to the lack of correlation in this study between glyceryl trinitrate consumption and anginal attacks, which incidentally is not obvious from the table of results published, I am sure that much depends on the patients' own interpretation of his symptoms. When assessing prenylamine in angina[1] I asked the patients to record only attacks which were severe enough to interfere with their activity at the time of the attack, and I believe this made it easier for the patient to keep a valid record.

Lastly, I am disturbed by the alarmingly high incidence of status anginosus on withdrawal of the active drug in the recent study, and I wonder if we might have some further details of these patients' histories prior to starting the trial. This aspect of the drug clearly requires further investigation.—I am, etc.,

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REFERENCE

1 Cardoe, N., *British Journal of Clinical Practice*, 1968, **22**, 299.

Disodium Cromoglycate in Asthma

SIR,—Although the article by Dr. H. Herxheimer and Miss Helga Bewersdorff (26 April, p. 220) deals mainly with the prevention of induced asthma, they blandly report negative lung function tests in five chronic asthmatics treated with cromoglycate. No details concerning the duration of treatment or the number of observations before, during, and after giving cromoglycate are reported, and until this information is available I think it hardly reasonable to compare these scanty observations with the far more extensive observations by other workers.

Disodium cromoglycate has now been used extensively in three centres for more than two years—Manchester,[1] Birmingham,[2] and Stoke-on-Trent.[3] These three centres have carried out not only double-blind trials but also long-term trials on the value of disodium cromoglycate in the prevention of asthma. All three double-blind trials came out strongly in favour of disodium cromoglycate compared with placebo, and the later long-term studies have also been most encouraging.

At a recent whole-day symposium on disodium cromoglycate (Intal), held at the Royal Society of Medicine in London,[4] a number of communications were given reporting favourably on the use of disodium cromoglycate in the prevention and control of asthma. My own observations concerned 52 patients who had been treated with disodium cromoglycate for periods ranging from three months to twenty months. Fifty per cent. of these patients were assessed as showing definite or marked improvement and a further 27% were assessed as showing marginal improvement. From these and further observations I would conclude that disodium cromoglycate affords complete protection to a few and partial protection to many asthmatics. Certainly, since giving disodium cromoglycate openly to these and other patients the management of asthmatics attending this department has been easier and there have been far fewer acute attacks requiring emergency treatment and resuscitation. Many patients have had less need of their usual adrenergic aerosols. Many of them on corticosteroids have been adequately controlled on a lower dosage, and in a few patients corticosteroids have been withdrawn completely since commencing disodium cromoglycate on a long-term basis.

I am not at all impressed with the contention[5] that it is not advisable to record forced vital capacity and F.E.V. in patients with asthma. In fact, it is accepted by most workers that these measurements are essential for the effective monitoring of patients. In many of the patients treated openly over months with disodium cromoglycate there has been not only a substantial improvement in these indices as well as symptomatic improvement, but also the whole pattern of the asthma condition has materially improved. —I am, etc.,

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REFERENCES

1 Howell, J. B. L., and Altounyan, R. E. C., *Lancet*, 1967, **2**, 539.
2 Morrison Smith, J., and Devey, G. F., *British Medical Journal*, 1968, **2**, 340.
3 Kennedy, M. C. S., *Lancet*, 1967, **2**, 838.
4 Disodium cromoglycate (Intal) symposium—March 1969. Proceedings in press.
5 Herxheimer, H., *Acta Allergologica*, 1963, **18**, 1.

