

influenzae resistant to trimethoprim is increasing rapidly. The suggestion was based on their finding that many strains showed long trailing end-points in sensitivity tests by both the disc and the serial dilution methods. The effects were first observed in the disc method and the authors then assumed that they were due to the use of a medium which contained substances that partially reversed the action of trimethoprim and the sulphonamides. However, they rejected this explanation when similarly long trailing end-points were seen in the determinations of the minimum inhibitory concentrations of trimethoprim in media which they considered to be free from inhibitory substances. They therefore read as their end-point the concentration of trimethoprim that gave 100% inhibition instead of the more usual 90% inhibition and concluded that of the 24 strains examined by the serial dilution method, 18 were resistant to 10 µg or more of trimethoprim per ml.

Thymidine is the major interfering substance for trimethoprim and the sulphonamides and it is probably present to a variable extent in all non-synthetic media. The addition of lysed horse red cells improves media for sensitivity testing to these drugs by converting thymidine to thymine, which for most organisms is less effective for reversing the inhibitory effects of these antibacterial agents than is the nucleoside. The media used by Professor May and Mrs. Davies for their minimum inhibitory concentration determinations were not synthetic and therefore their original explanations for the trailing end-points is still feasible.

Through the courtesy of Professor May, 17 of these apparently resistant strains were examined at the Wellcome Research Laboratories in North Carolina and the occurrence of long trailing end-points was confirmed; they occurred in a variety of media, including Wellcotest agar, Oxoid diagnostic sensitivity test agar, and Difco Mueller-Hinton medium. However, more extensive investigations, which included diffusion transfer techniques, impression slide methods, bactericidal tests, and protective tests in animals, gave the following results:

(1)—The organisms giving the long trailing end-points were shown to be morphologically abnormal and mostly dead. (2)—The few viable abnormal forms were incapable of further multiplication when transferred to medium containing the same concentration of trimethoprim as that in which they initially multiplied, and assumed normal morphology when transferred to trimethoprim-free medium. (3)—Though the 17 strains were not equally sensitive to the bactericidal action of trimethoprim, five of them were in fact killed by as little as 1 µg of trimethoprim per ml. (4)—In experiments in mice these allegedly resistant strains were no more resistant *in vivo* to trimethoprim than were the more usual ones. (5)—Serial passage in the presence of trimethoprim did not alter the end-points of strains with either long trailing or clear-cut end-points, indicating that long trailing end-points are not indicative of a phase in the development of resistance to trimethoprim. Details will be published elsewhere.

In vitro testing of sensitivity to sulphonamides has always presented difficulties and, though these are no less with trimethoprim, we conclude from the results of our study that these seemingly trimethoprim-resistant

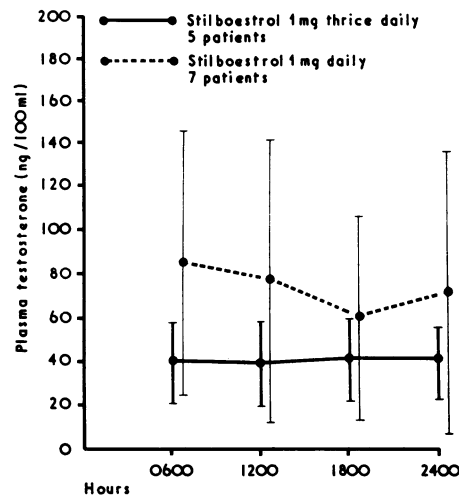
strains of Professor May and Mrs. Davies are sensitive to therapeutic concentrations of trimethoprim.—I am, etc.,

S. R. M. BUSHBY

Wellcome Research Laboratories,
Research Triangle Park,
North Carolina

Oestrogen Treatment in Carcinoma of the Prostate

SIR,—Dr. M. Shahmanesh and his colleagues (2 June, p. 512) suggest that stilboestrol should be regularly used in a dose of 1 mg daily in the treatment of carcinoma of the prostate. We have performed 6-hourly estimations of plasma testosterone by radioimmunoassay in 12 patients with prostatic cancer, and the results show that androgen suppression may be incomplete and variable with stilboestrol 1 mg daily. In contrast, stilboestrol 1 mg thrice daily provides consistent suppression of plasma testosterone which is maintained throughout the 24 hours (see fig.).



Mean plasma testosterone levels (\pm S.D.) at 6-hourly intervals, comparing the effects of stilboestrol 1 mg daily with 1 mg thrice daily.

We would therefore suggest that unless facilities are available for monitoring the effectiveness of hormone therapy—by plasma testosterone assay—a dose of 1 mg thrice daily may be more appropriate for routine use in the treatment of this disease.—We are, etc.,

R. J. SHEARER
W. F. HENDRY
J. D. FERGUSON

Institute of Urology,
London W.C.2.

Communication between Psychiatrists

SIR,—It seems to me that your leading article on this subject (2 June, p. 500) and similar pious exhortations are misguided. We have next to nothing by way of symptom analysis, signs, or tests that was not available to our by no means stupid colleagues of 50 years ago. It may even be mischievous to suggest that more time and publication space be given to going over and over the same material.

