definite conclusions concerning the precise mode of transmission in leprosy.

Since at least 50% of household contacts of tuberculoid patients show evidence of exposure to *M. leprae*, the much higher incidence of leprosy among household contacts of lepromatous patients (Doull *et al.*, 1942) cannot be explained as due to a higher risk of exposure alone. These studies have, however, shown that there is a lower proportion of responders among contacts of active lepromatous cases as compared to contacts of tuberculoid patients. These non-immune contacts are presumably more at risk of developing clinical leprosy.

This observation was unexpected since the lepromatous patients obviously are the most infectious. Though it was not found to be statistically significant, one may speculate on possible explanations. We did not find any evidence that patients with lepromatous leprosy were more segregated than others. Moreover, the (genetically unrelated) spouses who shared the bed of the patient showed similar conversion rates to other (genetically related) family members. Thus neither segregation nor genetic factors can explain the poor response among lepromatous contacts.

Further studies are needed before the mechanism behind this poor response can be fully characterized. But the tendency of lepromatous contacts to recover immunologically when the patient was put on antileprosy chemotherapy would indicate that their response was suppressed, possibly due to intensive exposure. This may be due merely to the entry of large numbers of bacilli into their body or they may be exposed through a "tolerogenic" route such as the gastrointestinal tract, which has been found to lead to unresponsiveness under experimental conditions (Battisto and Chase, 1963, 1965).

Thus, our observations suggest that the increased risk of acquiring leprosy among contacts of lepromatous patients may be related to a decrease of host resistance caused by "superexposure" to *M. leprae*. To our knowledge, in no other infectious disease has suppression of immunity of this type been reported. But it may be significant that overcrowded housing conditions which would predispose to "superinfection" have been recognized as a risk factor in both leprosy (Doull, 1962) and tuberculosis.

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Diagnosis of Gilbert's Syndrome: Role of Reduced Caloric Intake Test

D. OWENS, S. SHERLOCK

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Summary

Reduction in caloric intake to 400 a day for 72 hours resulted in a significant increase in the plasma bilirubin concentration in patients with Gilbert's syndrome and in normal subjects. This was due to an increase in unconjugated pigment. There was no significant increase in the bilirubin concentration in patients with liver disease or haemolytic anaemia.

The increase in unconjugated bilirubin was signficantly greater in Gilbert's syndrome than in normals but only when the initial bilirubin concentration was raised. It was usually seen within 24 hours of reducing the caloric intake. An increase of 100% or more suggests that unconjugated hyperbilirubinaemia is due to Gilbert's syndrome. In the normal subjects the unconjugated bilirubin level did not exceed 1·0 mg/100 ml.

The increase in unconjugated bilirubin concentration on reducing the caloric intake may be due to decreased hepatic bilirubin uridine diphosphate glucuronyl transferase activity, which was shown to be present in seven rats starved for 72 hours. The effect of a 400 calorie diet for 24 hours on the unconjugated bilirubin level may distinguish Gilbert's syndrome from other causes of unconjugated hyperbilirubinaemia.

Medical Unit, Royal Free Hospital, London WC1X 8LF
D. OWENS, M.B., M.R.C.P., Registrar (Present address: Department of Medicine, University of Liverpool, Liverpool L69 3BX)
S. SHERLOCK, M.D., F.R.C.P., Professor of Medicine

Introduction

Gilbert's syndrome, also known as idiopathic unconjugated hyperbilirubinaemia or constitutional hepatic dysfunction, is a common cause of unconjugated hyperbilirubinaemia (Gilbert and Lereboullet, 1901). In this disorder there is defective hepatic clearance of bilirubin (Billing *et al.*, 1964; Berk *et al.*, 1970) and also decreased activity of the enzyme bilirubin uridine diphosphate glucuronyl transferase which conjugates bilirubin (Arias and London, 1957; Black and Billing, 1969).

The syndrome is often diagnosed by finding a raised serum level of unconjugated bilirubin in the presence of a normal serum level of conjugated bilirubin and in the absence of any other obvious cause. Diagnosis in this negative manner is clearly unsatisfactory, but additional procedures such as needle biopsy to show histologically normal liver or isotopic bilirubin kinetic studies (Berk *et al.*, 1970) are not usually practical in the investigation of such a common benign condition.

