals to replace them are met with horror and indignation. The usual response is that, of course, they, after about six years' service as members of a committee, only now are able to appreciate nuances and subtleties of dealing with the Government representatives or with their own particular committee work. This says little for the average intelligence of most medical men, and I am sure it does not take all this time to appreciate the work of a committee and become *au fait* with the various intricacies of business, either as medical representatives or on regional hospital boards. This is due, I am sure, to the fact that none of the hospital committees, or very few of them, has any limit to the time for which their representatives can serve, and I regard this as the crux of the matter. I feel sure that the spark kindled by Dr. McQuitty has not been entirely damped out by the cavalier way in which his proposal was dealt with, and I wish him every success should he try again. I only hope that this could apply to the members who have been our representatives on consulting committees for the last 18 years, many of whom have become, I am sure, almost fossilized in their opinions.

It would appear that no medical man under the age of 35 is capable of dealing with our overlords. I might say that I myself served for a short time on the Central Consultants Committee, but now in no way could I represent the feelings of the present generation of consultants and have no wish to do so.

Like many of my colleagues all I am hoping for now is that I can get through the next seven years without too early an acquaintanceship with the obituary column.—I am, etc.,

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World Health Research Centre

SIR,—I should like to support Professor K. W. Donald's plea (25 July, p. 245) for a more balanced judgment regarding the establishment of a World Health Research Centre in this country. Your editorial (27 June, p. 1653) brought out many of the points against

the project without at the same time giving due weight to those in its favour. It is for instance scarcely fair to refer in slighting terms to the proposed centre "with half a million mice in Edinburgh" as a "grandiose misconception" without referring to the arguments put forward by those who have expended not only "sincerity and enthusiasm" but much thought and hard work in preparing the scheme. Certainly any unwise and overlavish expenditure is to be deprecated, but in a year when one leading country has trebled its expenditure on biological and chemical warfare, involving a sum over five times that envisaged for even the fifth year of the proposed research centre, it is at least refreshing to contemplate a project which will absorb medical men and scientists from many different countries into constructive activities, the results of which will be openly published. I am sure you will agree that international co-operation in the medical field is particularly important at the present time and that any scheme which promises to extend and deepen this co-operation should be given a fair hearing. Personally, I regard the progressive extension of international co-operation amongst medical men as a vital need not only for the progress of medicine

but as a means of creating saner and healthier contacts between nations.

Next year, 1965, has been designated International Co-operation Year by the General Assembly of the United Nations, during which it is suggested that existing co-operation between nations should be accorded greater emphasis not only by Governments but by non-governmental agencies. This would seem to offer a useful—and indeed exciting—opportunity for national and international medical societies to renew or extend their international contacts. The B.M.A., which has a fine record of achievement in this field, will no doubt be giving due consideration to this matter and to the various means by which it can be implemented. As Professor Donald implies national organizations should be able to rise to the challenge of international problems. It is scarcely comforting to think of the possible outcome should we fail.—I am, etc.,

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** The leader of 27 June stated: "The project has been described as a 'grandiose misconception.'" This description was *The Guardian's*—Ed., B.M.J.

Hyperparathyroidism and Cancer

SIR,—I read with interest the case report by Professor C. E. Dent and Dr. L. C. A. Watson (25 July, p. 218). The differential diagnosis of hypercalcaemia when more than one known cause is present is indeed a challenging problem, and I should like to mention a similar patient who was investigated recently by Professor L. N. Pyrah, Mr. M. Fox, Dr. C. K. Anderson, and myself.

A woman, aged 59 years, was admitted to this hospital in November 1963 with left loin pain. A radiograph of the renal tract revealed a large stone in the left kidney. There was also a hard mass in the left kidney on palpation. Radiographs of the skull and hands were normal except for very slight subperiosteal erosions in the metacarpals.

The serum total calcium varied between 15.2 and 16.3 mg./100 ml., phosphate 3.7 to 4.2 mg./100 ml., alkaline phosphatase 13 to 15 K.A. units, CO₂-combining power 22 mEq/l., urea 105 mg./100 ml., sodium 105 mEq/l., potassium 2.6 mEq/l., total protein 7.2 mg./100 ml., A/G ratio 0.7. An electrophoretic pattern of the plasma proteins showed slightly increased α_1 and α_2 globulins.

