The other important factor in keratinisation which might be affected by penicillamine is the presence of copper. In sheep which have been fed on a copper-deficient diet, the histochemical sulphydryl reaction extends from the basal cells along the fibre of sheep hair considerably farther than in the normal animal. Parallel to these histochemical findings, it has been shown that the total sulphur content of wool fibres in copper deficiency is 10–15% lower than normal. The fibres in copper deficiency are weak, as they were after artificial rupture of disulphide bonds. Obviously there is a slow setting of the fibres but the normal keratin pattern in the X-ray spectrogram is present also in copper-deficient fibres, so the setting finally does take place.

On this evidence Marston (1946) had little doubt that oxidative closure of the sulphydryl residues to disulphide linkages is catalysed by copper. In the normal integument this oxidation is completed within eight to twelve hours. In copper deficiency, the process takes three days or more for completion, and even then the fibre retains its plasticity in the proximal half of the hair.

It is intriguing to recall that the two most common and general reactions to cutaneous injury—hyperpigmentation and hyperkeratinisation—have in common a transformation of sulphydryl into disulphide groups, and in both cases these processes are catalysed by copper.

Penicillamine is a powerful chelating agent for copper and might affect keratinisation by producing a local copper deficiency. There is some slight supporting evidence for this in the work of Greiner and Nicholson (1964), who claimed that administration of penicillamine cleared the abnormal pigmentation of the skin and eyes induced by long continued high doses of chlorpromazine. They suggested that penicillamine, by removing copper, inhibited dopa oxidase and thus inhibited the formation of melanin from tyrosine. This hypothesis is attractive, but there is some evidence against. Gibbs and Walshe (1965) have shown that although penicillamine can significantly lower serum-levels of copper in Wilson's disease, it does not cause any change in the concentration of copper in hair so that the drug seems able only to remove excess stored metal from the body.

We hope that by further studies using histochemical techniques we may demonstrate induced changes in the respective concentrations of sulphydryl and disulphide groups in the epidermis and, for the present, suggest that penicillamine be regarded as a device to help in the elucidation of problems of disordered keratinisation.

Summary

Six cases of Darier's disease were treated with D(-)penicillamine hydrochloride. Three showed definite improvement after two months treatment and relapsed when the drug was discontinued. Two patients improved slightly and one failed completely to show any improvement. The mode of action of penicillamine is not known, but it seems likely that a structurally altered keratin may account for the clinical improvement.

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THE LONG-TERM VALUE OF FASTING IN THE TREATMENT OF OBESITY

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TREATMENT for obesity is desirable because of the serious complications which may otherwise ensue, and because the increased mortality-rate of obese people is reduced to normal if they lose weight (Metropolitan Life Insurance Company 1962). Overweight people, moreover, are more active and feel generally better if they lose weight, and they often become less isolated and less depressed (Walker 1954). Weight reduction is therefore both an important part of preventive medicine and a valuable therapeutic measure. Unfortunately, the results of treating obese patients at weight-reduction clinics are most disappointing: many patients default at an early stage and only a few achieve permanent weight-loss. Another approach, which is widely used in the United States since its introduction by Bloom (1959) and has been described by Thomson et al. (1966), is treatment by total fasting. Although this is generally safe and achieves rapid loss of weight, the long-term results of fasting have not been widely investigated. We report here the results of treatment of 62 obese patients by a period of total fasting who have been followed up for 1–3 years.

Patients and Procedure

Patients Treated

62 obese patients have been treated by fasting and followed up for over a year. 58 were women and 4 men, with ages ranging from 14 to 73 years. All the patients had previously attempted to lose weight, with or without medical advice, some for many years. Some had had complications of their obesity, including degenerative joint disease, genital prolapse, and intractable varicose ulcers, and several were completely incapacitated by their overweight. 9 women and 1 man had treated hypothyroidism, and another man had hypogonadism secondary to pituitary failure. The fasting procedure was explained to them and they all volunteered to attempt it.

Procedure

All patients were admitted to hospital, and on the day of admission the patients were weighed and received a normal diet. On the morning of the second day they were weighed again and fasting was commenced. No solid food was allowed but water, unsweetened black tea, or unsweetened black coffee were permitted without restriction; but most patients preferred water only. No vitamin supplements were given. The patients were not isolated and no measures were taken to prevent their seeing other patients eating. They were encouraged to be up throughout the day but no strenuous exercise was undertaken during fasting. They were weighed each morning and the urine was tested for ketoacids by the ferric-chloride test. After a

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10-day period of fasting a diet of 600–1000 kcal. was commenced and the patients left hospital the next day. They were reviewed at the outpatient clinic at intervals of 1–3 months and were weighed on a machine that had been checked with that in the ward. At these attendances, however, they were weighed in their outdoor clothes, which were heavier than their hospital attire: about 6 lb. (2·7 kg.) for women and 10 lb. (4·5 kg.) for men (Duncan 1964). Since this difference may vary between patients, and at different times of the year, we have not included it in comparing inpatient and outpatient weights. This means that weight-losses at follow-up will tend to be underestimated.