Gilbert and Herscher (1906) observed that the serum bilirubin concentration was higher when subjects were fasting. Felschen

et al. (1970) showed that when the caloric intake was reduced the serum unconjugated bilirubin concentration rose by a significantly greater amount in patients with Gilbert's syndrome than in normal subjects. In the light of these observations we have studied the effect of a reduction in caloric intake on the plasma bilirubin concentration in normal subjects, and in patients with Gilbert's syndrome, liver disease, and haemolytic anaemia to see if this would form a simple test for Gilbert's syndrome.

The increased concentration of unconjugated bilirubin must be due either to increased production of bilirubin (haemolysis) or to decreased hepatic clearance of bilirubin, or both. Estimation of plasma haptoglobins was used as a crude measure of changes in haemolysis (Laurell and Nyman, 1957). Decreased clearance might be related to a reduction in hepatic blood flow, and the plasma clearance of indocyanine green was used as an indirect measure of this (Cherrick *et al.*, 1960; Reemstsma *et al.*, 1960). The decreased clearance might be due to increased competition of some other substance with bilirubin for hepatic transport proteins Y and Z (Levi *et al.*, 1969). Cortisol metabolites would be candidates for such a role and the plasma cortisol levels were therefore measured before and after the reduced caloric intake (Fleischner *et al.*, 1972). Finally, decreased clearance of bilirubin might be related to reduction in the conjugating enzyme. This could not be measured before and after dieting in man, therefore Sprague-Dawley rats were used for this investigation.

Subjects and Methods

The 12 normal subjects were healthy members of the medical and laboratory staff. Seven of the 12 patients with liver disease had cryptogenic cirrhosis; three of these had had portacaval anastomoses and four had chronic portal systemic shunting. The diagnosis in the other five patients was fatty change in the liver, viral hepatitis, primary biliary cirrhosis, active chronic hepatitis, and Dubin-Johnson syndrome.

The plasma concentration of unconjugated bilirubin was raised in 10 of 12 patients with Gilbert's syndrome at the time of the study. Other liver function tests were normal. In 10 patients the liver was histologically normal by needle biopsy, and hepatic bilirubin uridine diphosphate glucuronyl transferase activity was reduced in the three patients in whom it was measured (Black and Billing, 1969). There was no evidence of gross haemolysis in any patient, but red cell survival studies were not perfomed. Unconjugated hyperbilirubinaemia was present in the close relatives of three of the patients.

The plasma concentration of bilirubin, though previously raised, was normal at the time of study in two of the patients with Gilbert's syndrome. One of these was receiving phenobarbitone 180 mg daily (Black and Billing, 1970).

One of the three patients with haemolytic anaemia suffered from thalassaemia major, while two had an acquired haemolytic anaemia of unknown cause. The haemoglobin concentration was stable at the time of study.

Each subject was studied for five days. During the first two days diet was normal. During the subsequent three days the caloric intake was reduced to 400 calories a day. Blood samples were collected in heparinized tubes between 9 a.m. and 10.30 a.m. each day and the plasma was stored in the dark. Estimations, in duplicate, of conjugated and unconjugated bilirubin were done within six hours (Michaelsson *et al.*, 1965). A bilirubin standard was estimated with each unknown. The coefficient of variation between estimations of the standard was 8%.

Haptoglobin concentration was measured by a radioimmunodiffusion technique (Mancini *et al.*, 1965) using rabbit antiserum against human haptoglobin (Hoechst).

The indocyanine green was administered intravenously in a dosage of 0·5 mg/kg of body weight and the plasma disappearance of indocyanine green was measured after an eight-hour fast and again after a 36-hour fast in four normal subjects and in one patient with Gilbert's syndrome.

Plasma cortisol levels were estimated (Murphy, 1967) before and after 72 hours on the reduced caloric intake. Blood was always collected between 9 a.m. and 10.30 a.m.

These studies were carried out with the informed consent of each subject.

