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 $\approx$ 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

were enlarged and infiltrated. The urogenital, endocrine, reticuloendothelial, and central nervous system were macroscopically normal. In the chest there were bilateral small straw-coloured pleural effusions. Both lungs were rather voluminous but firm, with a granular appearance and texture.

Histological examination of the formalin-inflated lungs revealed diffuse and focal interstitial fibrosis. Haematoxylin-van Gieson staining showed collagen in considerably increased amounts in the interstitium, with occasional areas showing even greater collagen deposition. Intra-alveolar fibrosis, as seen in organisation of proteinaceous exudates, was not evident. Some oedema was also seen. Occasional foci of plump expanded cells, probably of alveolar origin, were present, projecting into alveolar lumina. There was no evidence of *Pneumocystis* or fungi. A single very small focus of secondary adenocarcinoma was identified in one of numerous sections examined.

These findings confirm that this patient had interstitial fibrosis. As other aetiological factors have been excluded, we feel that the interstitial fibrosis developed as a result of therapy with 5-fluorouracil and mitomycin C.

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Practical problems with the Clinitest

SIR,—Recent reports in the *BMJ* (31 March, p 859) and elsewhere^{1,2} have highlighted the potential hazard to the management and control of diabetes in patients with congenital colour vision defects who use the Ames Clinitest. With congenital colour vision defects in 8% of the male population this represents a hazard to one in 12 male diabetics. Since diabetics are known to have acquired colour vision defects associated with their diabetes,³ we recently conducted a study⁴ aimed at determining how well diabetic patients in general coped with colour matching on the Clinitest. The study, conducted during May of this year, produced some surprising findings.

Although diabetics were found to make significantly more errors on the test than a control group with normal colour vision (the diabetics systematically overestimated their sugar concentration for concentration levels $\frac{1}{4}$ %, $\frac{1}{2}$ %, $\frac{3}{4}$ %, 1%), the control group also made errors in the same direction on the test. In particular, diabetics presented with a nominal $\frac{1}{2}$ % concentration of dextrose solution matched on average $1\frac{1}{2}$ Clinitest steps further towards the red (that is, indicating a higher sugar concentration). Furthermore, 14 out of 36 diabetic matches were in error by two Clinitest steps, so that a prepared solution of $\frac{1}{2}$ % sugar concentration (actually measured at 0.49%) was read as a 1% concentration. The control group of normal subjects, however, matched the same $\frac{1}{2}$ % solution on average at the $\frac{3}{4}$ % concentration level. So while the diabetic matches were one and two Clinitest steps away from the expected nominal test match, they were only up to one step further in error than the match achieved from subjects with normal colour vision. These matching errors, which were all of overestimation, occurred for prepared solutions in which the

measured dextrose concentrations were always marginally less than the nominal figure. The errors in matching were comparable whether made under typical domestic tungsten lighting (CIE illuminant A) or artificial daylight (CIE illuminant C).

Analysis by reflectance spectrophotometry of the prepared solutions and coloured reference papers showed that the solutions were indeed slightly redder than their nominal paper reference colours, thus substantiating the "errors" made by the control group of subjects with normal colour vision. Furthermore, for each concentration the solution-paper colour combination had characteristically different spectral reflectance curves (that is, were metameric), indicating that the matches are particularly vulnerable not only to changes in the type of illuminant being used but more importantly to changes in an observer's colour vision mechanisms.

We draw attention to these findings and ask whether their clinical implication for diabetic control is sufficient to warrant a thorough re-evaluation of the test.

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¹ Taylor, W O G, *Transactions of the Ophthalmological Society of the United Kingdom*, 1972, **92**, 95.

² Thompson, D G, Howarth, F, and Levy, I, *Lancet*, 1978, **1**, 44.

³ Lakowski, R, Aspinall, P, and Kinnear, P, *Ophthalmic Research*, 1972, **4**, 145.

⁴ Aspinall, P, Hill, A R, and Cameron, D, in *Proceedings of Fifth Symposium of the International Research Group on Colour Vision Deficiencies*, London, 1979 (in press).

