nutmeg appearance of chronic passive congestion. There was a small patch of necrosis, yellowish in colour, in the right lobe. This was rather friable. The gall bladder and biliary tract were normal.

Histology.—The liver showed changes of chronic venous congestion in most of the liver lobules and consisted of dilated central veins and dilated and congested sinusoids. A few cells around the dilated central veins showed changes of necrosis. The periportal connective tissue was slightly increased. In addition to this, in many areas the parenchymatous cells showed evidence of focal necrosis irregular in distribution (Fig. 2), and quite different from that seen in chronic venous congestion. These areas of necrosis morphologically resembled those produced by carbon tetrachloride injury in experimental animals. The necrosed cells showed pyknotic nuclei and indistinct cell walls. The cytoplasm showed hydropic degeneration and in places the presence of amorphous eosinophilic material. A few vacuoles could be seen in some cells. Kupffer cells were prominent and contained increased pigment. The bile ducts showed a moderate degree of proliferation. However, no stagnation of bile could be seen.

Discussion

Jaundice due to drugs is usually hepatocellular or cholestatic and rarely haemolytic. The clinical and biochemical differentiation of the various types is well known.

Ethacrynic acid has been reported to produce cholestatic jaundice in one patient (Merck Sharp and Dohme, 1964); however, to the best of our knowledge there are no reports of hepatocellular damage due to it. Experimentally, it has been proved that this drug is stored in the liver and secreted in the bile (Beyer *et al.*, 1965). The highest concentration of ^{14}C ethacrynic acid, after one week of its intravenous administration, was found in the liver, though this was only 2% of the dose, less than 3% being present in all the other organs (Merck Sharp and Dohme, 1964). We feel that in our patient this may account for the increase in jaundice for some days, even after the drug was withdrawn.

In our case the rise in S.G.O.T., S.G.P.T., and serum bilirubin and positive flocculation tests clearly indicates that the jaundice was hepatocellular in nature. The hepatocellular damage was probably due to ethacrynic acid, because on the first two occasions the jaundice developed when the drug was administered and regressed when it was discontinued. On the third occasion, however, after restarting the drug the patient developed hepatic coma and increasing jaundice. He recovered from the coma with appropriate measures, though the jaundice persisted. The irregular distribution of focal necrosis in the liver, quite different from that seen in chronic venous congestion, which shows centrilobular focal necrosis and resembling morphologically that produced by carbon tetrachloride in experimental animals, is in favour of its being due to the drug and not to acute or chronic heart failure. This correlates well with the clinical observations. As the drug is stored in the liver it is not surprising that hepatocellular damage was produced. Hence caution is required in the administration of this potent drug.

Summary

Ethacrynic acid is a new diuretic agent. Some of its side-effects and toxic effects are well documented, while others have been reported but rarely. A new toxic effect, hepatocellular damage, is reported in this communication.

The drug was supplied by the courtesy of Merck Sharp and Dohme Ltd.

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Preliminary Communications

Sugar Consumption in Acne Vulgaris and Seborrhoeic Dermatitis

Brit. med. J., 1967, **3**, 153–155

There is little concrete evidence that diet plays a part in the aetiology of disorders of the skin, except in nutritional deficiency diseases such as pellagra and kwashiorkor. Nevertheless, many authorities implicate diet—dietary excess rather than dietary deficiency—as an aetiological agent, notably in acne vulgaris and, to a less extent, in seborrhoeic dermatitis. Consequently, changes in diet are frequently recommended as part of the treatment of these diseases. Of 10 recent textbooks, diet is mentioned in 9 in connexion with the cause or treatment of acne, and in 6 in connexion with seborrhoeic dermatitis. In neither disease are the authors unanimous; most frequently mentioned, however, is an excessive intake of fat or of carbohydrate, or of both. In addition chocolate is several times specifically mentioned in connexion with acne.

There are three criteria by which one tests the hypothesis that a dietary component is implicated in the causation of a disease (Yudkin, 1953). Firstly, there should be evidence that the diet of persons with the disease differs significantly from that of persons without the disease. Secondly, the symptoms and signs should be those that are known to be, or at least are plausibly suspected of being, caused by dietary imbalance. Thirdly, correction of the dietary imbalance should result in correction of the signs and symptoms.

