Diabetic Nephropathy

SIR,—Your leading article (5 July, p. 5) carefully avoids the important problem of pathogenesis by substituting a plea for study of the "natural history." I also would wish to avoid discussion of the interesting biochemical theories which will account for the thickened permeable basement membrane. However, I wish to draw attention to other points which may truly lie at the root of the matter. The first is that in animal experiments I have shown that the mesangial cells show a diminished phagocytic capacity in streptozotocin-induced diabetes.[1] This could explain why fibrinoid material accumulates in the mesangial areas.

You note in your leading article that there comes a stage when a downhill course is certain. Dr. George Drivas and myself think that we have identified such a stage because our data on the clearances of microaggregated iodinated human serum albumin show a difference between diabetics without renal disease and those with established nephropathy. This may be briefly summarized as follows:

Half Life in Minutes or Microaggregated Albumin

8 "normal" diabetics	12·6±2·0	$t=3·74$ for 13 d.f.
7 K.W. diabetics	18·7±3·6	$P<0·005$

Thus in these patients there is an impairment of the phagocytic capacity of the Kupffer cells of the liver. As yet the reasons are speculative, and we are still performing more detailed kinetic studies. However, it might mean that these cells are loaded with lipoproteins. It might also indicate a general indisposition of phagocytic cells in diabetes and therefore an enhanced susceptibility to infection. Indeed, it is well known that leucocytes function at a disadvantage even early in diabetes. It may be that we are now able to identify those patients who have entered the "vicious cycle."—I am, etc.,

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1 Wardle, E. N., *Biomedicine*. In press, 1975.

Fifty Years in Tavistock Square

SIR,—The article Fifty Years in Tavistock Square (12 July, p. 90) calls to mind the controversial subject of the Epstein statues. When the third B.M.A. House at 429, Strand, was reconstructed, Jacob Epstein was commissioned to erect a series of statues on the front facing Agar Street at the level of the first floor. When these were revealed to the public there was at once a flood of violent criticism. They were condemned by a large number of critics as hideous and indecent. The sculptor at this time was only little known and his work was not appreciated as it subsequently came to be. In this case the B.M.A. was in advance of its time. —I am, etc.,

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Abortion (Amendment) Bill

SIR,—May I, through you, invite doctors or nurses to write to the Select Committee giving their views on the proposed alteration of the 1967 Abortion Act? Especially, as a member of the Select Committee, I should be interested to have views on the impact the phrases "*grave* risk to the life of the pregnant woman," and "risk of *serious* injury to the physical or mental health of the pregnant woman."

What the sponsors intend by these phrases is that Parliament wants to make it clear that "abortion on demand" was not the intention of the 1967 Act. Indeed, the sponsor, Mr. David Steele, introducing his Bill used these words: "It is not the intention of the promotion of the Bill to leave a wide open door for abortion on request."[1]—I am, etc.,

JAMES WHITE

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1 *Hansard*, House of Commons, 22 July 1966, col. 1075.

SI Units

SIR,—Hospital districts are receiving the circular H.S.C. (1S)140 (Metrication: Introduction into Medicine of the International System of Units) stating this should be implemented by 1 December 1975. This is in response to recommendations of a working party of eight bodies "representing scientific interests," and there appears to have been no consultation with the royal colleges (except that of the pathologists) or those in clinical charge of patients. In some instances SI units have nothing to do with metrication whatsoever.

This is being rushed through without adequate consultation, and clinicians should express their views strongly at district level before this becomes fait accompli, or else, like the recent reorganization, it will be too late to influence the course of events. Meanwhile SI units should not be accepted in hospital practice until there is a clear consensus opinion of their value and dangers expressed by clinicians with direct responsibilities for patients.—I am, etc.,

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Pyridoxine and Oral Glucose Tolerance in Pregnancy

SIR,—We should like to congratulate Drs. H. J. T. Coelingh Bennink and W. H. P. Schreurs on their study of the effect of pyridoxine on gestational diabetes (5 July, p. 13). Their view of the possible role of this vitamin in preventing insulin antagonism is extremely interesting, especially at a time when we are beginning to realize that the resistance to insulin on the peripheral uptake of glucose found in pregnancy[1] does not apply to its antilipolytic actions in adipose tissue from pregnant women (T. M. Coltart and Christine Williams, unpublished findings).

We feel, however, that another explanation of the effect of B_6 administration on glucose tolerance is possible. It can be seen that in situations where there is a relative deficiency of pyridoxine the production of nicotinic acid via this pathway is reduced. Since nicotinic acid is a potent antilipolytic agent[2] free fatty acid output in this situation could be enhanced. As the authors stated, free fatty acids have been suggested as a possible insulin antagonist[3] and could be responsible for the development of insulin resistance. The administration of B_6 with the concomitant increase in nicotinic acid production may result in a fall in free fatty release from adipose tissue, thereby removing another possible insulin antagonist.