Neonatal Meningitis Treated with Trimethoprim and Sulphamethoxazole

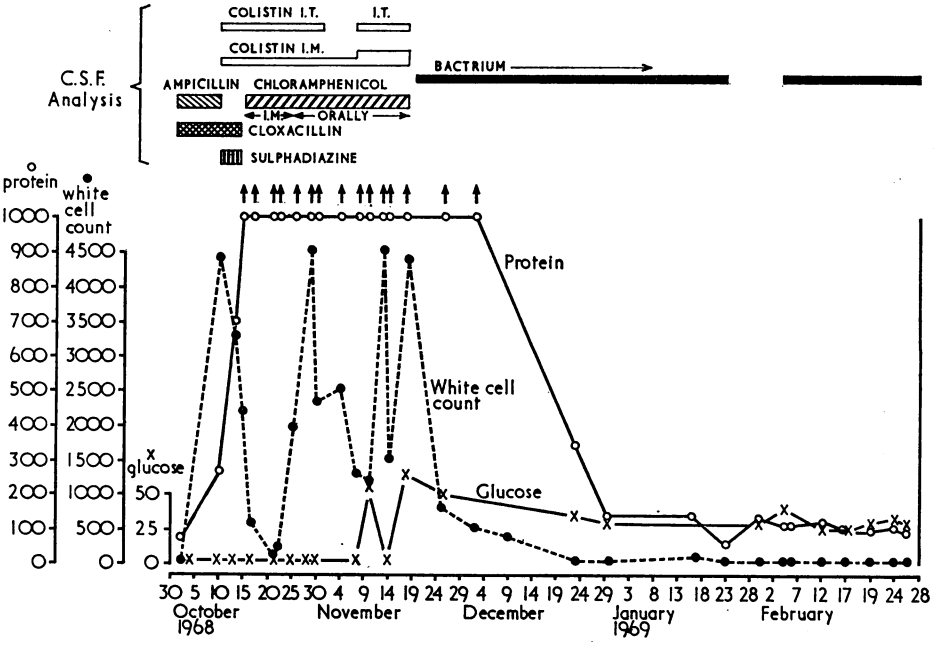
SIR,—The combination of trimethoprim and sulphamethoxazole promises to be more effective than any previously available therapy in certain conditions.[1–5] We report here the successful treatment of neonatal meningitis in an unpromising situation after other drugs had failed.

A female infant, born on 25 September 1968, had a small lumbar meningomyelocele repaired within 24 hours of birth by Mr. Malcolm Gough. She was later found to have an Arnold–Chiari malformation on air-ventriculography. At the age of 2 weeks she developed meningitis. From the cerebrospinal fluid a *Escherichia coli* was isolated which was sensitive to colistin, chloramphenicol, and tetracycline, and resistant to sulphonamides, ampicillin, and streptomycin. Treatment with intramuscular colistin and chloramphenicol (which was later given orally) and intrathecal colistin for nearly six weeks failed to control the infection in spite of the fact that the patient's serum and cerebrospinal fluid were shown to be bacteriostatic to the organism in a dilution of 1 in 8, and bactericidal in a dilution of 1 in 4 and 1 in 2 respectively. After the first week the cerebrospinal fluid (see diagram) protein content remained at a level higher than 1,000 mg. per 100 ml., the white cell count was higher than 1,200 per cu. mm., and no glucose was detectable although the fluid was sterile on culture. There was evidence of pus loculation on intraventricular taps and an air-ventriculogram. By this time the infant had received over 160 injections of colistin alone, and all injection sites showed considerable induration.

At this stage all other antibiotics were stopped and she was started on a combination of trimethoprim 20 mg. and sulphamethoxazole 100 mg. (Bactrim Paediatric tablets) by mouth twice a day. The cerebrospinal fluid gradually returned to normal and has remained normal since, except for a short period when the treatment was stopped and there was a rise in the white cell count and protein. At the age of 4 months a Rickham reservoir was inserted to facilitate cerebrospinal fluid removal to relieve pressure, and at the age of 5 months a Spitz–Holter valve was put in.

She is now 5½ months old, still receiving the same treatment, and her cerebrospinal fluid has remained normal. No significant drop in the haemoglobin or the platelet count has occurred, the total white cell count is within normal limits, and the polymorphs show no abnormalities.

This baby had a loculated purulent cerebrospinal fluid not controlled by a combination of intramuscular and intrathecal antibiotics, but which cleared while it was receiving an oral combination of trimethoprim and sulphamethoxazole. We suggest that this combination is useful in the treatment of neonatal meningitis and would be worth a trial in the treatment of any meningitis, as the penetration into the cerebrospinal fluid of the drugs to therapeutic levels appeared to be satisfactory in this case.