A surgical exploration of the neck was carried out by Professor Pyrah in December 1963, when a right superior chief-cell parathyroid adenoma weighing 442 mg. was found. Post-operatively the serum calcium fell to between 12.0 and 12.5 mg./100 ml. and remained at this level despite a second exploration of the neck when the mediastinum was divided and both the lower lobes of the thyroids were excised. The patient's condition gradually deteriorated and she died on 30 January 1964. At necropsy a poorly differentiated transitional-cell carcinoma of the renal pelvis was found with extensive squamous metaplasia. There was also extensive histological evidence of osteitis fibrosa cystica (Dr. C. K. Anderson). It seems probable that the residual hypercalcaemia following parathyroidectomy was due to the renal tumour. In retrospect I feel that greater attention should have been paid to the raised serum α_1 and α_2 globulin pattern, which is indicative of cancer.

The association of clinical and biochemical indications of primary hyperparathyroidism with malignant non-parathyroid tumours not

metastatic to bone is now well recognized.¹ It has long been suspected that these tumours might be producing parathyroid hormone or a very closely related protein,² and recent immunochemical evidence supports this view.³

Finally, I should like to refer to Professor Dent and Dr. Watson's comment on a recent paper of mine.⁴ Since this paper appeared there have been further reports⁵ indicating that bone involvement in primary hyperparathyroidism is more widespread than is generally believed. The present case provides further evidence of the limitations of x-rays and alkaline-phosphatase levels for detecting small bone changes. This and the evidence quoted in my paper strongly suggests that the distinction of primary hyperparathyroidism "with" and "without" bone disease is not warranted on scientific grounds though the distinction may well have clinical usefulness.—I am, etc.,

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Endocardial Fibroelastosis

SIR,—The paper by Professor J. O. Forfar and his colleagues (4 July, p. 7) on endocardial fibroelastosis interested me. However, I noted that the authors in their aetiological considerations did not mention recent findings suggesting a prenatal virus infection as a cause of endocardial fibroelastosis.

Fruhling and his co-workers¹ put forward the thesis of viral origin for morphological, virological, and epidemiological reasons. These authors studied 81 necropsies of children mostly under the age of 1 year with endocardial fibroelastosis. Virologic studies in the last 28 cases disclosed in 13 cases the presence of Coxsackie B (chiefly B3) in the myocardium. In a few cases the virus also was isolated from other viscera. In additional animal experiments and clinical observations the authors demonstrated evidence for placental transmission of Coxsackie B virus. They assume that sometimes immune tolerance acquired by the mother and/or the foetus against Coxsackie virus is responsible for the presence of the virus much later. Fruhling *et al.* conclude that endocardial fibroelastosis is a malformation caused by prenatal virus pancarditis in early pregnancy. They interpret the hypoplastic left-heart syndrome as involution by retractile sclerosis secondary to the same inflammatory process. There was an increase in the number of cases of fibroelastosis per year in Strasbourg corresponding to three epidemics of Coxsackie B infections in Eastern France between 1952 and 1961.

More recently Szanto and his colleagues² found myocarditis at necropsy in two-thirds of 60 cases of endocardial fibroelastosis. Whether or not this proves the aetiology of endocardial fibroelastosis remains an open question. But the viral theory certainly demands serious consideration.—I am, etc.,

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Drug and Viral Jaundice

SIR,—Your leading article (11 July, p. 69) on the epidemiology of infectious hepatitis is of interest to psychiatrists who may be faced with the problem of patients on monoamine oxidase inhibitor (M.A.O.I.) drugs who develop jaundice. Present virological and biochemical tests cannot distinguish between drug jaundice and infectious hepatitis in an individual case.

Epidemiological methods may be helpful. If a psychiatric patient who is on an M.A.O.I., chlorpromazine, or any other drug develops jaundice whilst in a hospital ward, serial S.G.O.T. and S.G.P.T. levels should be estimated in the rest of the patients and in the staff of that ward. If the jaundice is infectious on average 8 to 10 non-icteric cases will develop in about 10–50 days and will show rising transaminase levels, but this will not occur with purely drug jaundice.

In general practice and in out-patients the problem is more difficult. There is a good case for making infectious hepatitis a nationally notifiable disease. In the U.S.A., where the disease is notifiable, 7-year peak incidences are seen. If these peaks also occur in the U.K., and if a peak incidence coincides with the introduction of a new M.A.O.I. drug, the drug may appear to cause the jaundice. The

periodic variation in the incidence of infectious hepatitis may be one explanation why psychiatric drugs seem to have caused more jaundice in some years than in others.