In this paper we bring evidence of the first sort: that patients with seborrhoeic dermatitis consume significantly more sugar (sucrose) than persons without the disease. We believe that this is the first demonstration of a dietary difference in such patients. We have also shown that there is no such difference in patients with acne.

If the excessive amounts of a dietary constituent are thought to be a possible cause of disease, there are several reasons—evolutionary, historical, and metabolic—why sugar should be regarded as a likely candidate (Yudkin, 1963). It happens, too, than in practice it is more feasible to assess sugar intake than the intake of any other dietary constituent (Yudkin and Roddy, 1966). For these reasons, we measured the sugar intake of patients and control subjects with a short questionary that could be completed in 10–15 minutes by each of the subjects (see Appendix by J. Yudkin below).

The patients were referred to one of us at the skin clinics held at two hospitals. Seborrhoeic dermatitis was diagnosed when the patient presented with severe scaling of the scalp, together either with itchy scaly patches of the sternal or interscapular region or about the eyelids or nasolabial folds, or with intertrigo of the axillae, groins, or retroauricular areas, or with both types of lesions. All the patients had had previous

attacks, and the current attack had lasted at least one month. All except one of the 16 patients were males; the ages ranged from 14 to 68.

Acne was diagnosed on the basis of comedones on the face, back, or chest, together with papules, pustules, or cystic lesions. There were nine male and seven female patients, aged between 15 and 27.

The patients with acne and dermatitis were all those who were seen during the period of study, except that, as usual, we did not include in our final assessment those whose sugar consumption, by admission or by implication, had changed.

As control subjects we used two different groups of people. The first were patients suffering from warts and attending the same skin clinics. Again, they were selected only on the basis of their diagnosis and on the apparent constancy of their sugar consumption. They were listed in the order in which we saw them, and from the list we then selected those who matched, as well as possible, the age and sex of the patients with acne or the patients with dermatitis. This was important, because we have found a difference in sugar intake between men and women and at different ages (Salter and Yudkin, to be published). It was, however, possible to find only 13 control patients of appropriate age for the 16 patients with seborrhoeic dermatitis. Moreover, it was not possible to match the distribution of male and female control patients with the distribution of the nine male and seven female patients with acne. For these reasons we used a second group of controls for each disease. These were apparently healthy men and women, either from a London factory or from a large London office. Their sugar intake had been measured during a large-scale survey that was being carried out for other purposes. This second group of controls was also selected from the list of subjects, made in the order in which they were seen, by choosing the first subject in the list that matched in age and sex the first patient with acne or dermatitis, then the first subject that matched the second patient, and continuing until all the patients were matched with apparently healthy control subjects.

Results

The intake of sugar by the patients with acne was not significantly different from that of either group of control patients (Table I). On the other hand, the intake of sugar by the patients with seborrhoeic dermatitis was significantly higher than that of either group of control patients (Table II). This was true both for total sugar and for the sugar taken in tea and coffee ("beverage sugar"). Statistical analysis was carried out with the Mann-Whitney test for Control group 1, and with the Wilcoxon Matched-Pairs Signed-Ranks Test for Control group 2 (Siegel, 1956).

TABLE I.—*Sugar Intake of Subjects With Acne and of Control Subjects (Control 1: Patients With Warts; Control 2: Healthy Factory and Office Workers)*

Group	No.	Age (Mean, Years)	Sugar Intake (g./day)			
			Total		Beverage	
			Mean	Median	Mean	Median
Acne ..	16	19·5	121	103	65	70
Control 1	16	20·0	111	97	47	48
„ 2	16	19·7	120	118	63	55

No significant differences in sugar intake between groups ($P > 0.05$).

TABLE II.—*Sugar Intake of Subjects With Seborrhoeic Dermatitis and of Control Subjects (Control 1: Patients With Warts; Control 2: Healthy Factory and Office Workers)*

Group	No.	Age (Mean, Years)	Sugar Intake (g./day)			
			Total		Beverage	
			Mean	Median	Mean	Median
Dermatitis	16	38·2	170	185	104	109
Control 1	13	36·5	108	109	65	56
„ 2	16	38·1	110	110	61	57

Significant differences.—Total sugar intake: dermatitis and control 1—$P < 0.01$. Dermatitis and control 2—$P < 0.02$. Beverage sugar.—Dermatitis and control 1—$P < 0.02$. Dermatitis and control 2—$P < 0.05$.

