between the herpes simplex virus and its human host. In view of the hardening evidence implicating the herpes simplex virus type 2 (HSV 2) as an important aetiological factor in cervical carcinoma, one cannot escape wondering whether this agent has a similar role in some types of rectal and perianal carcinoma (particularly in the increasing male homosexual population).

Similarities between the mucosa of the cervix and the rectum certainly exist—for example, they both have glandular columnar epithelia and a squamocolumnar junction. Investigations similar to those which have established a close relationship between HSV 2 infection and carcinoma of the cervix would be of interest in rectal and perianal cancer.

M G DAVIES

St John's Hospital for Diseases of the Skin,
London WC2H 7BJ

Blindness after treatment for malignant hypertension

SIR,—It was with great interest that I read the account by Dr D H Cove and others (28 July, p 245) of two young women who became blind following treatment for malignant hypertension. In December 1976 I had a similar, but not identical, experience with an 18-year-old girl who presented with malignant hypertension. Her blood pressure fell quite gently over a five-day period, during which time her initial blurring of vision became worse. After her papilloedema had resolved she developed bilateral optic atrophy. This patient, fortunately, still has some useful vision, although she has been registered as partially sighted.

In this patient there was no precipitous drop in blood pressure to explain the optic nerve damage, and I wonder whether the optic atrophy in these three young females might be a direct result of severe papilloedema rather than the fall in blood pressure. The fact that this tragic complication has now been described in three young women raises the possibility that there are hormonal factors involved, for otherwise one might have assumed it more likely in older patients with pre-existing vascular degeneration.

JOHN H WETHERILL

Dewsbury, W Yorks WF13 4JT

Maturity-onset diabetes

SIR,—In their article on maturity-onset diabetes (7 April, p 938) Drs V Anne Ropner and J Anderson state that there is no reason to discontinue propranolol in diabetic patients receiving oral hypoglycaemic drugs. At the same time they point out that beta-blockers may potentiate hypoglycaemia and mask the warning symptoms and signs. In fact beta-blockers cause little or no potentiation of the actual fall in blood sugar after the administration of insulin,[1–4] and rarely seem to mask the warning symptoms.

Propranolol has been shown experimentally to delay recovery from hypoglycaemia induced by insulin,[1–4] and even to cause a temporary secondary fall in blood sugar during the recovery period[3]; while other beta-blocking drugs have little, if any, effect on the recovery from insulin reactions. The following case shows that this effect of propranolol is not just of theoretical interest, but also of practical importance in the management of diabetics.

A 26-year-old hypertensive insulin-dependent diabetic recently became pregnant. Her hypertension had been treated with propranolol in a dose of 80 mg twice daily for the past two years. She volunteered that she had been taking considerably longer to recover from insulin reactions since taking the drug, and that hypoglycaemic symptoms sometimes recurred before she had fully recovered. Insulin reactions would still tend to occur during the pregnancy, when good diabetic control is so important; and as propranolol leads to a marked rise in blood pressure and bradycardia in addition to the adverse metabolic effects during insulin reactions[5] the drug was stopped. Metoprolol was considered to be a safe alternative and was given in a dose of 100 mg twice daily. Insulin reactions still occurred, but the patient now found that she recovered from them normally.

Hypoglycaemia usually occurs in diabetics receiving insulin, but it may also occur when oral hypoglycaemic drugs are used, especially the longer-acting agents, and in the elderly. Whereas insulin reactions are usually recognised and rectified by the patient, hypoglycaemic symptoms due to oral drugs, particularly confusion, may be insidious and protracted and they could be seriously accentuated by propranolol.

Drs Ropner and Anderson rightly advise careful monitoring when combining therapy with oral hypoglycaemic drugs and propranolol, but we feel it would be wiser to choose a cardioselective beta-blocker such as metoprolol.

R H LLOYD-MOSTYN

King's Mill Hospital,
Sutton-in-Ashfield, Notts NG17 4JL

R M GOODFELLOW

Astra Chemicals Ltd,
St Albans, Herts

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Serum free thyroxine in pregnancy

SIR,—In a previous communication[1] we presented serum free thyroxine (FT4) values during each trimester of pregnancy as measured by the Corning Immophase kit.[2] Over 30% of our values were in the hypothyroid range, so we were forced to question the methodology of the kit. Subsequent discussions and correspondence[3] cast doubt on the derivation of the FT4 result from the measured kit parameters and offered alternative methods of manipulating the raw data. We would like to point out that Corning Medical have now modified the instructions which accompany the kit concerning the calculation of the results.

We have recalculated our FT4 results and the revised means are shown in the accompanying table together with similar means for total T4 and thyroxine-binding globulin (TBG). The latter values were also measured by Corning kits. The trend we originally reported, that FT4 falls significantly during the trimesters of pregnancy, is still apparent but now 90% of the FT4 values are within the range of the non-pregnant controls.

