the F.T.S.[1] The discoveries of Ohno and his co-workers on the kidney A.D.H. and β-glucuronidase enzymes [5-10] have established that the *Tfm* mouse does represent a true Jacob-Monod regulator mutation (non-inducible type). Ohno [11] has proposed that it might be possible to test the hypothesis of X-linked inheritance of the F.T.S. in man on the basis of possible in-vitro resistance of XY-FTS lymphocytes to ordinarily lethal doses of testosterone. In the case of such testosterone resistance it might be possible to detect two populations of lymphocytes in proven F.T.S.-heterozygotes—one sensitive to a high level of testosterone and killed by it, and another able to survive in such a lethal concentration of androgen. It is of obvious importance to develop such a test for the F.T.S., not only for purposes of counselling women who have had one affected child about their recurrence risk, but also for possible prenatal diagnosis of the F.T.S.

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HÆMOLYSIS WITH ETHACRYNIC ACID

SIR,—Lieberman and Kaneshiro [12] have pointed out the danger of in-vitro hæmolysis when ethacrynic acid ('Edecrin') is added to red blood-cells. Their report does not indicate the storage age of the red cells used, and our own observations indicate that hæmolysis may be a function of the storage age of the cells. Saline suspensions of 28-day-old red cells showed hæmolysis at 7·5 m*M* concentrations of ethacrynic acid after as little as two hours at 37°C, and at room-temperature after six hours. No hæmolysis was noted at 4°C. At concentrations of 15 m*M* (5 mg. per ml.) considerable hæmolysis was seen at 4°C, 20°C, and 37°C after two hours. The same cells examined after only three days' storage at 4°C in acid citrate dextrose were more resistant. No hæmolysis was noted at 4°C and 20°C, and only minimal lysis at 37°C. Cells incubated with ethacrynic acid and in compatible plasma showed no lysis at any concentration after six hours, suggesting a protective effect of plasma binding with ethacrynic acid.

Lysis by ethacrynic acid is probably a direct effect on red-cell membranes, and not due to rupture of cells by ingress of sodium. No spherocytosis was noted after six hours' incubation, even at 15 m*M* concentrations of the drug, and the osmotic fragility of fresh red blood-cells incubated with ethacrynic acid in physiological saline for six hours showed no significant increase in mean corpuscular fragility. The pH of incubated and control samples all lay within the range 7·6–7·8. Direct Coombs tests after six hours' incubation were negative using polyvalent antiglobulin serum. Mechanical fragility was, however, considerably increased.

Ethacrynic acid is an alpha-beta unsaturated ketone derivative of aroxyl acetic acid, and may possibly exert its lytic effect through an action of its acetyl radical. Glacial acetic acid is itself strongly lytic and is routinely used for this purpose in hæmatological practice. Our observations indicate that ethacrynic acid (M.W. 325) is considerably more lytic to red cells than equiosmolar concentrations of acetic acid or trichloroacetic acid.

Packed cells with a P.C.V. of 75–80% will be protected by a considerable amount of plasma-protein, and ethacrynic acid added to infusions of these cells in therapeutic doses is unlikely to produce hæmolysis. Whether post-transfusion cell survival is decreased by low concentrations of the drug is at present under study. Frusemide in concentrations that might conceivably come into contact with aged red cells has no lytic effect.

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FACIO-DIAPHRAGMATIC MYOCLONUS

SIR,—The post-mortem findings in my patient with myoclonus, chorea, and schizoaffective disorder [1] are now to hand. Necropsy and neuropathology were undertaken, respectively, by Dr. J. M. Cameron and Dr. Ivan Janota. Lesions in the brain of long enough standing to be related to the involuntary movements were as follows:

"There were several brownish yellow areas of old softening in the cerebral hemispheres: one, about 1 cm. diameter lateral to the head of the right caudate nucleus; one, a streak 1·4 cm. long extending from the medial border of the left putamen through the anterior limb of the internal capsule to the caudate nucleus; and one, about 2·5 cm. anteroposteriorly and 1·5 cm. across, which had replaced much of the right putamen. There was a fourth yellowish-brown streak, about 1 cm. long and 0·5 cm. wide, at the junction of the left basis pontis and the upper pontine tegmentum just medial to the middle cerebellar peduncle. Histological examination showed no significant changes other than arteriosclerosis in keeping with the severe atheroma found in the arteries at the base of the brain. The third ventricle and the lateral ventricles (with the exception of their temporal horns) were moderately dilated, but in all other long-term respects the brain appeared normal. Specifically, the cortex, thalami, subthalamus, hypothalamus, substantia nigra, and cerebellum revealed no abnormality. There were no Alzheimer plaques or neurofibrillary tangles seen."

It was concluded that the old softenings were due to cerebral vascular disease (rather than to anoxic brain damage sustained during electroconvulsive therapy), and that Huntington's chorea could be excluded. Incidentally, it was difficult clinically to exclude accompanying myoclonus of the palate, pharynx, or larynx, in view of the contraction of orbicularis oris.

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PROPRANOLOL FOR L.S.D.-INDUCED ANXIETY STATES

SIR,—The letter from Dr. Bonn and Dr. Turner [2] about their pilot study on the use of D-propranolol in anxiety prompts me to report the usefulness of propranolol ('Inderal') in three students with L.S.D. complications.

The first patient had taken 500 µg. of L.S.D. a month before consulting me. He sought my advice because of suicidal ideas and depression. During the course of discussion it became apparent that the presenting symptoms were in part a reaction to intermittent attacks of anxiety with severe tachycardia and associated feelings of doom. Chlorpromazine and diazepam only partially alleviated the symptoms. However, addition of propranolol 10 mg. three times daily banished the symptoms within a day and prevented further attacks when taken at the onset of anxiety symptoms.