Bilirubin uridine diphosphate glucuronyl transferase activity was measured in two groups of seven Sprague-Dawley rats. The rats in one group were given a normal diet, whereas the rats in the other group were starved for 72 hours. Both groups of rats were then killed and hepatic bilirubin uridine diphosphate glucuronyl transferase activity was estimated (Black *et al.*, 1970). This was expressed in two ways. Firstly, as the amount of bilirubin, in microgrammes, that was conjugated by one gramme of liver per hour in the presence of excess glucuronic acid, and secondly, as the amount of bilirubin that was conjugated by one gramme of liver protein measured as nitrogen, per hour (Lowy *et al.*, 1951).

Results

NORMAL SUBJECTS

The mean total plasma bilirubin concentration ± S.E. of mean in the 12 normal subjects on a normal diet was 0·5 ± 0·02 mg/100 ml. When the caloric intake was reduced the mean total bilirubin concentration rose to 0·8 ± 0·06 mg/100 ml after 48 hours. The total bilirubin concentration never exceeded 1·0 mg/100 ml (fig. 1). The increase in unconjugated bilirubin concentration was highly significant ($P<0·001$) from a mean of 0·3 ± 0·02 to 0·5 ± 0·06 mg/100 ml. Conjugated bilirubin did not change.

GILBERT'S SYNDROME

In 10 patients with Gilbert's syndrome and a raised unconjugated bilirubin level the mean total bilirubin concentration increased significantly from 1·8 ± 0·2 to 3·5 ± 0·3 mg/100 ml ($P<0·001$, $t = 15·0858$) within 24 hours of reducing the caloric intake. There was a further but insignificant rise in bilirubin level to 3·8 ± 0·3 mg/100 ml after another 24 hours on the reduced caloric intake ($P>0·05$, $t = 0·9384$) (fig. 1). The rise in the

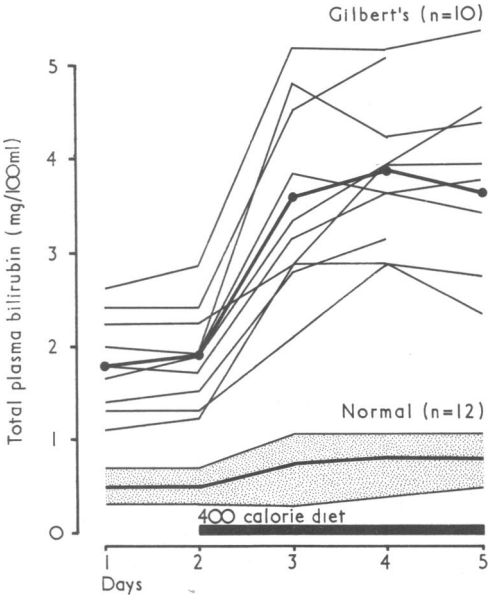

FIG. 1—Effect of a reduction in caloric intake on total plasma bilirubin concentration in 12 normal subjects and 10 with Gilbert's syndrome. Mean bilirubin concentration for each group is shown by heavy line. Range in normals is shown by shaded area.

bilirubin concentration was due to an increase in the unconjugated bilirubin level which rose from a mean of 1·5 ± 0·2 to 3·4 ± 0·3 mg/100 ml after 48 hours on the reduced caloric intake. There was no significant increase in the mean conjugated bilirubin concentration (P>0·05) (fig. 2). Plasma bilirubin concentration on the normal diet did not correlate with the increase observed after caloric reduction (P>0·05). The mean increase in the bilirubin concentration on reducing the caloric intake was significantly greater in these patients with Gilbert's syndrome (110%) than in the normal subjects (60%).

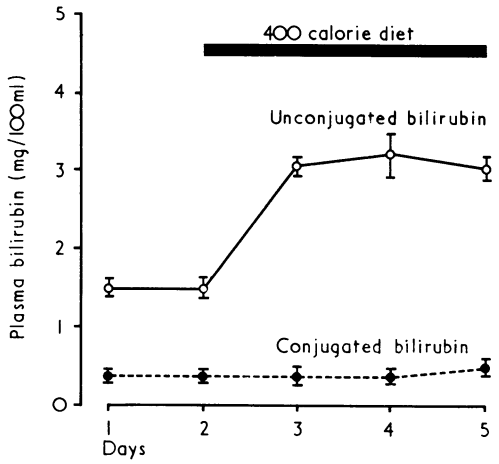

FIG. 2—Effect of a reduction in caloric intake on plasma unconjugated and conjugated bilirubin in Gilbert's syndrome. Each point represents mean bilirubin concentration and each bar one S.E. of mean.