We now believe that the Corning FT4 kit in its original form was subject to at least two different errors which acted in opposition. One, an error in the method of manipulating the data, tended to decrease FT4 values and this has now been corrected. The other, a non-specific binding effect, which is operator dependent, would tend to increase the FT4 values with increasing TBG concentrations. Since we did not measure the non-specific binding we are unable to correct for this effect, but this might be the explanation of the significant rise in the FT4 mean in the first trimester over the mean of the control group. We suggest that TBG rises significantly during this period before any change in FT4 which may occur.

As the Corning kit gives an indirect method of measuring FT4 we have compared our FT4 values with the total T4/TBG ratio, which is recommended as an indicator of thyroid state by several workers (for example, Burr, *et al*[4]), especially in abnormal TBG states. The significant downward trend is even more marked using this ratio, and in the third trimester 11 out of 19 values (58%) are below the lowest control value and are at risk of giving rise to misdiagnosis. Moreover, from theoretical considerations this ratio might be expected to fall during pregnancy without an associated fall in FT4.

Clearly, a precise, reliable, and cheap method of determining FT4 in abnormal states, such as pregnancy, is still awaited. The Corning kit will give euthyroid values for about 90% of pregnant patients, but direct FT4 values are needed before we can confidently state that FT4 values fall during pregnancy and remain low until term.

MARGOT BOSS
D KINGSTONE

Department of Medical Physics,
Royal Free Hospital,
London NW3

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SIR,—Low serum free thyroxine (T4) concentrations during pregnancy have been reported in your columns by Boss *et al*.[1] However, the commercial radioimmunoassay kit used by these workers (FT4 Immophase, Corning Medical) has recently been criticised[2 3] on the grounds that the presence in serum of raised serum thyroxine-binding globulin (TBG) concentrations leads to anomalous results using the method as originally described.

It is clearly important that changes in binding protein concentration should not artefactually influence free T4 measurements since these are primarily undertaken when a suspected variation in serum T4 binding undermines the diagnostic usefulness of total serum thyroxine determination. Modification of the method of calculation of assay

Corrected FT4, T4, and TBG concentrations and T4:TBG ratios (means and standard deviations)

	No of subjects	FT4 (pmol l)	T4 (nmol l)	TBG mg l	T4:TBG
Controls	22	17·6 ± 2·19	101 ± 16·6	21·8 ± 12·9	3·69 ± 0·61
First trimester	22	20·2 ± 2·70	138·5 ± 19·0	32·2 ± 7·4	3·46 ± 0·66
Second trimester	28	18·4 ± 3·3	162·5 ± 22·5	45·2 ± 7·3	2·86 ± 0·64
Third trimester	19	15·6 ± 2·7	152·3 ± 25·2	50·1 ± 9·6	2·41 ± 0·52

Conversion: SI to traditional units—FT4: 1 pmol l ≈ 0·078 ng/100 ml. T4 1 nmol/l ≈ 0·78 ng/ml.

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.

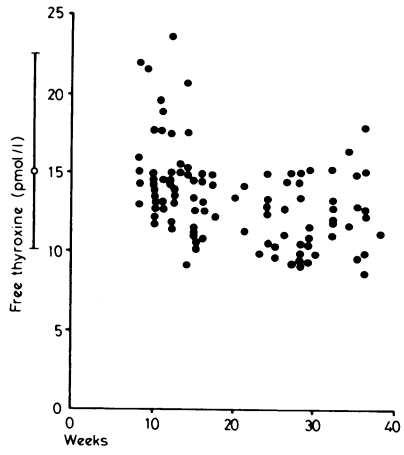
Meanwhile a reduction in free T4 concentration during pregnancy has also been reported by a number of other workers (for example, Avruskin *et al*[5] and Arango *et al*[6]) using a variety of conventional free T4 assay techniques (albeit the magnitude of the effect has been less than that reported by 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, Ekins[7]). 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 ^{125}I-labelled T4. Serum standards for the system have been calibrated by an equilibrium dialysis technique relying on direct radioimmunoassay of T4 in the dialysate.[8] (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 homoeostatic 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.

ANTONY KURTZ
KEVIN DWYER
ROGER EKINS

Subdepartment of Molecular Biophysics,
Department of Nuclear Medicine,
Middlesex Hospital Medical School,
London W1N 8AA

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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.

GODFREY FOWLER

Department of Social and Community Medicine,
Oxford OX1 3QN

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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.

H C R SIMPSON

Department of Regius Professor of Medicine,
John Radcliffe Hospital,
Oxford OX3 9DU

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