We wish to thank Dr. B. D. Bower and Mr. M. Gough for permission to report this case and for their guidance in the preparation of this report.

—We are, etc.,

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REFERENCES

1 *British Medical Journal*, 1968, **2**, 380.
2 *British Medical Journal*, 1969, **1**, 525.
3 Darrell, J. H., Garrod, L. P., and Waterworth, P. M., *Journal of Clinical Pathology*, 1968, **21**, 202.
4 Reeves, D. S., Faiers, M. C., Pursell, R. E., and Brumfitt, W., *British Medical Journal*, 1969, **1**, 541.
5 Grüneberg, R. N., and Kolbe, R., *British Medical Journal*, 1969, **1**, 545.

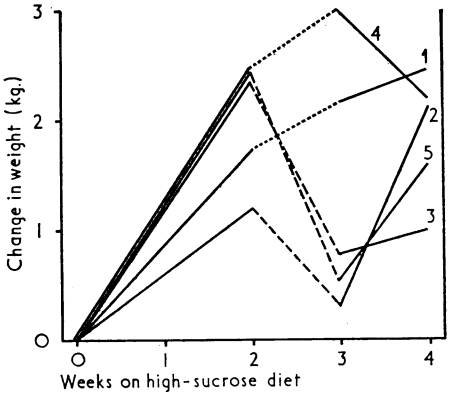
Diguanides and Weight Reduction

SIR,—In their interesting study of the effect of the diguanides phenformin and metformin on weight reduction, Dr. L. J. P. Duncan and his colleagues conclude, "The cause of the weight loss cannot be established until the various effects of diguanides have been more fully elucidated" (5 April, p. 13). We believe that a recent study of our own may add usefully to our knowledge of these effects.

We investigated the effect of increasing the sucrose in the diets of 19 men, all apparently healthy and with normal glucose tolerance.[1] The increase in dietary sucrose was chiefly at the expense of starch, so that caloric intake was not altered. After two weeks, six of the men showed an increase of weight of some two kilograms, which was lost during the next two weeks when the men reverted to their normal diet. The same six subjects also developed hyperinsulinism and an increase in platelet stickiness during the high-sucrose diet; these too became normal two weeks after the return to their normal diets. In the remaining 13 subjects the sucrose produced neither a gain in weight nor hyperinsulinism nor an increase in platelet stickiness. It appears therefore that only some individuals are susceptible to the effect of sucrose in producing these changes, which we have called "sucrose-induced hyperinsulinism."

We then selected a further five subjects who were susceptible in this way, and studied the effect of phenformin upon the weight gain and the hyperinsulinism induced by sucrose. After two weeks on a high-sucrose diet three of the subjects were given phenoformin 50 mg. orally twice daily for seven days, and the other two subjects were given placebo tablets. The subjects continued to take the high-sucrose diet for that week and for a further week after the tablets were withdrawn. At the end of each phase of the experiment the weights of the patients were recorded, and the immunoreactive insulin measured both in the fasting state and at intervals during a glucose-tolerance test (50 g. glucose orally).

The sucrose-induced hyperinsulinism, which was seen in all five subjects, was reduced in those that were given phenformin but not in those given placebo tablets (see Table). Similarly, the increase in body weight induced by the sucrose was to a large extent reversed in the subjects given phenformin, but not in the control subjects (Figure). There was no change in glucose tolerance during the experiment.



Effect of phenformin (– – –) or placebo (· · · ·) on body weight of five subjects showing sucrose-induced hyperinsulinism. High-sucrose diet fed for four weeks: phenformin or placebo given during third week.

