results eliminates the principal source of error which has given rise to problems encountered with the Corning kit, and the manufacturers have now incorporated this change into their recommended protocol.¹ Nevertheless other, albeit relatively minor, TBG-dependent effects (for example, the "non-specific" binding of radioactive T₄ to the solid-supported antibody used in this kit) may influence free T₄ determinations made on the basis of the recommended Corning assay procedure, and thereby distort free T₄ values in subjects in whom thyroxine-binding protein concentrations are significantly altered. The physiological significance of small changes observed in pregnant subjects in serum free T₄ (as measured using the Corning technique) may in consequence be questionable, although the use of this kit in a diagnostic role may not be significantly compromised by any minor residual sources of error that it may contain.

Meanwhile a reduction in free T₄ concentration during pregnancy has also been reported by a number of other workers (for example, Avruskin *et al.*² and Arango *et al.*³) using a variety of conventional free T₄ assay techniques (albeit the magnitude of the effect has been less than that reported by Boss *et al.*). Many of these techniques have likewise proved to be methodologically suspect, yielding apparent free T₄ values significantly higher than those observed with modern "direct" methods (see, for example, Ekins⁴). Were the observation of a reduced free thyroid hormone concentration in pregnancy to be confirmed, however, speculation must arise regarding the physiological role of the free hormone moiety and the nature of mechanisms governing thyroid hormone transport and control.

In attempting to establish the validity of the reported changes in pregnancy, we have used a new "direct" method for free T₄ measurement developed in this laboratory. In brief, the method involves the incubation, at 37°C for one hour, of serum with T₄ antiserum linked to a particulate solid support (Sephadex) followed by separation of the antibody from the serum; subsequently the amount of T₄ bound to antibody is estimated by "back titration" with ¹²⁵I-labelled T₄. Serum standards for the system have been calibrated by an equilibrium dialysis technique relying on direct radioimmunoassay of T₄ in the dialysate.⁵ (This method represents an entirely novel approach to free hormone measurement, the theoretical and methodological basis of which will be presented in detail elsewhere.)

Serum samples were collected from normal women attending a gynaecological clinic for contraceptive advice (none were on oral contraceptives) and also from pregnant patients attending the antenatal clinic. To minimise any possible methodological bias normal and pregnancy sera were placed as alternate samples within each assay batch. The normal samples yielded a mean free T₄ concentration of 15.12 pmol/l (1.17 ng/100 ml) (n = 100, SE of mean 0.32 (0.02)) with a range of 9.8–22.4 pmol/l (0.76–1.74 ng/100 ml). For the pregnancy samples the mean concentration was reduced to 13.6 pmol/l (1.06 ng/100 ml) (n = 123, SE of mean 0.26 (0.02); *t* = 3.68). The results of the 101 patients whose stage of pregnancy was known are shown in the figure. The free T₄ concentration appeared lower in the second half of pregnancy, with a mean value of 12.2 pmol/l (0.95 ng/100 ml) (n = 45, SE of mean 0.33 (0.02)); in the first half of pregnancy the results were near normal (mean concentration 14.4 pmol/l (1.12 ng/100 ml) (n = 56, SE of mean 0.4 (0.03)).

Thus our results, using a different analytical method, give some support to the original data of Boss *et al.*, notwithstanding the errors introduced into their observations by their use of an invalid calculation procedure. Recalculation of their FT₄ results (see their letter on p 550) alters the nature of the agreement between their data and ours (in as much as we do not confirm a rise in FT₄ in the first trimester); the latter observation may reflect the minor residual errors that are suspected to remain in the Corning assay procedure.

Apart from the fundamental questions these

Relationship between the serum free T₄ concentration and the stage of pregnancy in 101 subjects; the bar indicates the mean and normal range in non-pregnant controls.

Conversion: SI to traditional units—T₄: 1 pmol/l ≈ 0.08 ng/100 ml.

observations, taken together, must raise relating to the nature of the pituitary homeostatic mechanism governing circulating thyroid hormone levels and thyroid hormone delivery to peripheral cells, they are clearly relevant to the diagnosis and management of thyroid disease in pregnancy.