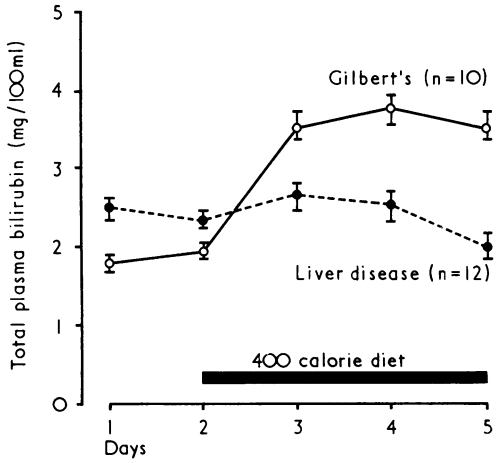

FIG. 3—Effect of a reduction in caloric intake on mean total plasma bilirubin concentration in patients with liver disease. Mean total bilirubin concentration in Gilbert's syndrome is shown for comparison. Each bar represents one S.E. of mean.

The unconjugated bilirubin level rose by more than 100% in eight of these patients with Gilbert's syndrome within 24 hours of reducing the caloric intake. In a ninth the unconjugated bilirubin concentration had increased by 113% after 48 hours on the diet. In the 10th patient the increase was 90% after 48 hours.

The two patients with Gilbert's syndrome and normal plasma bilirubin concentrations showed a response similar to the normal subjects, with an increase from 0·5 to 0·9 mg/100 ml in one and from 0·6 to 1·0 mg/100 ml in the other.

LIVER DISEASE

The mean total plasma bilirubin concentration in the 12 patients with liver disease was 2·3 ± 0·3 mg/100 ml on a normal diet. The mean unconjugated bilirubin level in these patients was 1·3 ± 0·4 mg/100 ml, which is similar to the mean unconjugated bilirubin in the patients with Gilbert's syndrome. When the caloric intake was reduced there was a small but insignificant increase in the mean total bilirubin concentration from 2·3 ± 0·3 to 2·5 ± 0·5 mg/100 ml (P>0·05, $t = 1·7912$) (fig. 3). The mean increase of 8% in unconjugated bilirubin was not significant. In one patient the increase was 50%.

HAEMOLYTIC ANAEMIA

The number of patients with haemolytic anaemia was small. The mean total plasma bilirubin concentration in these patients was 2·6 ± 0·8 mg/100 ml with a mean unconjugated bilirubin concentration of 2·0 ± 0·8 mg/100 ml. When the caloric intake was reduced the mean total bilirubin level rose by 0·8 mg/100 ml to 3·4 ± 1·4 mg/100 ml. However, this small increase in bilirubin concentration was not significant (P>0·05, $t = 3·2510$) (fig. 4). The mean increase of 40% in unconjugated bilirubin was likewise not significant.

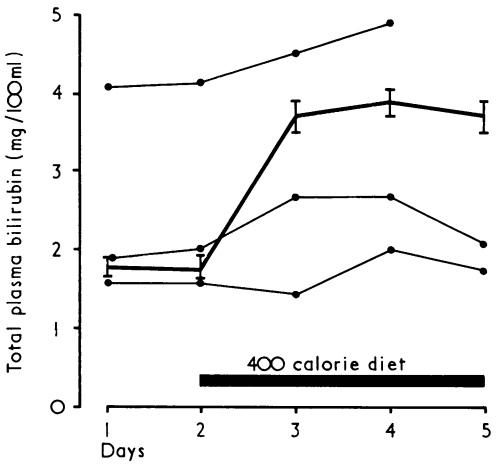

FIG. 4—Effect of a reduction in caloric intake on total plasma bilirubin concentration in three patients with haemolytic anaemia (thin lines). Mean total bilirubin in 10 patients with Gilbert's syndrome is shown for comparison (heavy line).

