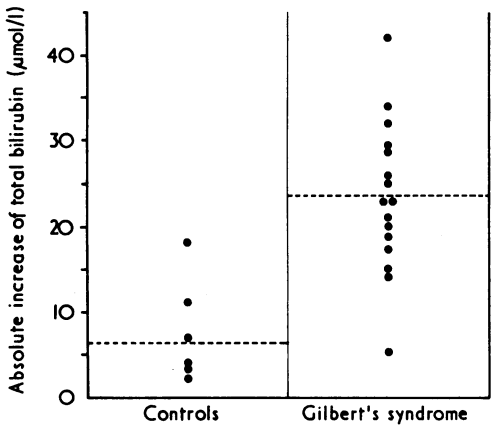
Reduced Caloric Intake and Nicotinic Acid Provocation Tests in the Diagnosis of Gilbert's Syndrome

Gilbert's syndrome is a benign condition characterized by a mild unconjugated hyperbilirubinaemia without severe haemolysis or liver disease. Fluctuations in the blood bilirubin levels can make the diagnosis difficult. We have compared the results of two tests—the fasting or reduced caloric intake test, and the nicotinic acid provocation test—which have recently been advocated for diagnosing Gilbert's syndrome.[1 2]

Patients, Methods, and Results

All 16 male patients with Gilbert's syndrome had otherwise normal liver function tests, reticulocyte count, and histological appearances of a needle liver biopsy specimen. For the fasting or reduced caloric intake test the patients were admitted to hospital and after one to three days were given a 1·67 MJ (400 calorie) diet for 48 hours. The nicotinic acid test was carried out, usually in outpatients, after an overnight fast. Fifty mg nicotinic acid was given by slow intravenous injection over 30 seconds and blood samples for the estimation of plasma bilirubin were withdrawn at 30-minute intervals for two hours, and then hourly for a further three hours. All the patients experienced mild flushing, and several noted a transient metallic taste. Plasma total and unconjugated bilirubin levels were estimated using Michaelsson's method (normal values less than 17 μmol/l). The reduced caloric intake test was carried out in 13 patients with Gilbert's syndrome. The mean plasma total and indirect-reacting bilirubin levels rose during the 48 h period, but this rise failed to reach statistical significance: mean ($\pm$1 S.D.) plasma bilirubin 30·1$\pm$15·4 μmol/l before and 35·2$\pm$17·8 μmol/l at the end (t=2·06; 0·05>P<0·1). Four patients showed a rise of over double but in the others the rise was less; indeed, in one patient the bilirubin level fell from 49·6 to 44·5 μmol/l. In only one patient was the initial bilirubin level within the normal range, and the rise in this patient was less than half.

The mean bilirubin levels during the nicotinic acid provocation test in six control subjects had risen within 30 minutes after the injection, with a plateau from 90 minutes and falling after 180 minutes. This rise was due to an increase in the indirect-reacting, and therefore probably unconjugated, fraction. In 16 patients with Gilbert's syndrome there was a similar rise in bilirubin, but the increase was greater, and peak values occurred later at 180 minutes when there was a definite difference between control subjects and the patients. The mean increase in plasma bilirubin at 180 minutes compared with initial levels was significantly higher in the patients (23·3$\pm$8·9 μmol/l) than in the controls (6·5$\pm$4·8μmol/l) (P<0·001) (see fig.). In two patients initial bilirubin levels were normal, and rose by 20·5 and 17·1 μmol/l after nicotinic acid.



The increase in plasma total bilirubin level 180 minutes after the administration of nicotinic acid in control subjects and patients with Gilbert's syndrome. Mean values are shown by dotted lines.

Discussion

We found that the reduced caloric intake test was less reliable than reported.[3-5] An increase of 100% occurred in only four of our patients tested, and this uncertainty is likely to be greater when routine bilirubin estimations are done. Admission to hospital is also necessary. The diagnosis of those patients whose initial bilirubin levels are normal is difficult; our patient, and two of Owens and Sherlock[2] in this condition, showed only small rises.

The effect of nicotinic acid injection on bilirubin levels was first described by Mattei,[5] and it has been studied in patients with Gilbert's syndrome.[2] The mechanism is unknown. We found the nicotinic acid provocation test more reliable in distinguishing between patients with Gilbert's syndrome and normal subjects. Only one measurement at 180 minutes after the administration of nicotinic acid is needed, and this test is also easier to perform on outpatients than is the reduced caloric intake test, while a positive response was found even in the two patients with normal plasma bilirubin levels. It could therefore prove valuable as an additional investigation in patients with suspected Gilbert's syndrome and especially in those in whom the bilirubin level has fallen to normal.

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Co-trimoxazole in Chronic Brucellosis: A Two-year Follow-up Study

The relatively recent introduction of co-trimoxazole for acute brucellosis[1-3] has given good results and low relapse rates.[4] There is limited information on the drug's efficacy in the chronic disease—the most difficult therapeutic problem.[5] We report a two-year follow-up of 20 treated patients with chronic brucellosis.

Patients, Methods, and Results

During 1971 and 1972 20 patients who fulfilled the following criteria were studied: (*a*) admission to hospital for brucellosis elsewhere six to 12 months before admission; (*b*) isolation of *Brucella mellitensis* in blood or bone marrow cultures; (*c*) treatment with broad-spectrum antibiotics commonly used in acute brucellosis. Their main symptoms were arthralgia, general malaise, weight loss, backache, and low grade fever. Alternative diagnoses were excluded in all of them. They all had high serum agglutination titres and no evidence of localized disease. Brucella was not isolated in either the blood or bone marrow cultures. They were given co-trimoxazole (Septrin); three tablets twice daily until they became afebrile and then two tablets twice daily for a total of two months. Investigations were performed regularly for possible side effects on the bone marrow and on liver and renal function. After two months of treatment and for two years all patients completed a detailed questionnaire on any possible complaints attributable to the disease or to the drug.

Fever subsided in all within two to seven days, though disappearance of other symptoms was delayed (table). Every patient's general condition was improved on discharge. Serum agglutination titres fell significantly in 11 patients and became negative in seven patients after two years. Two patients relapsed one month after the end of treatment. They were given a further course of co-trimoxazole with tetracyclines and were excluded from follow-up. No serious side effects required discontinuation of treatment. Three patients developed a transient rash which subsided quickly with the use of antihistamines.

Discussion

The main difficulties in the treatment of brucellosis are to prevent relapses and to cure the disease totally. The appearance of relapses three months after the onset of the disease suggests chronicity. It is not always easy to distinguish between relapses and true reinfections, since patients return to their infected areas. We selected our patients to exclude that possibility. They were all confirmed cases of brucellosis who had been treated with broad-spectrum antibiotics and had been advised to avoid all possible sources of infection. None of them had the typical clinical picture of the acute onset of the disease. Two patients relapsed quickly after the cessation of treatment suggesting