We need new weapons of attack if we are to extend our nosology. The computer appears to have failed us. Recent changes in our

diagnostic habits have come from responses to treatment. Electric convulsion therapy and chemical antidepressants have led us to see as depression much we used to call chronic neurosis, and steroids have changed many diseases formerly classified as psychosomatic into the organic category. It is very interesting and even possibly useful to compare national diagnostic habits, but apart from that it is not, in my view, right of you to encourage the further flogging of a dead horse, at any rate before we have a new whip.—I am, etc.,

E. A. BURKITT

Darlington

Mini-clinics in General Practice

SIR,—Mini-clinics (Drs. P. A. Thorn and R. G. Russell, 2 June, p. 534) are a means of stimulating and maintaining interest in the management of groups of patients. Could the principle be extended to other groups?

Antenatal clinics have been successfully run for many years on a mini-clinic basis. They have enabled a pattern of practice to be imposed, albeit gently, on the general practitioner. In return for this both the G.P. and the patient benefit from the less formal and more complete care that can be given in general practice. Other clinics run by hospitals which might be adapted to general practice are obesity clinics, asthma clinics, and encopretic and enuresis clinics, to name but a few. These are all dealing with problems that require a broader understanding of the family environment than a hospital doctor can hope to have.

Would mini-clinics be a valuable means of overcoming the problem of exchange of ideas between family and hospital medicine? Drs. Thorn and Russell mention an annual visit by the consultant to the mini-clinic as being welcomed by the family doctor. It must enable the relationship between consultant and G.P. to be put in its correct perspective, with the patient and his disease as the focus of the contact. The potential value of this alone might justify the extension of the mini-clinic idea.—I am, etc.,

P. H. BRUNYATE

Royal Devon and Exeter Hospital,
Exeter

Coeliac Disease and Schizophrenia

SIR,—Dr. Dermot Walsh, in commenting on the report by Dr. M. Mylotte and others (24 March, p. 703) of an exceptionally high incidence of coeliac disease in three western counties of Ireland, suggested (28 April, p. 242) "that a good case can be made for looking at the relatives of coeliac children in the west of Ireland . . . to see whether there is a raised incidence of schizophrenia among them." The suggestion is, I believe, an excellent one and well supported by: (1)—his demonstration¹ of a very high first admission rate for schizophrenia in Ireland (particularly in the western counties) compared with England and Wales and other countries; (2)—epidemiological and experimental evidence² that cereal grains may be harmful in schizophrenia as well as in coeliac disease; (3)—clinical and pathological observations^{2,3} suggesting that both diseases have many manifestations in common and may be genetically related; and (4)—the considerably greater per capita consumption of cereal

grains in Ireland than in England and Wales.⁴

Additional support is afforded by our recent report.⁵ We found that relapsed schizophrenics who on admission ate a cereal-free, milk-free diet for a relatively brief period were discharged from hospital twice as fast as those who had been on a high-cereal diet. The disappearance of this beneficial effect when wheat gluten was secretly added to the cereal-free diet indicates that it was not due to non-specific psychological factors.

Though findings such as these need full confirmation before acceptance or application, I believe they, plus previous evidence, amply justify further studies. In addition to genetic-epidemiological studies such as the one suggested by Dr. Walsh and more extensive dietary experiments, I suggest that unmedicated, relapsed schizophrenics consuming a high-gluten diet for weeks or months should be investigated for coeliac-like histological and metabolic abnormalities. In particular, peroral multiple biopsies of the small intestine should prove fruitful, since prior to the use of phenothiazines—a time when cereal grain consumption was much greater than now—patchy pathological changes in the small intestine, more or less similar to those more recently described in coeliac and dermatitis herpetiformis patients, were found at necropsy in a high proportion of schizophrenics.⁶⁻⁸—I am, etc.,

F. CURTIS DOHAN

Eastern Pennsylvania Psychiatric Institute,
Philadelphia, Pennsylvania

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Haemolytic-Uraemic Syndrome with Pericarditis and Pleurisy

SIR,—The report by Drs. J. A. Utting and D. R. Shreeve (9 June, p. 591) of pleural and pericardial haemorrhage occurring late in the course of the haemolytic-uraemic syndrome raises three important points.

First, streptokinase was given for twice as long as the manufacturers' recommended five-day period. Prolongation beyond this time may give rise to complications arising from the development of antibodies.

Second, the data provided do not allow a firm conclusion to be reached concerning the cause of the haemorrhagic pericardial and pleural effusions which occurred one month after admission. The absence of a rise in blood urea argues against recurrence of the original disease process. A very marked rise in serum fibrin degradation products was recorded but, in the absence of other evidence of increased intravascular coagulation (recurrence of thrombocytopenia, fall in coagulation factor levels, increase in circulating fragmented red cells) this might have been caused by lysis of fibrin within the haemorrhagic effusions. It would therefore

be of value to know the platelet count at the time of the haemorrhage and also the degree of prolongation of the thrombin clotting time resulting from heparin therapy.

