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.

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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.

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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 period³; 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 reactions⁵ 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.

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¹ Deacon, S P, and Barnett, D, *British Medical Journal*, 1976, 2, 272.

² Newman, R J, *British Medical Journal*, 1976, 2, 447.

³ Davidson, N McD, *Scottish Medical Journal*, 1977, 22, 69.

⁴ Deacon, S P, et al, *British Medical Journal*, 1977, 2, 1255.

⁵ Lloyd-Mostyn, R H, and Oram, S, *Lancet*, 1975, 1, 1213.

⁶ Sandström, B, *British Journal of Obstetrics and Gynaecology*, in press.

Serum free thyroxine in pregnancy

SIR,—In a previous communication¹ 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 correspondence³ 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.

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¹ Boss, M, Djahanbakhch, O, and Kingstone, D, *British Medical Journal*, 1978, 3, 1496.

² Free T4 ¹²⁵I Radioimmunoassay Test System. Corning Medical, Halstead, Essex.

³ Ekins, R, *Lancet*, 1979, 1, 1190.

⁴ Burr, W A, et al, *British Medical Journal*, 1977, 1, 485.

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.