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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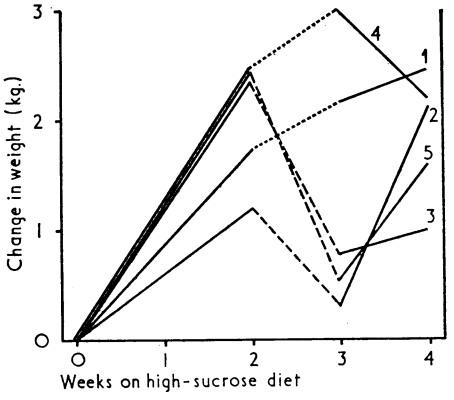
Diguanides and Weight Reduction

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 The subjects continued to take the high-sucrose diet for that week and for a further week after the tablets were withdrawn.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

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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

serum potassium was 4·45 mEq/litre, and this rose steadily thereafter to 5·1 mEq/litre one week later. His urinary potassium excretion likewise fell to 25 mEq/24 hours with restoration of the *p*H to normal.

The possibility of a primary hyperaldosteronism (Conn's syndrome) was considered, but the fall in the urinary potassium output with the progressive rise in serum potassium in the presence of adequate sodium repletion tended to be against this; also the fact that the specific gravity of his urine, while originally 1010, rose after repletion to 1015 and 1020. Familial periodic paralysis was likewise considered, but did not seem likely from the history. The low calcium levels may be associated with increased calcium excretion, which, while not estimated in this case, has been reported to occur in patients on carbenoxolone therapy and may be influenced by the accompanying sodium retention.

It is felt that this case is of interest in two ways: (*a*) The fact that a dangerous degree of hypokalaemia occurred in a patient taking this drug for a period within the prescribed time and not in excessive dosage and not in association with diuretics; and (*b*) that the hypokalaemia induced was initially refractory to replacement therapy even in large amounts. Whether or not this was due to carbenoxolone lying in quantities in an atonic bowel is open to conjecture. Although the other possible diagnoses have been mentioned and perhaps may still have to be borne in mind, it would seem most likely that this man's hypokalaemia was Duogastrone-induced, since he is now well and maintains his serum potassium within normal levels.—We are, etc.,

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Dangers of Perchlorethylene

SIR,—There has been recent public interest[1] in the possible dangers associated with the use of perchlorethylene in coin-operated dry cleaning machines. It was therefore felt appropriate to report the following case.

A 68-year-old man worked a few hours a day maintaining a launderette. On 5 January 1969 a container of perchlorethylene spilt over him, soaking his clothes. He was anaesthetized by the material, and lay unconscious for half an hour before being found. He was resuscitated in the casualty department of the local hospital. He was noted to have erythema and blistering amounting to 30% of his surface area, involving his neck, shoulders, left side of his chest and abdomen, left thigh, and perineum. As these were in the nature of chemical burns he was transferred to the burns centre. His appearance on admission was of a 30% superficial burn, and he was therefore treated with intravenous plasma, and antibiotics were commenced. The areas were exposed; the blisters were not deroofed, as they were very small. Five days later the erythema had subsided considerably and the blistering had gone; there was no cracking of the skin.

The patient was discharged and has been followed up by his general practitioner, Dr. G. R. C. Fisher, who reports that his burns have healed very well, apart from some dryness and irritation. There is slight staining of the skin on the areas injured.

This case illustrates the two effects of perchlorethylene, which has anaesthetic properties and on prolonged contact can produce "defatting" of the skin. The damaged skin is likely to crack and thereby become infected. Perchlorethylene, however, is far less dangerous than carbon tetrachloride.—I am, etc.,

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REFERENCE
1 *The Guardian*, 28 March 1969.

Lymphoblastic Leukaemia

SIR,—The interesting paper by Dr. H. C. Laurie[1] demonstrating that strong periodic-acid–Schiff (P.A.S.) reactivity in the primitive cells of lymphoblastic leukaemia is inversely related to the progression of the disease has prompted us to review our experience with a large series of patients diagnosed and treated at the Clinical Center, National Cancer Institute, National Institutes of Health.

