of being able to distinguish autosomal recessive cases. We need no longer be quite so cautious about genetic heterogeneity in giving genetic counsel, in evaluating methods of carrier detection, in investigating the mechanism, or in attempting the treatment of the disease. A minor consequence is that we may now assume that all mothers of isolated cases who are not carriers of the X-linked gene are ipso facto the mothers of new mutants. By proportional studies of the rate of detection of such mothers and of known carriers by serum creatine kinase estimation, together with a count of the incidence of isolated cases in the population, it is possible to make a relatively direct estimate of the mutation rate. In the North of England it is about 10.5×10^{-5} per gene per generation²—a very high figure, which is, however, confirmed by the use of Hal-dane's classical indirect method.—I am, etc.,

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Trimethoprim-sulphamethoxazole in Typhoid

SIR,—We read with interest your leading article and three articles on the treatment of typhoid fever and the carrier state with trimethoprim-sulphamethoxazole (8 August, pp. 297, 318, 320, and 323).

We have just completed an uncontrolled clinical trial of trimethoprim-sulphamethoxazole in 50 cases of typhoid fever which was started in October 1969 and ended in June 1970. The diagnosis was confirmed by isolation of *Salmonella typhi*. Although our results are similar to the findings reported, two of our cases failed to respond to treatment. One of these was a 16-year-old African male admitted in a semicomatose and dehydrated state. He was treated for three days but on the third day had a severe melaena and died. The other was a 36-year-old African female who had five days of treatment for a pyrexia of unknown origin which responded and she was discharged home on no treatment. One week later she was readmitted seriously ill, when the diagnosis of typhoid fever was established on blood culture and trimethoprim-sulphamethoxazole therapy was re-instituted. She failed to respond and in vitro sensitivities showed that the *Salmonella typhi* isolated was resistant to trimethoprim-sulphamethoxazole. She had a stormy recovery subsequently on cloxacillin and chloramphenicol, and was in hospital for a total of 15 weeks owing to the development of a carrier state.

In the remaining 48 cases the temperature returned to normal in 4 days and there were no relapses, and the side effects noted were minimal. One patient inadvertently received four times the recommended twice daily dosage (1,280 mg. of trimethoprim and 6,400 mg. of sulphamethoxazole) for two and a half days. One day later she developed jaundice, which persisted for two and a half weeks, but the aspartate transaminase

(S.G.P.T.) was only slightly elevated. Three months later at follow-up she was well and had normal liver function tests.

All our patients received three weeks' treatment, at the end of which time three rectal swabs and urines were taken for culture. No carriers were detected apart from the case reported above. The long-term follow-up is obviously most important.

Our findings agree with the previous papers on this subject that trimethoprim-sulphamethoxazole is indeed a useful drug in the acute stages of typhoid fever, and it would appear hopeful that it would be just as effective in the carrier state. It is our intention to repeat this series in detail in the future.—We are, etc.,

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Respiratory Effects of Biological Detergents

SIR,—As many reports are being published in connexion with the harmful effects of so-called "biological detergents"¹⁻³ I thought that your readers might be interested in the results of the investigations carried out by a group of doctors on the workers of a company near Venice concerned with the production of biological detergents.

A study was made of 155 randomly selected workers, the majority of whom were non-smokers.

No. of Workers	Symptoms	Skin Test Positive
31 ..	None	2
27 ..	Chronic Rhinitis	2
52 ..	Chronic Rhinitis Hoarseness Persistent Dry Cough	14
27 ..	Cough Persistent Catarrh Dyspnoea of a Continuous Type	11
18 ..	Typical Asthma	17

Thus 20% only of this randomly selected group showed no symptoms involving the airways, and in 35% who had symptoms an allergy to enzymes existed. In subjects having a positive skin test, immediate positive reactions were noted, often severe, when making challenge tests using aerosols of extracts of enzymes, and sometimes there were delayed respiratory manifestations. In ten patients the challenge was repeated after the administration of disodium cromoglycate; this afforded complete protection, thus confirming the allergic nature of response.—I am, etc.,

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Diet and Athletics

SIR,—I read with interest your leading article on "Diet in Athletics" (15 August, p. 361) and would certainly agree that the diet of many athletes is greatly influenced by fads which probably have no effect on physical fitness, if one ignores the psychosomatic effect.