The second patient had acute anxiety feelings following the use of L.S.D. These were also effectively relieved by the same dosage of propranolol.

1. Crawford, J. P. *Lancet,* 1970, ii, 660.
2. Bonn, J. A., Turner, P. *ibid.* 1971, i, 1355.

The third patient had taken 2500 μg. of L.S.D. Believing the tablets to be out-of-date, he had swallowed the whole amount. The day after, I saw him in a very depressed state which was relieved with chlorpromazine. Two months later, he reported morbid and continuous ruminations over abstruse questions such as the meaning of life, religion, and the universe. He was anxious and depressed, but chlorpromazine and diazepam were of little help. Addition of propranolol 10 mg. three times daily rapidly relieved his symptoms, both objectively in reducing his tachycardia and signs of anxiety, and subjectively in bringing the compulsive thinking under control.

Whatever the underlying psychodynamic or pharmacological mechanisms of these anxiety states following the use of L.S.D., the value of propranolol clinically has been so striking that further clinical and pharmacological investigation would be seen to be indicated.

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VASODILATOR TREATMENT OF HEART-FAILURE

SIR,—I have just seen the paper by Dr. Majid and his colleagues in your issue of Oct. 2 (p. 719). In fact, the idea is not new, since I described the relief of acute left ventricular failure by intravenous tolazoline as long ago as 1952.[1] At that time, I suggested that the results obtained by the method warranted further trials, and it is gratifying that my original observation has now been confirmed, albeit nineteen years later.

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KININ RELEASE IN THE CARCINOID SYNDROME

SIR,—The communication of Dr. Mashford and Dr. Roberts (Oct. 9, p. 817) contains an implied criticism of the earlier conclusions of Oates et al.,[2] who found raised kallikrein and kinin levels in carcinoid hepatic venous blood. Dr. Mashford and his colleague claim that, because of the rapid destruction of kinin in the lung, it is more relevant to the flushing mechanism to measure kinin levels in peripheral arterial blood. For a similar reason, Mashford and Zacest [3] expressed surprise at the finding by Zeitlin and Smith [4] of raised kinin levels in peripheral venous blood during the carcinoid syndrome.

Oates et al.[2] have shown that it is not merely free kinin which is released from the carcinoid tumour, but active kallikrein. While the life of free kinin in the circulation is a matter of seconds,[5] kallikrein has a half-life measured in minutes [5] and must recirculate several times. The active kallikrein reacts with plasma-kininogen to release free kinin, which is rapidly removed from the blood. Thus, at any moment in time and at any point in the circulation, a dynamic equilibrium exists, and the measurable free-kinin level must depend mainly on the rate of formation of kinin and the rate of its destruction at that site. At the sites where the rate of formation is even more rapid than the rate of removal, significant levels of free kinin will occur.

The rapid destruction of kinin in the lung presumably ensures low levels of free kinin within the lung and in the arterial blood leaving it. It should have little or no influence on the kinin levels in the cutaneous microcirculation. On balance it would seem that the assay of circulating kallikrein [2] or the simultaneous measurement of kinin and kininogen levels in the venous blood draining an area of vasodilatation [4] would give an indication of the state of the kinin-forming system at least as valid as the measurement of arterial free kinin alone.

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MYDRIATIC DRUGS FOR ROUTINE FUNDAL INSPECTION

SIR,—Dr. Smith is to be congratulated on his interesting and stimulating article (Oct. 16, p. 837). Rapid and adequate pupillary dilatation, with minimal interference with accommodation, and short duration of effect are, of course, the criteria for the ideal mydriatic. Dr. Smith presents a good case for 0·5% tropicamide to fill this role. I must take issue with him on his condemnation of 0·1% cyclopentolate and 0·5% homatropine for fundal inspection. To combat the possible danger of precipitating angle-closure glaucoma, the use of a miotic, at least in all patients over 40 years of age, should be regarded as mandatory whatever the mydriatic previously instilled. I have found that 0·25% physostigmine in the case of antimuscarinic mydriatics, and 1% pilocarpine following sympathomimetic mydriatics, normally counteract the pupillary dilatation adequately within 30 minutes or so. The patient is requested to remain in the waiting-room until this is observed. The patient is also asked to return if redilatation of the pupil, accompanied by pain, is noticed within the next few hours.

In view of the possibility of idiosyncrasy to tropicamide, it appears to me both unnecessary and unjustifiable to remove those very useful mydriatics, 0·1% cyclopentolate and 0·5% homatropine, with miotic cover in appropriate cases, from our list of mydriatics.

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TOBACCO SMOKE AND GASTRIC SECRETION

SIR,—The report of Dr. Wilkinson and Mr. Johnston (Sept. 18, p. 628) is of interest. We have also shown that "smoking doses" of nicotine and tobacco-smoke condensate depress gastric-juice volume, acid concentration and acid output, and peptic activity in both gastric-fistula rats and Shay rats.[6–8] Nicotine-induced gastric secretory depression is also observed [6,8] in rats treated with maximal doses of histamine, or maximal or submaximal doses of pentagastrin. On the other hand, in rats the subcutaneous or oral administration of nicotine for 2 weeks results in gastric secretory stimulation.[9,10] Moreover, in these animals inhibition of gastric secretion by acute nicotine exposure is still present,[11] indicating that tolerance to the inhibitory effect of the alkaloid on gastric

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