Bone marrow "squash" smears from 44 patients with acute lymphocytic leukaemia were evaluated prior to initial therapy. The mean age was 6 years. The term acute lymphocytic leukaemia encompassed all leukaemic "blasts" that showed any degree of lymphoid differentiation, and undoubtedly included many cases that are referred to as "acute stem cell" leukaemia by others.[2] A P.A.S. scoring system similar to that proposed by Quaglino and Hayhoe[3] was used. The leukaemic blast cells were graded from 0 to 3+, and arbitrarily scores above 100 were considered elevated. In those cases with elevated scores (61% of group, or 27 patients) 2 and 3+ reactive cells constituted 57 to 96% of the P.A.S.-positive cells. In the group with scores between 50 and 100 (four cases) 23% of the positive cells were 2 and 3+, and in the lowest group (13 cases) 7% of the cells were 2+ or 3+.

Laurie reported that his patients could be readily divided into a group with less than 40% P.A.S.-negative blast cells and a group with greater than 55% P.A.S.-negative blast cells. The median survival in the former group was 25 months but only 11½ months in the latter. Analysing our data, a natural division was found with greater or less than 50% P.A.S.-negative blast cells. The median survival of both groups, 16 and 18 cases respectively, using life table methods, was 37·5 months for the weak P.A.S.-positive group and 33 months for the strong P.A.S.-positive group; not statistically significant. Another minor subdivision was created with a group having 75% or more P.A.S.-negative blasts (nine cases) and the other group 25% or less P.A.S.-negative blasts, 34 cases. The median survival of both groups was identical, namely 36 months. In all of the four groups there were at least two or more patients living and well a minimum of 3½ years from initiation of therapy.

Therefore, although our studies confirm the presence of significant amounts of P.A.S.-positive material in the cytoplasm of leukaemic lymphoblasts from the majority of patients with acute lymphocytic leukaemia, the data do not support the usefulness of the P.A.S. reaction in predicting individual patient remission or survival.

These two studies also differ in their chemotherapeutic programmes. The patients studied by Laurie were treated initially with prednisone and 6-mercaptopurine or vincristine.[4] Then, after remission induction, cyclical therapy with 6-mercaptopurine, methotrexate, and cyclophosphamide was administered sequentially. Some of our patients were initially treated with a combination of four drugs (vincristine, prednisone, methotrexate, and 6-mercaptopurine), or "VAMP." Twenty-four received an intensification of this programme, including monthly "pulses" for one year.[5] It might be appropriate to point out that neither initial duration of symptoms nor leucocyte counts correlated with the duration of the first remission. Though the remission duration periods are approximately the same for both groups (60–65 weeks), there is a longer survival in our series. Whether this is due to a greater reduction in leukaemic cells or a change in the kinetic behaviour of the cells is unclear. This additional period of prolongation of life in these children, however, may offset and conceal any difference that may have been detected by the P.A.S. method.—We are, etc.,

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Management of Acute Salicylate Poisoning

SIR,—We were very interested to read the valuable contribution by Drs. A. G. Morgan and A. Polak (4 January, p. 16), and the ensuing correspondence (18 January, p. 185; 1 February, p. 315; 8 February, p. 383; and 17 March, p. 577). As we have several years' experience of the treatment of salicylate poisoning, including the use of acetazolamide, we should like to make certain comments.

It is generally agreed that the renal excretion of salicylate depends partly on urine flow rate and partly on the alkalinity of the urine, but the relative importance of the two factors does not appear to have been worked out. We have therefore analysed our own records and also those which Dr. Morgan has kindly supplied to us and have calculated the crude clearance of salicylate (deriving free salicylate levels in plasma from total salicylate levels using the data of Moran and Walker).[1] We then attempted to determine the separate effects of flow rate and alkalinity on the clearance.

The results are summarized in the Table and indicate that, to get the best clearance, (1) if relying mainly on alkalinity the urine flow should be at least 3 ml./min. and, except at high flow rates, the urine *p*H should be greater than 7·5; (2) if relying mainly on