I should, however, like to qualify your statement that no evidence, in terms of success in athletic events, is yet available to support the work of Astrand and his colleagues.¹ For some years the International Athletes' Club has been aware of the possible significance of the work of Saltin,² Astrand, and others in terms of enhancing endurance in athletics. In May 1968 the Club organized two trial 40-kilometre races for 10 top-class walkers. In the first trial half of them prepared by following a diet similar to that recommended by Astrand, and in the second the other half did so. The trials were under the direction of Dr. L. G. Pugh of the Medical Research Council. It was found that the athletes on the high carbohydrate diet walked significantly faster over the final 10 kilometres.

These findings were passed on to the British competitors in the endurance events in the Olympic Games in Mexico in 1968. No follow-up survey has been made to find out how many athletes have adopted the diet, but outstanding individual cases are known. Dr. Ron Hill used the diet before winning the European Marathon Championship in Athens in 1969 and the Commonwealth Championship in Edinburgh this year. Dr. Michael Turner also achieved his best-ever cross-country performance this year after preparing for the International Cross-country Championships with the diet. It is also being used by competitors in long-distance fell races such as the Lake District Mountain Trial.

We are at present engaged in field trials involving measuring changes in the respiratory quotient of an athlete during a three-hour run after various diets. Expired air is collected at intervals in a Douglas bag in a car driven alongside the runner. It is known that the respiratory quotient falls as glycogen reserves become exhausted. If a diet has enriched the glycogen reserves then this should postpone the drop in respiratory quotient which is, of course, accompanied by a feeling of exhaustion and an enforced slowing down.—I am, etc.,

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Potassium and Chronic Renal Failure

SIR,—With reference to the study by Dr. G. S. Stokes and others (18 July, p. 126) we should like to present a case of refractory hypertension in a patient despite long-term low sodium haemodialysis, which successfully responded to use of a potassium-free dialysate, suggesting a possible rele-

vance of potassium to this form of hypertension.

The patient, a man of 44 with one remaining kidney (right nephrectomy 15 years ago for lithiasis), has been under our care since 1967 with severe hypertension and a raised blood urea. Despite conservative treatment he became semistuporous in November 1968. His blood urea was then 200-300 mg./100 ml., and creatinine clearance 2-4 ml./minute. An arteriovenous fistula was established and the patient was put on twice weekly haemodialysis with a R.S.P. Travenol artificial kidney, using Ultra Flo 100 or E X-01 dialysers at a blood flow rate 200-300 ml./minute for six-eight hours. The dialysate concentration consisted of Na 132, acetate 35, Cl 102, Ca 3, Mg 0.8, and K 2.5 mEq/l. His diet contained 50 g. protein, 15-20 mEq of potassium and 70-75 mEq of sodium. He also received 500 mg. of methylodopa daily. Immediately after starting haemodialysis the secretion of urine stopped completely. The patient's general condition improved. The haematocrit increased spontaneously from 22 to 30% without any transfusion, and the blood urea was between 60 and 150 mg./100 ml. However, daily blood pressure was consistently high: 180-240/110-140 during the first ten months of treatment. He had papilloedema, haemorrhages, and exudates in both fundi.

A potassium-free dialysate was then instituted. The diet was unaltered, but the potassium intake augmented from 15-20 to 70-80 mEq. His blood pressure, systolic and diastolic, gradually responded to antihypertensive treatment, and for six months remained around normal limits. It is now stabilized at 140-170/90-105 without any medication. The fundal lesions have also completely disappeared. The patient presented no symptoms or signs of hypokalaemia, with a serum potassium from 2.25 to 5.75 mEq/l. between two successive haemodialyses.

This patient was treated for nearly a year with a dialysate containing 2.5 mEq/l. of potassium and remained hypertensive. The additional repeated depletion of potassium of 250-300 mEq twice weekly caused the high blood pressure to fall gradually, and the ocular lesions to regress. This observation is in accordance with experimental and clinical data indicating that a potassium-deficient state is characterized by a decrease of vascular reactivity to certain stimuli, especially to the renin-angiotensin system, and may lower high blood pressure in rats with renovascular hypertension.¹⁻⁴—We are, etc.,

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Ethics of Research and the Developing Countries

SIR,—While agreeing with some of the sentiments expressed by Professor B. Ringelmann (12 September, p. 643) I feel that he presents a rather one-sided picture concerning collaborative studies undertaken partly in the developing and partly in the developed countries.

Anyone who has worked in the developing countries would know, as even Professor Ringelmann admits, that facilities for many investigations are not available, and that some studies can only be undertaken in collaboration with colleagues in the developed countries. It would be sad to conclude that these studies should not be undertaken, especially as often ideas as well as blood samples emanate from the developing countries. Naturally, these studies have to be truly collaborative, and if facilities and staff are available the greater part should be undertaken on the spot.