Discussion

The numbers of patients with either skin disease was small, chiefly because we made every effort to choose those in whom the diagnosis was not in doubt. Apart from this, there was no selection either of the patients with skin disease or of those acting as controls. The selection of the second group of control subjects from the factory and the office was only on the basis of age and sex. The lists of the patients and of the healthy control subjects had been drawn up in the order in which they were seen. This latter list was scanned from the beginning until a subject was found that matched in age and sex the first patient. This procedure was repeated with the next patient, and continued until all the patients had been matched.

In spite of the small number of subjects, we found a significantly higher intake of sugar in patients with seborrhoeic dermatitis than in control subjects. We believe, therefore, that this represents a real difference. We cannot of course say whether or not this relation between disease and sugar intake is a causal one. The findings, however, do suggest that it would be worth while to determine in a controlled experiment the effect of a reduction of dietary sugar on the course of the disease.

Our findings indicate that patients with acne have an intake of sugar no different from that of control subjects. This does not of course mean that diet is not involved in the causation of the disease or that changes in diet would not affect its progress. But further and more elaborate investigation would be required to test this possibility.

Summary

The consumption of sugar (sucrose) by patients with seborrhoeic dermatitis was found to be significantly higher than that of two groups of control subjects. On the other hand, the consumption of sugar by patients with acne vulgaris was found to be no different from that of control subjects.

Mrs. Jill Morland was in receipt of a personal grant from the Medical Research Council while this work was being carried out.

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Appendix: Measurement of Sugar Consumption by Questionary

We have reported several studies in which we have measured the consumption of sugar (sucrose) by a method based on a simple questionary. The original method involved the completion of the form by an interviewer (Yudkin and Roddy, 1964). More recently, the questionary has been simplified further so that it can be completed by the subject himself (Yudkin and Morland, 1967). We have given reasons for our belief that the method is reliable (Yudkin, 1964) and we have more recently tested its reliability against the method that

involves the subject recording in a diary all the food and drink consumed over a period of seven days (Yudkin and Roddy, 1966).

The simplified questionary is set out below. In all of our studies we have attempted to consider only those persons who, so far as we can ascertain, have had a constant sugar consumption for many years. For this reason we include questions relating to "special" diets, and we eliminate from our final assessments those subjects who we have reason to believe have changed their sugar consumption.

The calculation of the amount of sugar in prepared foods and drinks is made from analyses published in food tables or from figures supplied by manufacturers. As for sugar itself, we take a heaped teaspoon as containing 6 g., a level teaspoon 4 g., a heaped dessertspoon 15 g., and a level dessertspoon 10 g.

I am grateful to Janet Roddy and Jill Morland, who helped to devise and test this questionary, and to the Medical Research Council, who supported the work.

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DIETARY QUESTIONARY

NAME ..... AGE .....
N.B.—IF THERE IS AN ALTERNATIVE MARKED* PLEASE CROSS OUT THE ONE WHICH DOES NOT APPLY
If your weight has increased in the last few years, are you making a serious effort to check or decrease it? Yes/No*
If "Yes," are you restricting sweet or sugary foods, or sugar? .....
.....
.....
.....
If you are on a special diet *now* why are you on this diet? .....
.....
How long have you been on this diet? .....
Have you *ever* been on any other special diet? Yes/No*
If "Yes"
Why were you on this diet? .....
Approximately when did you start this diet? .....
How long did it last? .....
If your eating habits have permanently changed as a result of being on the diet, in what way? .....
.....