The haptoglobin levels were low in the patients with haemolytic anaemia. However, there was no significant change in the haptoglobin concentration after 72 hours on the reduced caloric intake in any of the groups (table I).

TABLE I—*Effect of a Reduction in Caloric Intake on Plasma Haptoglobin Concentration. Figures are Mean ± S.E. of Mean*

	Normal Diet (mg/100 ml)	After 72 Hours on 400 Calorie Diet (mg/100 ml)	Difference
Normal subjects (n = 12)	157 ± 21	180 ± 21	N.S.
Gilbert's syndrome (n = 10)	149 ± 22	109 ± 11	N.S.
Liver disease (n = 12)	101 ± 21	95 ± 25	N.S.
Haemolytic anaemia (n = 3)	10 ± 10	6·6 ± 6·6	N.S.

N.S. = Not significant (P>0·05).

The mean half-disappearance time ± S.E. of mean of indocyanine green after intravenous injection was 2·77 ± 0·4 minutes after an eight-hour fast in four normal subjects and in one patient with Gilbert's syndrome. This was not significantly different from the half-disappearance time of 2·05 ± 0·09 minutes after a 36-hour fast in the same subjects (P>0·05, $t = 1·7915$).

The mean plasma cortisol levels were not significantly different after 72 hours on the reduced caloric intake (table II).

TABLE II—*Effect of a Reduction in Caloric Intake on Plasma Cortisol Concentration. Figures are Mean ± S.E. of Mean*

	Normal Diet (μg/100 ml)	After 72 Hours on 400 Calorie Diet (μg 100/ml)	Difference
Normal subjects (n = 12)	7·6 ± 0·6	8·4 ± 1·2	N.S.
Gilbert's syndrome (n = 10)	10·2 ± 1·2	9·0 ± 0·4	N.S.
Liver disease (n = 12)	7·9 ± 0·8	7·5 ± 0·6	N.S.
Haemolytic anaemia (n = 3)	0·8 ± 0·8	3·6 ± 3·3	N.S.

N.S. = Not significant (P > 0·05).

The mean cortisol levels were unusually low in the patients with haemolytic anaemia. Only three patients were studied, however, and the range was wide.

The mean liver weight ± S.E. of mean in the seven rats given food was 10·3 ± 0·46 g compared with 5·3 ± 0·25 g in those starved for 72 hours. The mean hepatic bilirubin uridine diphosphate glucuronyl transferase activity ± S.E. of mean in the seven rats allowed food was 764·3 ± 45·7 μg bilirubin per gramme of liver per hour (2,467 ± 187 μg bilirubin per gramme of liver protein per hour). The mean level of the enzyme in the starved rats was 409·3 ± 36 μg bilirubin per gramme of liver per hour (1,058 ± 93·8 μg bilirubin per gramme of liver protein per hour). The hepatic bilirubin uridine diphosphate glucuronyl transferase activity was significantly lower in the starved rats than in those allowed food ($P < 0·01$, $t = 6·7292$) (fig. 5).

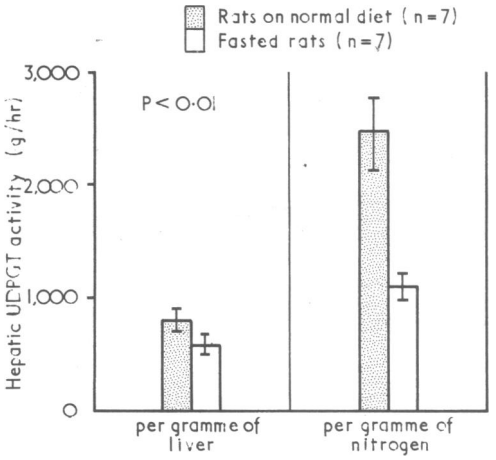

FIG. 5—Hepatic bilirubin uridine diphosphate glucuronyl transferase (UDPGT) activity expressed as amount of bilirubin, in microgrammes, conjugated per hour, per gramme of liver, and per gramme of liver protein measured as nitrogen, in the two groups of rats studied. Means ± S.E. of means are shown.