These collaborative studies, apart from their scientific value, often bring not only the individuals affected but whole departments closer together, and in fact lead to the goal for which Professor Ringelmann is striving.—I am, etc.,

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Wrong Operations

SIR,—Mr. T. K. Lyle (19 September, p. 711) rightly adumbrates various safeguards against the disaster of operating on the wrong area; name bracelets and indelible pencil marking are mooted, and no doubt other measures are in vogue. But most cogent of all in Mr. Lyle's commentary is the fact that a responsibility lies with the surgeon personally to examine the patient. I would go further than Mr. Lyle, however, in his maintaining that this obligation is necessary for deciding what operation is to be undertaken and other purely technical desiderata.

In my credo this personal, preoperative contact is imperative because the patient is a human being and not a computerized symbol. He has feelings, is under stress and full of anxieties, and these will in no way be allayed on a trolley journey into a totally impersonal, imponderable anaesthetic-laden ambience.

"Sustained and soothed by an unfaltering trust . . . lies down to pleasant dreams", as the American poet, William Cullen Bryant, has it, will be the inestimably more desirable state of composure when the man of conscience evokes his innate kindness as well as the use of his capable surgeons' hands.—I am, etc.,

DANIEL LAMONT.

Grimsby, Lincs.

Living it up with Concorde

SIR,—Your interesting leading article (19 September, p. 661) surveys some physical factors of importance to supersonic travel, but does not afford much space to the physiological aspects of such flights.

Of special interest in that direction is the inevitable disturbance of diurnal (or solar) rhythm. This affects passengers and crew

alike, and stems from the crossing of time zones at high velocity. Such a phenomenon is familiar to present-day long-distance jet commuters, flying to East or West. The same journeys, made at twice the speed of sound, promise to be even more traumatic to the control of bodily rhythm. Clinically it is well recognized that after such a flight the passenger may require a week or longer to adapt to the solar time rhythm of his new environment. During this period of adaptation he may suffer disturbances of sleep rhythm, lethargy, mental sluggishness, and even frank depression of mood. Biochemically there is change from the normal ebb and flow of water and electrolytes. This disturbance has been said to result from conflict between man's intrinsic circadian rhythm and normal solar rhythm, the latter being "put out of joint" temporarily by the abrupt exchange of one solar time for another.

Future Concorde travellers may find this effect greatly magnified, especially if crossings are undertaken frequently, as is inevitable for aircrews. The resulting loss of efficiency could have serious consequences on safety in the air.—I am, etc.,

KLAUS HEYMANN.

London W.11.

Recovery from Overdose with Glibenclamide

SIR,—Experimental evidence with glibenclamide, a sulphonylurea recently put on the market which is effective in the management of diabetes, suggests that it has a different mechanism of action from other sulphonylureas, giving slower and more prolonged effects on blood glucose and insulin concentrations than tolbutamide.¹ I should like to report a case of overdose with rapid and complete recovery.

A 15-year-old boy was admitted to casualty at 6.45 p.m. on 19 June deeply unconscious. No history was available at the time, but subsequently it was found out that during the evening he had smoked cannabis and taken an unknown number of Mandrax tablets. He had returned home with a hangover for which he had taken some aspirins and swallowed a number of his father's supply of 5 mg. glibenclamide tablets. The exact number is not known, but it was certainly not less than 20. At 4 a.m. his father found him apparently asleep, but when he appeared still to be asleep more than 13 hours later—5.30 p.m.—he brought him into the casualty department.

On examination the boy was deeply unconscious and totally unresponsive to all stimuli. Blood pressure was 110/70, pulse was 72, with sinus arrhythmia.

An overdose of drugs was suspected, and after blood was taken for tests, an intravenous infusion of normal saline was set up. Laboratory investigations were all within normal limits except for the blood glucose which was 22 mg./100 ml. Blood count was normal. On finding the marked hypoglycaemia, treatment was changed to intravenous dextrose and he was given 500 ml. normal saline, 1,000 ml. of 5% dextrose, and 120 ml. of 50% dextrose in one hour. Two hours after admission he developed torsion spasm with prolonged cyanosis. Because of these attacks he was given two doses of 5 mg. diazepam intravenously. The spasm thereafter subsided. Nine and a half hours after admission he had recovered fully and his blood sugar was within normal limits. After three days he was allowed to