Go through an average day in your mind, and write down how many cups of tea and coffee you consume:

	Tea	Coffee	Other hot beverages (Cocoa, chocolate, etc.)
Before breakfast	..... cups	..... cups	..... cups
At breakfast	..... cups	..... cups	..... cups
Mid-morning break	..... cups	..... cups	..... cups
Midday meal	..... cups	..... cups	..... cups
Teatime	..... cups	..... cups	..... cups
Evening meal	..... cups	..... cups	..... cups
Bedtime	..... cups	..... cups	..... cups
Other	..... cups	..... cups	..... cups

How much sugar do you take in tea? .....teaspoons
Are the spoons level or heaped? .....
How much sugar do you take in coffee? .....teaspoons
Are the spoons level or heaped? .....
Have you always taken the same amount of sugar in these beverages? Yes/No*
If "No," how much did you take before? .....
When did you change? .....
Do you *regularly* use artificial sweeteners, e.g. saccharine, saxine, etc. Yes/No*
How long have you used them? .....
How much of the following do you eat or drink *per week*?
Sweets, toffees, and fancy chocolates .....lbs. .....oz.
No. of 2-oz. chocolate bars .....
Fizzy drinks, non-alcoholic .....glasses
(inc. tonic water, ginger-beer, etc.) .....small bottles
Fruit squash .....glasses
Fruit juice (tinned or bottled) .....glasses
How many a *week* do you have of the following:
Porridge .....portions
Plain breakfast cereals .....portions
Sugar-coated breakfast cereals .....portions
Jam or marmalade .....teaspoons
Sweet biscuits .....number
Pudding or sweet at midday (including tinned fruit) .....portions
Pudding or sweet for tea or evening meal (including tinned fruit) .....portions
Individual cakes and/or slices of cake .....number
How many spoons of sugar do you take on breakfast cereals? .....
Are they teaspoons or dessertspoons? .....
Are they level or heaped? .....
How many spoons of sugar do you take on porridge? .....
Are they teaspoons or dessertspoons? .....
Are they level or heaped? .....

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Medical Memoranda

Hepatitis with Biliverdinaemia in Association with Indomethacin Therapy

Biliverdin is the first bile pigment formed in the catabolism of the haem portion of haemoglobin. In man biliverdin is almost entirely reduced to bilirubin, which is excreted in the bile. The development of biliverdinaemia and biliverdinuria in association with disease, or as an iatrogenic effect, has not been reported. We here present a case of biliverdinaemia and biliverdinuria which developed after the administration of indomethacin (1-*p*-chlorobenzoyl-5-methoxy-2-methylindol-3-acetic acid).

CASE REPORT

A man aged 46 was employed as an unskilled labourer not at risk of exposure to toxic materials or gases. He was admitted to hospital on 14 May 1966 with a four-year history of intermittent joint pains which had been treated with salicylates and phenylbutazone outside hospital. For three weeks before admission he was having indomethacin 75 mg. daily.

On 7 May he had noticed that his urine was green, and soon was off his food and complaining of occasional abdominal pains. The only relevant feature in his past history was that he had suffered from brucellosis in 1957.

On physical examination the skin of the whole body presented a greenish hue, most evident on the trunk, while the conjunctivae were of normal colour. The temperature was 100° F. (37.8° C.); pulse 76/min. and regular; respiratory rate 20/min.; weight 62.6 kg.; and height 160 cm. The liver was palpable 7.5 cm. below the right costal margin. It was firm but not tender. The spleen was not palpable, and there were no intra-abdominal masses. Both hands showed early changes of rheumatoid arthritis. No physical abnormalities were detected elsewhere.

LABORATORY FINDINGS

Hb 13.9 g./100 ml.; P.C.V. 47%; R.B.C. 4,800,000/cu. mm.; reticulocytes 1.8%; leucocytes 7,200/cu. mm., with a normal differential count; blood film—slight anisocytosis, some spherocytic forms, and very occasional poikilocytes, no basophilic, polychromatic, or nucleated erythrocytes; osmotic fragility of erythrocytes—initial lysis at 0.48% NaCl (control at 0.46% NaCl), complete lysis at 0.28% NaCl (control at 0.30% NaCl); E.S.R. 15 mm. in first hour (Westergren); one-stage prothrombin time 17 sec. (control 15 sec.); bone-marrow smear—normoblastic erythropoiesis, normal myeloid series.

The serum was of a definite green colour. The van den Bergh reaction was delayed direct and the total serum bilirubin 3.3 mg./100 ml. Serum aspartate aminotransferase, 55 i.u./l.; alanine aminotransferase 94 i.u./l.; alkaline phosphatase 55 K.-A. units/