Discussion

Persons with unconjugated hyperbilirubinaemia due to Gilbert's syndrome may be distinguished from normal subjects or patients with liver disease or haemolytic anaemia by the response of the unconjugated plasma bilirubin to a reduction in caloric intake. The increase in bilirubin concentration was significantly greater in patients with Gilbert's syndrome than in normal subjects where the total bilirubin level did not exceed 1·0 mg/100 ml. The increases were usually seen within 24 hours and usually exceeded 100% of the pre-diet value. It did not correlate with the initial bilirubin concentrations. The two patients with Gilbert's syndrome and normal plasma bilirubin concentrations showed a similar increase to that seen in the normal subjects. One of the patients was receiving phenobarbitone, which is known to lower bilirubin concentration and to induce bilirubin uridine diphosphate glucuronyl transferase in Gilbert's syndrome (Black and Billing, 1970). The bilirubin concentration is known to fluctuate in this condition and was normal at the time of study in the other patient (Foulk *et al.*, 1959). Reduced caloric intake cannot be used to diagnose Gilbert's syndrome at a time when the plasma bilirubin is normal.

Carbon monoxide production and excretion by the lungs is an index of haem catabolism. This increases on fasting in normal subjects and patients with Gilbert's syndrome, but the rise is insufficient to account for the observed changes in bilirubin level (Bloomer *et al.*, 1971). In our subjects plasma haptoglobin did not fall. It is, therefore, unlikely that the observed rise in bilirubin concentration was due to increased haemolysis.

Bloomer *et al.* (1971) found that hepatic clearance of ^{3}H-bilirubin was decreased on fasting in three normal subjects and two patients with Gilbert's syndrome. Multicompartmental analysis of their data showed a decrease in the fractional transfer rate between the plasma pool and the unconjugated hepatic pool of bilirubin. The rise in unconjugated bilirubin levels can be interpreted as due to decreased hepatic clearance probably caused by a decreased rate of transfer of bilirubin from the blood into the liver.

Decreased hepatic clearance of bilirubin is unlikely to be due to decreased hepatic blood flow, for the clearance of indocynanine green was not altered significantly by reducing the caloric intake.

Two transfer proteins Y and Z are probably concerned with the uptake of bilirubin into and transport through the liver cell (Levi *et al.*, 1969). They also bind cortisol and cortisol metabolites (Fleischner *et al.*, 1972). As plasma cortisol and presumably the levels of cortisol metabolites did not rise after reduction in caloric intake, it is unlikely that decreased hepatic clearance of bilirubin is due to these metabolites displacing bilirubin from the binding proteins. Recently it has been shown that Z protein also binds fatty acids (Ockner *et al.*, 1972). These increase during fasting and could displace bilirubin from the binding protein so interfering with the hepatic uptake of bilirubin. This merits further investigation.

In rats starvation led to a significant decrease in hepatic uridine diphosphate glucuronyl transferase activity which was not due to generalized catabolism of liver protein. The stress of starvation, of course, was much more severe for the rat than reduced caloric intake for man. It remains a possibility that the diet did, in fact, reduce the conjugating enzyme, though it is unlikely to be the entire explanation. Bloomer *et al.* (1971) found that decreased clearance of ^{3}H-bilirubin on fasting was associated with decreased rate of transfer of bilirubin into the liver cell. This is presumably independent of subsequent conjugation. In only one patient did they find evidence for decreased conjugation. Moreover, Gunn rats that have no detectable hepatic bilirubin uridine diphosphate glucuronyl transferase activity develop raised plasma bilirubin levels during starvation (Bloomer *et al.*, 1971).

Black and Billing (1969) showed that hepatic bilirubin uridine diphosphate glucuronyl transferase activity is less than normal in Gilbert's syndrome and often greater than normal in liver disease. A similar decrease in hepatic uridine diphosphate glucuronyl transferase activity in patients with Gilbert's syndrome, liver disease, and in normal subjects would, therefore, have the greatest effect on bilirubin levels in Gilbert's syndrome. Perhaps plasma bilirubin concentration did not rise significantly in liver disease because there was initially an increased hepatic bilirubin uridine diphosphate glucuronyl transferase activity.