Results

The average weight-loss during the 10-day fast was 16·3 lb. (7·4 kg.). The smallest weight loss in any patient was 7 lb. (3·2 kg.) and the greatest was 39 lb. (17·7 kg.). Ketonuria was noted on the second or third day of the fast and persisted until feeding was restarted. Most patients felt well throughout their fast and none complained of hunger, although almost all said they could eat a meal if it were provided, and anorexia at the end of the fast was not observed. The fast had to be terminated early, at 4–6 days, in 5 patients, because of nausea or vomiting and in 1, diarrhœa also. Several other patients had mild diarrhœa when lemon juice was added to their drinking water, and so the other patients were advised against this. The only other complication was in a 64-year-old woman who became drowsy during the fast, refused to drink, and had suppurative parotitis, which soon resolved with antibiotic treatment and rehydration.

TABLE I—RESULTS OF TREATMENT BY FASTING AFTER 1, 2, AND 3 YEARS

Yrs. after fast	Total no. of patients	No. of patients with weight change of:			Lost to follow-up
		Loss > 7 lb.	No change (±7 lb.)	Gain > 7 lb.	
1	62	25	14	7	16
2	33	8	8	6	11
3	12	4	1	4	3

Table I shows the changes in weight in all the patients followed for 1, 2, and 3 years after their initial fast. We considered a loss in weight of more than 7 lb. (3·2 kg.), not counting the difference in clothing, to be a satisfactory result. Of the 62 patients followed up for 1 year, 25 (40%) had lost weight, while the figures for patients followed for 2 and 3 years were 24% and 33%, respectively. In the first year, 13 patients (21%) defaulted from the clinic and did not respond to three letters inviting them to attend; 3 patients died.

In 15 patients a second period of fasting was undertaken at the patient's request, and 4 more undertook more than one. The results in this group are shown in table II; they are not significantly better than those in the patients who fasted once only. Multiple fasts were carried out in a few patients in whom drastic weight-loss was considered necessary; 1 patient with severe symptoms due to genital prolapse undertook eight fasts, each of 10 days, over a period of 10 months, and her weight fell from 259 lb. to 191 lb. (117·7–86·8 kg.). Operation for prolapse repair, which had originally been considered too hazardous because of her obesity, was then carried out uneventfully.

TABLE II—RESULTS IN PATIENTS TREATED BY TWO OR MORE PERIODS OF FASTING

Yrs. after fast	Total no. of patients	No. of patients with weight change of:			Lost to follow-up
		Loss > 7 lb.	No change (±7 lb.)	Gain > 7 lb.	
1	19	9	5	2	3
2	12	8	1	3	0
3	7	2	2	3	0

Discussion

Prolonged fasting has been known to be compatible with life since the days of Moses, but it was first introduced as a specific therapy for obesity by Bloom (1959), and its effectiveness has been confirmed by many workers in the United States and by Thomson et al. (1966). All workers have found that a period of total fasting results in a rapid decrease in body-weight, although the amount of weight lost during fasting varies (van Riet et al. 1964). In our series the average loss was 16·3 lb. (7·4 kg.) over a 10-day period.

Our observations confirm the fact that obese people can survive a period of total starvation in comfort and without ill-effects, apart from nausea and vomiting in a few patients. The absence of complaints of hunger during fasting is striking, and this has been noted by most workers, but like Silverstone et al. (1966) and Thomson et al. (1966) we did not observe the anorexia reported by Drenick et al. (1964). No serious side-effects were noted in our patients, apart from suppurative parotitis in 1 patient. 5 of the 62 patients, because of nausea and vomiting, did not complete the 10-day fast. Many workers have confirmed the safety of fasting in obese patients, but undesirable effects have been noted in rare instances: these include gout (Drenick et al. 1964), death associated with lactic-acidosis (Cubberley et al. 1965), cardiac arrhythmia (Duncan et al. 1965), renal failure (Duncan et al. 1965), Wernicke's encephalopathy (Drenick et al. 1966), and (as in one of our patients) parotitis (Thomson et al. 1966). Because of these reports we believe it is prudent to recommend fasting only in hospital, and to terminate the fast in any patient who becomes unwell.

The long-term results of fasting have not been widely studied. It is important to know whether the weight-loss achieved during fasting is maintained when the patients leave hospital and resume their normal life, since if the weight were regained over the ensuing months it would be difficult to justify fasting as a useful form of treatment. In a group of patients followed for periods of 1–32 months after fasting, Duncan et al. (1963) found that 17% continued to lose weight and 43% maintained their initial reduction, while in a postal survey of patients from the same hospital (Hunscher 1966) 23% said that they had not regained the weight lost during fasting over the subsequent 1-to-3-year period. Only half the patients replied to the survey, however, and we feel that patients' statements about their weight obtained in such a manner must be regarded cautiously.