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¹ Boss, M, Djahanbakhch, O, and Kingstone, D, *British Medical Journal*, 1978, 2, 1496.

² Hale, T I, *Lancet*, 1979, 1, 980.

³ Ekins, R, *Lancet*, 1979, 1, 1190.

⁴ Fullerton, J, and Lidgard, G P, *Lancet*, 1979, 2, 51.

⁵ Avruskin, T W, *et al*, *American Journal of the Medical Sciences*, 1976, 271, 309.

⁶ Arango, G, *et al*, *Mayo Clinic Proceedings*, 1968, 43, 503.

⁷ Ekins, R P, in *Proceedings of the International Symposium on Free Thyroid Hormones*, Venice, 1978 (*Excerpta Medica*, in press).

⁸ Ekins, R P, and Ellis, S M, in *Proceedings of the Seventh International Thyroid Conference*, Boston, Massachusetts, 1975.

General practitioners' advice against smoking

SIR,—The many and serious health hazards of cigarette smoking are undisputed; almost daily the evidence grows. Yet, despite brave talk, little action follows and doctors are as culpable as any.

The findings of Dr M A H Russell and others (28 July, p 231) therefore have great significance. Their conclusion that GPs, collectively, could produce half a million ex-smokers a year should be an irresistible challenge—the opportunity to make a major contribution to the health of our patients and reduce the 50 000 excess deaths a year attributable to cigarette smoking. Even the "six-minute consultation" is surely no excuse for failure to give the simple, firm, anti-smoking advice, anti-smoking leaflet, and threat of future inquiry which their study demonstrates to be effective. The feelings of impotence which at present inhibit action must be dispelled.

One minor anxiety, however, relates to the presumed low deception rate reported by Dr Russell and his colleagues; stronger

evidence for this would have been reassuring especially in view of the findings of Sillet *et al.*¹ Furthermore, with the substantial influence of social class on cigarette smoking and especially on smoking cessation,² the absence of social class information is particularly regrettable.

These comments apart, the message seems clear. Instead of awaiting government anti-smoking measures, we should ourselves accept the challenge and let no smoker leave the consultation unsolicited.

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¹ Sillet, R W, *et al*, *British Medical Journal* 1978, 2, 1185.

² Capell, P J, *Health Trends* 1978, 10, 49.

Comparison of buprenorphine and diamorphine in suspected myocardial infarction

SIR,—I read with interest the article by Dr M J Hayes and others (4 August, p 300) comparing buprenorphine and diamorphine after myocardial infarction. They state that no major side effects were experienced with either drug, but do not mention respiratory depression specifically. Presumably this was not a problem, but it may well be that none of the 95 patients to whom intravenous buprenorphine was administered had severe airways disease. Anyone treating myocardial infarcts experiences the occasional patient who is unduly sensitive to diamorphine's respiratory side effects, and naloxone has proved itself as a life-saving drug in this respect. The makers claim that buprenorphine does not depress respiration dangerously, but it certainly can do so postoperatively when used in combination with other drugs. Unfortunately naloxone does not cause quick reversal of buprenorphine-induced respiratory depression.

Sublingual buprenorphine gave as effective analgesia as intravenous, though it was slower in onset. This is an important point for home coronary care, as a frequent reason for failure of treatment at home is recurrence of pain not responding to oral analgesics. If patients were given an intravenous dose of buprenorphine or diamorphine, and told to take sublingual buprenorphine six hourly for 24 hours, this reason for hospital admission might be avoided more often.

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Interstitial fibrosis in a patient treated with 5-fluorouracil and mitomycin C

SIR,—We reported a case of interstitial lung disease in a patient treated with 5-fluorouracil and mitomycin C (26 August 1978, p 602). The results of the investigations reported in the paper were consistent with, though not diagnostic of, fibrosing alveolitis. The patient has now died.

At necropsy the patient was severely cachectic and jaundiced. The cardiovascular system was normal and there was no residual neoplasm in the gastrointestinal system. The liver (2120 g) was enlarged and contained numerous tumour deposits, and the lymph nodes at the porta hepatis