Information from 56 general practitioners whose patients were treated for depressive illness in the out-patient department at St. Thomas's revealed that in the period 1958–63 there were three cases of jaundice in patients on antidepressant drugs, 17 cases on chlorpromazine, and 33 cases not on these drugs who were diagnosed as infectious hepatitis. These figures are not very informative unless we know the total patients on these drugs and the attack rate of infectious hepatitis in the practice populations in a 5-year period.

We can make some guesses. Fifty-six practices, averaging 2,500 patients each, showed 33 cases of infectious hepatitis in five years. For every icteric case there would be about 10 non-icteric cases who have subsequent immunity, and a substantial majority of adults who remain uninfected, or are not susceptible. We may guess that only one-tenth are at risk for developing clinically icteric infectious hepatitis. Rough estimates from personal inquiries suggest that on average about 60 patients in one practice may be on M.A.O.I. drugs at some time in a 5-year period and about 200 on chlorpromazine. This gives an incidence rate of jaundice from the above figures of 1 in 425 for infectious hepatitis with jaundice, 1 in 1,120 for antidepressant drugs, and 1 in 660 for chlorpromazine, for the populations at risk and during a 5-year period.

We hope that the Committee on Safety of Drugs will soon have something more positive to offer than warnings on the use of M.A.O.I. drugs, as they are collecting national figures; but these will not mean much unless the incidence of jaundice indistinguishable from drug jaundice is known on a national scale. Perhaps the Royal College of Psychiatrists will be able to collaborate with the College of General Practitioners on this subject.

We must remember salvarsan jaundice. This disappeared when needles were autoclaved in V.D. clinics.—I am, etc.,

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Chlormethiazole

SIR,—Your "To-day's Drugs" section (18 July, p. 171) reviews the above-named drug (Heminevrin), recommended for acute alcoholic and manic states, stating that as yet no trials have been carried out in this country or the U.S.A., and that there was still in-

sufficient evidence to assess the value of the drug when given orally.

A controlled, double-blind trial comparing this drug with a placebo has just been completed at St. Bernard's Hospital. The patients concerned included approximately 100 male and female alcoholics admitted in states of varying degrees of alcoholic intoxication; they were given the drug in the form of tablets for six days. Patients were observed by doctors and the nursing staff during this period in regard to their general condition, to certain symptoms, and to possible side-effects. There was a statistically significant difference between the effects of the active drug and the placebo, as can be seen in the Table below.

Your review states that the drug should not be given in the presence of depression. No evidence could be found in our trial to support this statement. Thus, of 24 alcoholics who were *not* depressed at the time of admission, and received the placebo, 10 developed depression subsequently during the trial period, whereas the corresponding figures in the patients receiving the active tablets were two out of 21 patients; this difference is statistically probably significant ($0.05 > P > 0.01$). Out of a total of 49 alcoholics in the Heminevrin group one was still depressed on the sixth day of the trial, as against 10 out of 48 patients in the placebo group. This difference is statistically significant at the 1% level. So many alcoholics are in a state of (reactive) depression when presenting themselves for treatment (in our present series over 50%) that it seems important to us to stress the point that in our experience depression in itself does not contraindicate the administration of Heminevrin, which we found to be a valuable drug in the management of the withdrawal period in alcoholics.

We hope to be able to publish a more detailed report of the trial in the near future.—We are, etc.,

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M. M. GLATT.
H. R. GEORGE.

T.A.B. Reactions

SIR,—Reference the letter from Dr. A. J. Zuckerman (11 July, p. 119), intradermal T.A.B. was introduced into the Army at the time of the Suez crisis to enable vaccinated men to proceed without delay, and not to be incapacitated by systemic reactions. It was never suggested that there would be no local reaction.

Although a day's rest is ideal after intradermal T.A.B., it is not essential. Anyone who has experienced both types of vaccination will have no hesitation in choosing intra-

Day of Treatment	Preparation	No. of Patients	Assessment of Therapy by Doctor		Comparison between Preparations χ^2 -value and Level of Significance
			Greatly Improved and Improved	Unchanged and Impaired	
1	Heminevrin	48*	24	24	7.599 0.01 > P > 0.001
	Placebo	48	11	37	
2	Heminevrin	49	33	16	15.765 P < 0.001
	Placebo	48	13	35	
3	Heminevrin	49	35	24	8.748 0.01 > P > 0.001
	Placebo	48	20	28	

* 1 form incomplete.