Some of our patients certainly regained their lost weight rapidly, and 1 year after the fast at least 21 of the 62 patients (34%) had either returned to their original weight or were heavier. If it is assumed that the patients who defaulted also failed to maintain their weight-loss, then 55% of our patients derived no long-term benefit from their fast in hospital. When it is remembered, however, that all the patients had previously attempted (unsuccessfully) to lose weight, some for many years, it can be seen that an initial period of fasting is of long-term benefit to some patients, since 40% were still less than their initial weight after 1 year, while 4 of 12 patients observed for 3 years had lost weight. These results are better than those reported in patients who have attended weight-reduction clinics, of whom 24–28% do not return after their first visit (Stunkard and McLaren-Hume 1959,

Seaton and Rose 1965), while of 100 overweight patients only 2 had lost weight after 2 years (Stunkard and McLaren-Hume 1959).

Since the 19 patients who undertook repeated fasts were a selected proportion of the total, in that they requested further treatment by fasting, we cannot draw conclusions about the value of repeated fasts in general. It cannot be predicted, however, that the long-term benefit of repeated fasts will necessarily be greater than if only one fast were undertaken; the results shown in table II suggest that in some patients at least the end-result is no better. There are, on the other hand, some patients in whom rapid weight-loss is considered to be urgently indicated, and for them repeated fasts may be of particular value. Alternatively, a very prolonged single fast has been suggested, and patients have been successfully fasted for periods of 117 days (Drenick et al. 1964), 245 days (Henneman and King 1964), and 249 days (Thomson et al. 1966). For most patients and their physicians, however, intermittent 10-day fasts, with the patients in hospital only during the fasts, are more practicable, and the results may be as good. Thus our patient described above who underwent eight 10-days fasts, and carried on her normal life outside hospital between the fasts, lost the same amount of weight, and the same fraction of her original weight as the patient of Thomson et al. (1966) who fasted continuously in hospital for 249 days.

It is not known why the benefits of fasting should persist in some patients beyond the period of starvation itself, but several factors may be responsible. During the first few days of fasting the weight-loss is due mainly to decrease in the amount of extracellular fluid and to protein catabolism, with high nitrogen excretion (Henneman and King 1964). At the same time hormonal changes occur, with a decrease in thyroid function (Alexander et al. 1964) and increased secretion of growth hormone (Roth et al. 1963) which result in decreased protein catabolism and increased mobilisation of fat. It is not known for how long these changes persist after the end of the fast; they may continue to promote weight-loss from fat-catabolism when eating is resumed. Secondly, it has been shown that patients' appetites are less at the end of a fast than before it (Silverstone et al. 1966) so that fasting may enable some patients to become satisfied with a low-calorie diet although they found it insufficient before. Thirdly, the rapid weight-loss during fasting is of psychological benefit to patients who were previously convinced that " dieting " was hopeless or that they had a glandular disease. These patients may be sufficiently encouraged by the results of fasting to adhere more strictly than before to a weight-reduction diet.

Summary

62 obese patients, who had previously attempted, unsuccessfully, to lose weight, were treated by a 10-day period of total fasting in hospital, followed by a weight-reducing diet on discharge. The average weight-loss during the 10-day fast was 16·3 lb. (7·4 kg.). In 5 patients, the fast had to be terminated because of gastrointestinal symptoms, and 1 other patient had suppurative parotitis. The remaining patients felt well throughout the fast and did not complain of hunger.

The patients were followed up for 1–3 years after their fast. After 1 year, 40% of the patients had not returned to their original weight, and of 12 patients followed for 3 years, 4 had maintained their weight-loss. In 19 patients, two or more fasts were undertaken but the results in these patients were not significantly better than those in patients having only one period of fasting, except where rapid weight-loss was urgently indicated. Possible reasons for the long-term benefits of a short fast are discussed. The results are considerably better than those in patients attending weight-reduction clinics. Fasting in obesity is generally safe and not unpleasant, but it should be undertaken only in hospital.

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PLASMA-TESTOSTERONE LEVELS IN KENYAN MEN IN RELATION TO CANCER OF THE NASOPHARYNX

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Clifford and Bulbrook (1966) found that African men excreted less urinary 11-deoxy-17-oxosteroids and more urinary œstrogens than British men. They concluded that the urinary assay results were evidence for hyper-œstrogenisation in the Africans and that this might be a contributory factor in the high prevalence of nasopharyngeal cancer in Kenyan men.

Deductions concerning the physiological stimuli to a target organ that are based on results of assays of urinary steroid metabolites must be regarded with some caution. A more direct approach is the measurement of plasma levels of the hormones from which the urinary steroids are derived. The most important androgen in men is testosterone, and the levels of this hormone could have an important bearing on the net œstrogenic stimulus to the nasopharyngeal epithelium. This paper reports on comparison between the levels of plasma-testosterone in Kenyan men of the Central Bantu or Nilo-hamitic ethnic groups and those of British men.

Methods

Heparinised blood-samples (20 ml.) were collected from Kenyan men shortly after admission to hospital. Except for 7 patients with cancer, the remaining Africans were admitted