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 Hall-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-