Furthermore, we should like to sound a word of caution concerning the possible influence of diet and changes in weight on their results. They state on the one hand that patients were put on a diet and in the next breath they renounce any effect, in their hands, of diet on glucose tolerance. The example they cite of a 27-year-old para 2 who lost 2·5 kg in weight between 29 and 36½ weeks is an unphysiological situation by obstetric standards. Since both diet and weight changes are known to influence oral glucose tolerance we feel these factors should be taken into account before coming to any definite conclusions.—We are, etc.,

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1 Burt, R. L., and Davidson, I. W., *Journal of Obstetrics and Gynecology*, 1974, **43**, 161.
2 Butcher, R. W., Baird, C. E., and Sutherland, E. W., *Journal of Biological Chemistry*, 1968, **243**, 1705.
3 Randle, P. J., *et al.*, *Lancet*, 1963, **1**, 785.

Cigarette Smoking and Plasma Cholesterol

SIR,—The plasma cholesterol levels that we found in a study of 30 subjects who had been smoking cigarettes for over one year are interesting.

Blood samples were collected in the post-absorptive state after overnight abstinence from smoking.[1] The subjects were then asked to smoke one cigarette of their own brand. Immediately after and again after 90 minutes blood samples were collected and analysed for plasma cholesterol. There was a statistically significant increase in plasma cholesterol from the basal presmoking level (t by null hypothesis is 10·90, $P<0·0001$). After 90 minutes cholesterol levels in more than 65% of cases were still a little higher than the basal levels (t is 2·068 and $P=0·05$).

We know of no report about the statistically significant increase in plasma cholesterol immediately after smoking one cigarette in humans except that of Short and Johnson,[2] who reported changes in blood cholesterol for 60 to 90 minutes in five normal habitual smokers while they were smoking cigarettes. There was no mention of the number of cigarettes smoked. A slight tendency to an increase in cholesterol during tobacco smoking was noted.

Recently there was a report on cigarette smoking and serum chemistry by Dales *et al.*[3] Their experimental situation was different from ours. They compared age-specific cholesterol values in White and Black smokers and non-smokers. They observed that cholesterol levels were higher in the White men who smoked but not in the Black male smokers. We report our results, firstly, because of the association of smoking cigarettes with an immediate rise in plasma cholesterol, and, secondly, to show that if the basal level is to be obtained from a cholesterol estimation the subject must refrain from smoking for a period of at least

four to five hours before the blood sample is taken. Failure to take this precaution may result in fluctuating results.—We are, etc.,

C. SITA DEVI
C. R. R. M. REDDY
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1 Zak, B., *American Journal of Clinical Pathology*, 1957, **27**, 583.
2 Short, J. J., and Johnson, H. J., *Journal of Laboratory and Clinical Medicine*, 1938, **24**, 590.
3 Dales, L. G., *et al.*, *Journal of Chronic Diseases*, 1974, **27**, 293.

Fractures and Fluoride

SIR,—Opponents of water fluoridation are already quoting the results reported by Dr. J. Inkovaara and others (12 July, p. 73) as proof that fluoride causes fractures in old people. Before this assertion passes into the popular mythology of the antifluoridation movement there are a number of pertinent points to be made.

The fluoride intake of patients in the group given prophylactic treatment by the Finnish workers was the equivalent of drinking 25 litres (44 pints) of water at 1 p.p.m. F each day for five months and 25 litres each day on two days every week for a further three months. The reader can judge how relevant this regimen could possibly be to water fluoridation.

Patients with known osteoporosis were included in the trial but the report does not say how many were in the group given prophylactic fluoride treatment and how many were in the control group, nor how many of the fractures were sustained by these osteoporotic patients. Nevertheless, the authors believe that fluoride was "probably partly responsible" for the fractures in the treatment group but it is doubtful whether this view, cautious though it be, is upheld by the evidence. The incidence of fractures in the elderly increases exponentially with age. The mean age may not therefore be the appropriate statistic to use in order to demonstrate that the treatment and control groups were comparable with respect to this important variable. In one respect the groups were certainly not comparable: 83% of the treated patients were women compared with 74% of the controls. Since the incidence of fractures among elderly women is two to three times that of elderly men of the same age one would expect, on this basis alone, more fractures in the treatment group than among the controls.

It is difficult from the information in the paper to determine which denominators should be used in seeking to assess how significant is the excess of five fractures in the treatment group over the course of the trial. Assuming that all patients with fractures were hospitalized there were 42 patients in the treatment group and 35 controls hospitalized for other reasons. Subtracting these numbers and the numbers "discontinued" from the numbers at onset would leave 157 in the treatment group and 175 controls. The distribution between the two groups of the 17 fractures that occurred during the trial could easily have arisen as random variation (χ^2 with Yates's correction $= 1{\cdot}51$; $0{\cdot}2 < P < 0{\cdot}3$).

It is not clear how much account should be taken of the three fractures that occurred in the treatment group in the month after the trial was ended. How many fractures occurred in each group the following month and the month after that? The trial ended in January 1972, and one would wish to have rather more information about the subsequent experience of the two groups in a report than appears in print three and a half years later. But even if these late fractures are added to the number of earlier ones, using the same denominators as before, the difference between the groups in the frequency of fractures is still not significant at the conventional 5% level (χ^2 with Yates's correction $= 3{\cdot}49$).