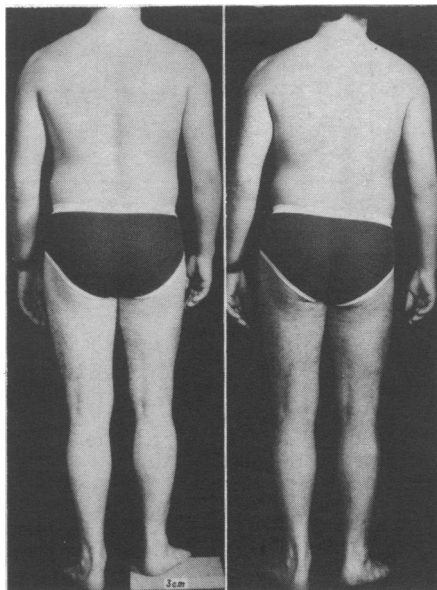
Third, the clinical improvement which occurred in parallel with the introduction of aspirin and dipyridamole is not necessarily evidence of a cause-and-effect relationship.—We are, etc.,

M. H. WINTERBORN
R. H. R. WHITE
J. STUART

Departments of Nephrology and Haematology,
Children's Hospital,
Birmingham

Congenital Hemihypertrophy

SIR,—The memorandum by Dr. M. Henry and others on congenital hemihypertrophy with aortic, skeletal, and ocular abnormalities (13 January, p. 87) is of interest. The authors mention possible lines of pathogenesis, and in a subsequent letter Dr. A. W. Johnston (17 March, p. 678) has reported that out of nine cases of congenital asymmetry only one had abnormal chromosomes. The accompanying photograph illustrates a further case of greater development of one side of the body than the other. The longer left side was noted from infancy, and the ultimate leg length difference of 3 cm produced a scoliosis, corrected by an appropriate raise. There was no special congenital disorder present and no chromosome studies are available.



The more dramatic features of patients with hemiatrophy or hemihypertrophy should not be allowed to overshadow the patients who have asymmetry extending to the lower limbs only. Greater clinical awareness is required, since asymmetry of this kind is not apparently as gross as that associated with hemihypertrophy. Once suspected, accurate measurement is required. The tape-measure or iliac crest palpation may give misleading results, as was shown when they were compared recently with a simple x-ray method¹ involving no more radiation than that for an x-ray of the pelvis, suitable protection being used as necessary. The x-ray taken erect gives accurate in-

formation about the actual discrepancy in the height of the femoral heads. It is interesting to note that any scoliosis observed clinically always appears greater on the x-ray. Lesser degrees of scoliosis may not be detected clinically, and this and other clinical features are obscured by obesity.

Though the least discrepancy worth correcting is still not clearly established, there are good clinical grounds for believing that it is at least $\frac{1}{2}$ in (12.5 mm), and in a report on one very large series based on radiological measurements it was suggested that 7 mm is the upper limit of the normal range.²—I am, etc.,

GEOFFREY CLARKE

London E.11

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Antibiotic Sensitivity of Klebsiella

SIR,—In our report on the contamination of E.C.G. electrode pads (19 May, p. 400) we stated that the *Klebsiella aerogenes* isolated appeared sensitive to ampicillin on disc sensitivity testing, and despite the finding that the minimum inhibitory concentration was well into the resistant range we do not share Dr. T. D. M. Martin's concern (9 June, p. 614) regarding our antibiotic sensitivity methods. Disc testing of this organism has produced the same results in two separate laboratories on several occasions.

We used the word "appeared" advisedly as the problems of interpreting disc sensitivity results of β -lactamase-producing organisms are well known. Almost all strains of *K. aerogenes* produce β -lactamase to a greater or lesser extent. Even with well-controlled disc sensitivity methods false results are easily obtained for such organisms, apparently as a result of small differences in inoculum. Hence in this paper, as elsewhere, when β -lactamase-producing *K. aerogenes* appears sensitive to ampicillin on disc testing, we would use the minimum inhibitory concentration as an essential and more accurate indication of susceptibility.—We are, etc.,

EUNICE LOCKEY

National Heart Hospital,
London, W.1.

M. W. CASEWELL

St. Thomas's Hospital,
London S.E.1

Epidemiology of Simple Hypospadias

SIR,—Our colleagues Dr. C. J. Roberts and Mrs. Setsuko Lloyd reported (31 March, p. 768) that there was a marked seasonal variation in the incidence of hypospadias among 93,000 newborn infants in South Wales during the period 1964-6. This seasonal fluctuation was even more marked if the date of last menstrual period was used as the index of incidence. A similar finding had also been reported from the United States for 1963-5 by Wehrung and Hay.¹

In England and Wales the local public health authorities keep a register of all congenital malformations which are reported at birth, from which the Registrar General has kindly provided a tabulation of hypospadias or epispadias for each month during the past five years, notified from the whole country. This is given in the table.