Plasma Insulin Levels (Immunoreactive Insulin was Measured at Intervals during a Glucose Tolerance Test)

Subject and Sex	Age	Treatment	Duration	Insulin (μU/ml.) 0	30′	60′	120′
1 M	28	Normal diet	—	17	61	78	28
		Sucrose diet	2 weeks	22	92	98	73
		Sucrose plus placebo	1 week	20	103	90	61
		Sucrose diet	1 week	25	86	112	69
2 F	23	Normal diet	—	10	17	34	30
		Sucrose diet	2 weeks	21	79	92	68
		Sucrose plus phenformin	1 week	23	70	43	29
		Sucrose diet	1 week	27	105	98	82
3 M	37	Normal diet	—	27	26	54	41
		Sucrose diet	2 weeks	35	127	108	69
		Sucrose plus phenformin	1 week	20	71	52	37
		Sucrose diet	1 week	23	68	50	39
4 M	31	Normal diet	—	21	53	57	18
		Sucrose diet	2 weeks	28	79	81	52
		Sucrose plus placebo	1 week	29	83	72	30
		Sucrose diet	1 week	32	108	100	64
5 M	30	Normal diet	—	19	57	60	33
		Sucrose diet	2 weeks	29	112	92	68
		Sucrose plus phenformin	1 week	20	58	11	30
		Sucrose diet	1 week	39	129	97	81

Thus it appears that phenformin can reverse both the hyperinsulinism and the increase in body weight induced by sucrose in susceptible subjects. Since we believe that sucrose-induced hyperinsulinism may be related to atherogenesis, we are continuing our studies upon the effects of phenformin.—We are, etc.,

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REFERENCE

1 Szanto, S., and Yudkin, J., *Proceedings of the Nutrition Society*, 1969, **28**, 11A.

Hypokalaemia Complicating Carbenoxolone (Duogastrone) Therapy

SIR,—The prolonged use of carbenoxolone sodium in the treatment of gastric ulcer has been known to be associated with the risk of hypokalaemia. This risk is believed to be increased when the drug is combined with a thiazide diuretic to counter the aldosterone-like effect of fluid and sodium retention, which is believed by some authorities to be more marked when the patient is ambulant.

The use of position release capsules (Duogastrone), which are believed to rupture at the pylorus and discharge their contents of 50 mg. carbenoxolone sodium into the duodenum, are now employed widely in the treatment of duodenal ulcer. We have recently encountered a case of marked hypokalaemia believed to be due to the use of these capsules used alone and not in conjunction with a thiazide diuretic.

The patient, a 45-year-old man with a long-standing history (20 years) of typical ulcer-type dyspepsia and known radiologically to have a chronic ulcer, was admitted to this hospital with profound muscle weakness. This was asymmetrical in distribution, affecting principally the right arm, left leg, and right side of face. In addition to this he felt so ill and weak that he had been unable to get out of bed. These symptoms had developed over the preceding four to five weeks, during which time he had been on Duogastrone therapy for ulcer exacerbation. On clinical examination, apart from the muscle weakness described, he was mentally clear. Blood pressure was 160/100 mm. Hg. All tendon reflexes were absent, but no sensory disturbances could be detected. Apart from the right facial weakness mentioned the remainder of the central nervous system was clinically normal. Optic fundi were normal. E.C.G. showed the classical S–T and T wave changes of hypokalaemia. Chest x-ray revealed some cardiac enlargement with a calcified lesion in the right midzone thought to be consistent with old tuberculoma or hamartoma; this opacity had been known to be present for several years. Lumbar puncture was carried out, the fluid being normal in all respects. Paul–Bunnell test was negative, and no porphyrin could be detected in the urine. Haemoglobin was 93%, E.S.R. 40 mm. in the first hour (Wintrobe); blood film normal. Micro-Astrup estimation showed a *p*H of 7·43, base excess of −3·6, buffer base 43·5 mEq/litre blood, standard bicarbonate 21·5 mEq/litre plasma, P_{CO_2} 30 mm. Hg. These findings suggested a metabolic alkalosis. Serum potassium was 1·7 mEq/litre, serum sodium 143 mEq/litre, chloride 94 mEq/litre, calcium 8·5 mg./100 ml., magnesium 2·4 mEq/litre, blood urea 28 mg./100 ml.

He was given immediate intravenous potassium supplements at a rate of approximately 15 mEq. per hour. The calcium levels were exceedingly slow to rise despite continued potassium replacement, and four days after his admission the serum potassium level was still only 2·65 mEq/litre. Urinary potassium excretion was 31·2 mEq per 24 hours in 2·5 litres of urine. There was no aminoaciduria. Approximately 14 days after the discontinuation of Duogastrone his