In one respect the results reported were reassuring. They indicate how rapidly the free ionized fluoride levels in plasma came to approximate the control level in elderly persons receiving 50 mg fluoride a week additional to their diet, having previously been given relatively massive doses (25 mg a day) for five months.—I am, etc.,

G. WYNNE GRIFFITH

Beaumaris, Gwynedd

Prolactin, Bromocriptine, and Haemostasis

SIR,—In the past two years we have treated large numbers of rats, guinea pigs, and mice with prolactin and the prolactin-suppressing drug bromocriptine. We have repeatedly noticed that blood from prolactin-treated animals clots very rapidly, and this has caused problems in the conduct of experiments. We have just attempted to quantify this effect by making observations on 40 Balb/c mice.

Ten mice were treated for 14 days with control saline injections, 10 with 500 µg/day ovine prolactin, 10 with 500 µg/day bromocriptine, and 10 with both prolactin and bromocriptine. Under ether anaesthesia the terminal 1 cm of tail was cut off. With the tail hanging down the blood was allowed to drip. The drops were removed by filter paper without touching the tail itself until the bleeding stopped. After one minute of bleeding three drops were collected on a clean microscope slide, which was then rocked backwards and forwards at room temperature until coagulation occurred. The results are shown in the table.

Effects of various treatments on bleeding time and whole blood coagulation time in Balb/c mice. Bleeding time was taken as the time from collecting first drop of blood to coagulation. Results expressed in seconds ± S.E.M.

Treatment	Bleeding Time	Coagulation Time
Control saline	353 ± 42	371 ± 22
Prolactin 500 µg /day ..	305 ± 55	211 ± 21
Bromocriptine 500 µg/day	192 ± 30	359 ± 36
Prolactin + bromocriptine ..	236 ± 26	373 ± 21

Prolactin shortened the bleeding time by a non-significant amount whereas both bromocriptine ($P < 0{\cdot}025$) and prolactin + bromocriptine ($P < 0{\cdot}05$) shortened it significantly. Only prolactin given alone had any effect on the coagulation time, which was highly significantly reduced ($P < 0{\cdot}001$).

We recognize that sophisticated techniques are required for the full investigation of changes in haemostasis and coagulation. We are not in a position to follow up this work but we hope someone else may do so. Prolactin levels are raised during surgery,[1] admission to a coronary care unit,[2] and oral contraceptive therapy,[3] so the effects could have clinical significance. We wish to point out that bromocriptine opposed the action of injected prolactin on coagulation and so could not have been working by suppressing prolactin secretion. We have argued elsewhere that bromocriptine may block prolactin actions peripherally as well as suppressing its secretion centrally,[4] and these results support that view.

We thank Professor E. Flückiger of Sandoz, Basel, for the bromocriptine and the North of England Cancer Campaign and the Ernest Hart Fund of the British Medical Association for financial support.

—We are, etc.,

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1 Noel, G. L., *et al.*, *Journal of Endocrinology and Metabolism*, 1972, **35**, 840.
2 Horrobin, D. F., *et al.*, *Lancet*, 1973, **2**, 1261.
3 Buckman, M. T., and Peake, G. T., *Journal of Clinical Endocrinology and Metabolism*, 1973, **37**, 977.
4 Horrobin, D. F., *Prolactin*. Montreal, Eden Press, in press, 1975.

Hormones, Elderly Testes, and Carcinoma of the Prostate

SIR,—Your leading article (5 July, p. 2) rightly draws attention to the wide variation in Leydig cell function found in men of advanced years but does not indicate the possible significance of these findings in the management of carcinoma of the prostate. Hormonal manipulation with oestrogen therapy or bilateral orchidectomy is widely used in the treatment of advanced prostatic cancer, but as yet no attempt is made to assess the testicular function of the patient before therapy is commenced. Though there are individual patients whose symptoms and signs respond dramatically either to bilateral orchidectomy or to oestrogen administration, there are also patients whose tumour does not respond to hormonal therapy.

We have found a wide variation in the Leydig cell function (as measured by serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) concentrations) of elderly men presenting with untreated carcinoma of the prostate. Our preliminary unpublished results show that some patients have good Leydig cell function comparable to that observed in young men. Others, however, have a hormone profile similar to that observed after castration. During the week after bilateral orchidectomy there is a dramatic fall in the concentration of testosterone and the concentration of LH and FSH is increased in the patients with normal Leydig cell function, but, as might have been expected, there is little or no change in the already abnormal concentrations of testosterone, LH, and FSH in men with pre-existing Leydig cell failure.

Provided that the tumour is intrinsically hormone dependent it seems reasonable to suggest that the response of carcinoma of the prostate to orchidectomy, and possibly administration of oestrogens, should correlate with the degree of hormonal deficit created by therapy. We are currently testing this hypothesis in a study designed to determine whether the response of carcinoma of the prostate to orchidectomy or oestrogen administration is dependent on the initial Leydig cell function of the patient and whether routine measurement of the concentrations of testosterone, LH, and FSH in serum might provide a basis for identification of those patients whose tumour will respond to hormone manipulation.—We are, etc.,

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