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/

100 ml. Blood urea 30 mg./100 ml. and total plasma cholesterol 630 mg./100 ml. Total serum protein concentration 6.0 g./100 ml., with albumin 3.0 g./100 ml. Filter paper electrophoresis showed a slight reduction in serum albumin, with some increase in alpha$_1$- and alpha$_2$-globulins, a significant reduction in betaglobulin, and some increase in gammaglobulins. Serum uric acid 6.2 mg./100 ml. and serum pseudocholinesterase 160 units/100 ml. (range of normal sera 130–310 units/100 ml.). The latex fixation tests for C-reactive protein and the R.A. factor were positive.

The urine was a dark green. It had a *p*H of 5.8 and contained a trace of protein but no glucose or reducing substances. No urobilinogen or urobilin was detected. Fouchet's test gave a strong green spot indicative of biliverdin. The diazo reaction was negative even on the addition of ethyl alcohol. The sediment contained only an occasional crystal of calcium oxalate. *Pseudomonas pyocyanea* was not cultivated from the urine. The faeces were green in colour and also gave a strong green spot with Fouchet's reagent.

The pigment in the urine was isolated in large quantities and identified as biliverdin by the absorption spectrum of its solution in 5% methanolic hydrochloric acid and that of its zinc complex after oxidation with iodine. The spectra observed agreed with those reported by Gray *et al.* (1961a ; 1961b) for biliverdin.

Histological sections (Fig. 1) of liver tissue obtained by percutaneous puncture on 23 May showed centrilobular degeneration, swelling and some fatty change of parenchymal cells, and regeneration of hepatic cells. Both the parenchyma and portal zones contained many neutrophils and mononuclear cells, including plasma cells. Bile stasis, mostly within Kupffer cells, adjacent to the foci of necrosis was evident. van Gieson staining showed increased collagen deposition around the central veins but no increase in the portal tracts. There was some bile-duct proliferation, but the ducts were not obstructed. The overall picture was that of an acute hepatitis.

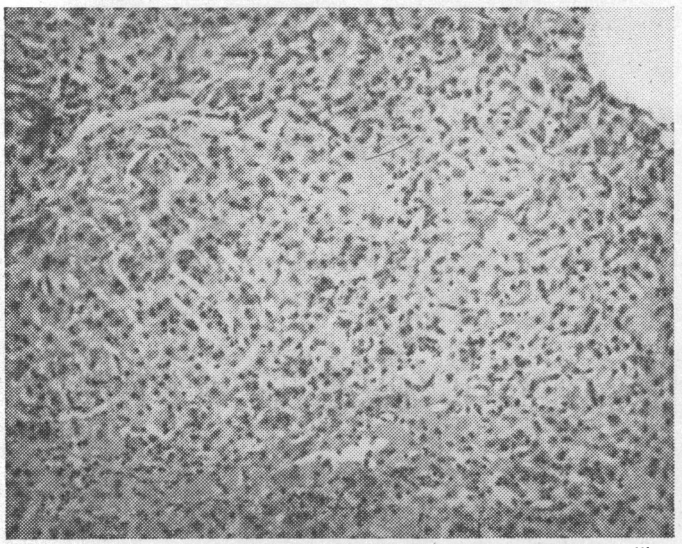

FIG. 1.—Section of liver tissue. Centrilobular degeneration, swelling and some fatty change of parenchymal cells, and regeneration of hepatic cells. There is infiltration of both the parenchyma and portal zone by many neutrophils and mononuclear cells, including plasma cells. (Haematoxylin and eosin. ×165.)

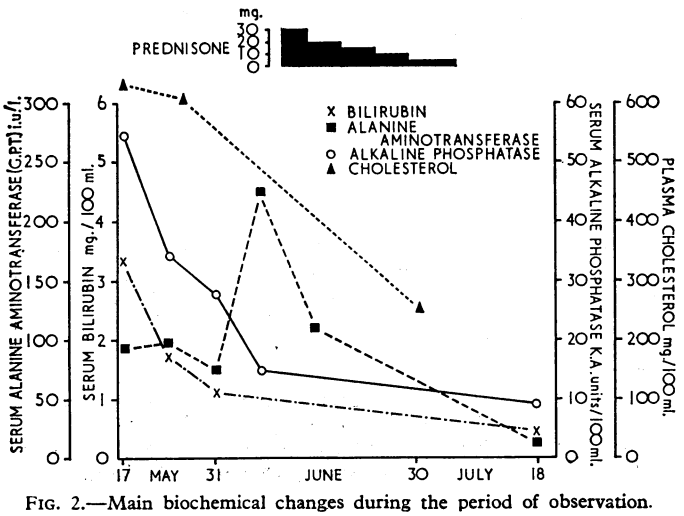

FIG. 2.—Main biochemical changes during the period of observation.

Indomethacin therapy was stopped, and conservative treatment was instituted, with bed rest, a high protein and carbohydrate diet with elimination of fats, and parenteral vitamin supplements for the first three weeks.

The main biochemical changes during the period of observation are shown in Fig. 2. As the serum alanine aminotransferase rose considerably above the level on admission, prednisone was prescribed at an initial dose of 30 mg. daily. This was followed by sustained progress. Within six weeks of the start of prednisone therapy the liver was no longer palpable, the urine and faeces had regained their normal colour, and the serum chemistry became normal.

The patient was discharged from hospital on 5 August 1966 and has remained well.

COMMENT

Temporary mental or neurological symptoms, haemorrhages, haemocytopenias, and even fulminating infections have been reported in the course of indomethacin therapy (W.H.O., 1966). Bruckner and Randle (1965) reported hepatotoxicity associated with indomethacin, but the evidence they produced is very tenuous. In a personal communication the manufacturers claim that there has been no proved case of hepatotoxicity produced by indomethacin. However, Kelsey and Scharyj (1967) have reported a case of fatal hepatitis which was probably due to indomethacin.

The tests of liver function employed and the histological changes in the liver seen in the case presented here are consistent with the diagnosis of cholestatic hepatitis similar to that produced by drugs such as chlorpromazine. In the present case salicylates and phenylbutazone had been taken several months before the illness, while indomethacin had been taken for three weeks before admission to hospital.

Biliverdinaemia presumably results from blockage of the reduction of biliverdin to bilirubin. Singleton and Laster (1965) have demonstrated the existence of high biliverdin reductase activity in guinea-pig liver and spleen. They also demonstrated biliverdin reductase activity in human liver. The development of biliverdinaemia and biliverdinuria has not yet been recorded. Two explanations for its occurrence may be suggested. It is possible that in producing hepatitis indomethacin severely inhibited the activity of biliverdin reductase in the patient's liver, and probably also in the spleen. It is also possible that the patient has a congenital partial deficiency of biliverdin reductase, which came to light as a result of the hepatitis.

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