The grumbling appendix

SIR,—It is interesting that this myth should still need a leading article (4 August, p 294)—interesting also that your recent references mostly come from America. In Britain the incentives for retaining the diagnosis "chronic appendicitis" are nowadays seldom tangible, but they are nevertheless difficult to resist. For, however stringent the chief may be in eliminating lily-white appendicectomies he is up against the enthusiasm of young men keen on surgery, and of young patients and parents who are even keener on surgery. We can all remember our early days, when such an alliance enabled us to get our appendicectomy time down to single figures! So let us not be too hard on these young men who make the most of their opportunities, or indeed on the young patients for making full use of a syndrome which has solved many a conflict for them.

But what are we to tell the anxious parents? Firstly, we must say, there is no present evidence of disease, acute or chronic, in the appendix. Secondly, the child may nevertheless develop an acute appendix at some time, like anyone else. Thirdly, they will ask "What, then, is the trouble?" and it is no use saying, "There is nothing wrong." Patients and parents will be reassured if we offer a reasonable physical explanation; for these cases I found one very acceptable (and frequently true) label: "Inflamed internal glands—he'll grow out of it."

There is one point which will help in trying to sort out the rare genuine interval case from the spurious: the pain of onset in acute

appendicitis is typically in the mid-epigastrium, not at the umbilicus. But don't let our patients get to know this.

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Doctors and children's teeth

SIR,—With reference to the letter by Professor P J Holloway (11 August, p 390) on the subject of fluoride tablet dosage, we have been using the dosage (up to 2 years 0.5 mg/day, 2-10 years 1 mg/day) first recommended in your columns¹ and no adverse reaction report (yellow card) has been sent to the DHSS in respect of dental fluorosis.

Higher dosages are commonly used in Australia and have not led to complaints from either dentists or members of the public. Only one paper dealing with dosage has been published in the *British Dental Journal* in recent years.² This actually suggested a higher dosage, 0.75 mg, for the ages of 16-24 months while reducing the dosage in the first eight months to 0.25 mg. Since Professor Holloway admits that greater protection is given by the larger dose we are prepared to take the very remote risk of a claim from a member of the public for causing fluorosis in view of the fact that our sales average 40 million tablets a year.

It is not irrelevant to remark that tablets of 0.25 mg, while available at many dentists, are not in general stocked by pharmacies.

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¹ *British Medical Journal*, 1956, **1**, 1312.

² Geddes, D A M, Jenkins, G N, and Stephen, K W, *British Dental Journal*, 1973, **134**, 426.

Disposable insulin syringes

SIR,—Dr Arnold Bloom and colleagues (2 June, p 1467) report the satisfactory use of "disposable" insulin syringes on more than one occasion. The availability of modern syringes is also of assistance in relation to the precision of administering insulin. The British Standard insulin syringes, with a Luer needle, have a "dead space" of about 0.05 ml, which contains 4 units of 80 U/ml insulin. Thus, if one mixes two insulin types into a single syringe, there can be considerable inaccuracy, particularly if one of the doses of insulin is small. In addition, the large dead space also causes an unnecessarily large air bubble in the syringe on drawing up insulin, and patients have to be instructed in the techniques of injecting the bubble back into the insulin bottle. When the syringe is washed after use insulin to the value of 1.5p may be discarded.

We have recently undertaken a clinical trial of 1-ml disposable syringes (Becton-Dickinson, sterile-fluid-path, Plastipak syringes) in 17 children and 22 adult insulin-dependent diabetics. Instead of the usual 20 marks/ml, the syringes were compatibly marked with 80 marks/ml for use with only 80 U/ml insulin. The dead space of about 0.01 ml meant that the air bubble on drawing up the insulin was small enough to be ignored. Twenty-two patients had an insulin dose less than 10 U, but none had difficulty in measuring the small doses, the syringes being marked at 2-unit intervals. One of the fears relating to the