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Requests for reprints should be addressed to: Professor Sheila Sherlock, Royal Free Hospital, Gray's Inn Road, London WC1X 8LF.

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Possible Role of Hormones in Treatment of Metastatic Testicular Teratomas: Tumour Regression with Medroxyprogesterone Acetate

H. J. G. BLOOM, W. F. HENDRY

British Medical Journal, 1973, 3, 563-567

Summary

Three patients in a consecutive series of 16 cases of metastatic malignant teratoma testis have shown well-marked tumour regression during hormone treatment. In two cases multiple lung metastases had previously failed to respond to actinomycin D therapy, and following treatment with medroxyprogesterone acetate one patient had well-marked selective tumour regression for nine months while the other is alive, well, and free from disease at seven years. The third case was treated with a combination of actinomycin D and medroxyprogesterone acetate and is alive and disease-free at two years.

Attention is drawn to this preliminary study in the hope of stimulating interest in the possible value of hormones, either alone or combined with chemotherapy and irradiation, in the treatment of metastatic testicular teratoma. Multicentre prospective clinical trials are now needed if knowledge is to be advanced in this field.

Introduction

Early death is to be expected for most patients with teratoma of the testis once blood-borne metastases appear. In recent years, chemotherapy has brought some hope of prolonging useful life in a few of these cases (Hill *et al.*, 1972; Smithers, 1972). At the present time, however, it seems likely that long-term control or cure can be achieved in no more than about 10% of cases of metastatic teratoma using cytotoxic drugs, though perhaps some degree of regression, which is usually brief, can be seen in up to 50% of such cases (Mackenzie, 1966; Kennedy, 1970; Foley *et al.*, 1972).

Radiotherapy may achieve regression of extensive pulmonary metastases from testicular teratoma with temporary relief of distressing symptoms (Cox *et al.*, 1972). This treatment may be of greater value than chemotherapy in cases with limited lung deposits (Werf-Messing, 1973).

The testis is a member of the endocrine system and a target organ for pituitary gonadotrophins. It was therefore only natural to consider whether hormonal changes may influence testicular tumours, as with other tumours arising in target organs such as the breast and prostate. During a series of animal experiments in which the effect of various hormones on dimethylnitrosamine-induced renal tumours in rats was being investigated in our laboratories, we observed severe testicular atrophy after prolonged administration of medroxyprogesterone acetate (MPA) (H. J. G. Bloom and J. Dalton, unpublished observations, 1965). Other workers have reported inhibition of spermatogenesis with atrophy of testicular tubular epithelium in experimental animals after administration of this agent (Ericsson and Dutt, 1965; Ronzoni *et al.*, 1969). Depression of plasma testosterone by MPA has been reported in man (Rivarola *et al.*, 1968). The inhibitory effect of MPA on the normal testis, and its known anti-tumour effect in patients with cancer of the endometrium, breast (Briggs *et al.*, 1967), and kidney (Bloom, 1964, 1971; Samuels *et al.*, 1968) suggested a trial of this hormone against metastatic testicular teratomas, particularly since chemotherapy had met with such limited success in this disease. MPA is a powerful synthetic progestational agent which can be given by mouth. Unlike cytotoxic agents it has minimal side effects, even in high doses, and often produces subjective improvement.

The main purpose of this paper is to report objective improvement in three of 16 patients with metastatic testicular teratoma treated with MPA, in two of whom actinomycin D had already failed to control the disease, and to try to revive interest in the possible value of a hormonal approach to the treatment of these highly lethal tumours once surgery and radiotherapy are no longer feasible.

Case Reports

CASE 1

The patient, aged 49, underwent right orchidectomy for a testicular tumour in October 1965. Histological examination showed a malignant teratoma "intermediate type B" of the British Testicular Tumour Panel and Registry (T.T.P.R.) classification, or "embryonal carcinoma" of the American Armed Forces Institute of Pathology

Royal Marsden Hospital and Institute of Cancer Research, London SW3 6JJ and St. Peter's Group of Hospitals and Institute of Urology, London WC2
H. J. G. BLOOM, M.D., F.F.R., Consultant Radiotherapist
W. F. HENDRY, CH.M., F.R.C.S., Senior Lecturer in Urology