The fact that the inheritance of diabetes does not conform to the pattern expected on the single-gene hypothesis is of importance in the study of potential diabetes.

We have shown that the offspring of two diabetic parents are at a relatively low risk of becoming clinically diabetic. They cannot all be assumed to be future diabetics, and it is therefore unjustifiable to refer to them as prediabetic. A recent study of "prediabetes" (Taton *et al.*, 1964) assumed that children of two diabetic parents and identical twins of diabetics could be regarded as equally at risk. Yet only 5% of the former are diabetic, as compared with about 50% of the latter (Joslin *et al.*, 1959 ; Harvald and Hauge, 1963).

Our results suggest that no more than one-quarter of the children of conjugal diabetics will become diabetic, assuming that they develop the disease at the same ages as is true of the general diabetic-clinic population—and it may well be that the number will be less. However, it seems that the children of young-onset diabetics are more likely to develop the disorder than those of older onset.

We are collecting more data in order to get a clearer idea of the risk of diabetes developing in the children of patients of different ages (and will welcome news of diabetic couples).

Summary

A cooperative study of the children of conjugal diabetic couples has been made on behalf of the British Diabetic Association. Of 362 children of 164 couples both of whom were diabetic 16 (4.4%) were diagnosed as having diabetes. This is a greater number than was found in control couples in whom neither or one parent was diabetic.

Diabetes is commoner in the children of diabetic parents who develop diabetes early in life than in those of older couples.

If diabetes depends upon a single recessive gene all the offspring of the conjugal diabetic pairs should eventually become diabetic. However, the incidence so far suggests that only about one-quarter will do so.

We are grateful to the physicians who sent us the material upon which this report is based, and to Miss Mary Wall for statistical advice.

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Follow-up Study of Cases from the Delhi Epidemic of Infectious Hepatitis of 1955-6

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The vast majority of patients with infectious hepatitis make an uneventful recovery without any sequelae (Havens, 1944 ; Barker, Capps, and Allen (1945a ; Hoagland and Shank, 1946 ; Bothwell, Martin, Macara, Skone, and Wofinden, 1963). Only a small proportion develop either immediate complications or short-term and long-term persistent liver derangement (Barker, Capps, and Allen, 1945b ; Sherlock and Walshe, 1946 ; Kunkel, Labby, and Hoagland, 1947). Immediate mortality from an acute attack varies from 0.12 to 0.4% (Lucke, 1944). Exceptionally high mortality figures have been reported among women during pregnancy (Malkani and Grewal, 1957 ; Naidu and Viswanathan, 1957).

From reported observations it seems that approximately one-fifth of the patients are likely to have delayed or abnormal convalescence. This may be in the form of persistence of abnormal flocculation tests, prolonged hyperbilirubinaemia, recurrence of jaundice, and features of post-hepatitis syndrome (Havens, 1944 ; Barker *et al.*, 1945b ; Hoagland and Shank, 1946 ; Neefe, 1946 ; Kunkel *et al.*, 1947 ; Marion, 1947 ; Klatskin and Rappaport, 1947). Though many reports describe the transition of acute viral hepatitis to chronic forms, including cirrhosis (Roholm and Iversen, 1939 ; Krarup and Roholm, 1941 ; Dible, McMichael, and Sherlock, 1943 ; Sherlock, 1948 ; Volwiler and Elliott, 1948 ; Wyllie and Edmunds, 1949 ; Baltz, Steele, and Hartman, 1949), the precise relationship of viral hepatitis to cirrhosis is not clear. It is not possible on the basis of reported observations to ascertain the frequency with which long-term sequelae develop after acute viral hepatitis, as the observations deal with selected cases admitted to hospitals and there are no adequate controls. The type of cirrhosis described as an end-result of viral hepatitis has been variable. Some describe it as post-necrotic cirrhosis (Volwiler and Elliott, 1948 ; Klatskin, 1958) and others as unspecified type (Krarup and Roholm, 1941 ; Dible *et al.*, 1943 ; Wyllie and Edmunds, 1949). There is a long interval between the onset of hepatitis and the discovery of cirrhosis, and during this period other factors could have operated to produce a chronic stage of the disease. In addition, the initiating event which

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Infectious Hepatitis—*Chuttani et al.*

is regarded as viral hepatitis may not be really so in many cases, because a similar clinical and histological picture can be produced by other factors such as drugs and hepatoxic agents.

In the absence of specific methods for consistent isolation and demonstration of the hepatitis virus and of reliable serological tests, prospective epidemiological studies are a useful means for an elucidation of this problem. An explosive outbreak of infectious hepatitis occurred in the city of Delhi in 1955–6 (Viswanathan, 1957). A random sample survey at the time of the epidemic revealed that approximately 29,300 persons had icteric disease over a short period of six weeks (Sidhu and Nair, 1957). The outbreak started in the first week of December 1955 and reached its peak in less than two weeks and declined equally suddenly, so that it was all over by the end of January 1956. It was ascertained that the epidemic was caused by the accidental pollution of the water supply at the Wazirabad pumping station by the Najafgarh Nallah sewage drain from 4 to 17 November 1955. The population in the areas of the city supplied by this polluted water had a significantly higher incidence of hepatitis (2.33%) than those which had an alternative source of drinking-water (0.34%). This outbreak was investigated by a study group constituted by the Indian Council of Medical Research, and their findings have been published (Gupta and Smetana, 1957 ; Sidhu and Nair, 1957 ; Viswanathan, 1957). Five years later another project was sponsored by the Council to study the long-term sequelae of the epidemic. The present report deals with the findings of this study.

Material and Methods

The material studied consisted of 304 persons who were known to have had hepatitis during the 1955–6 epidemic and 1,070 who were members of the families of these afflicted persons but who themselves did not suffer from overt jaundice during the epidemic. The bulk of these have been traced from the records of addresses collected during the sample survey at the time of the epidemic and the remainder from the records of the hospitals in Delhi. Males were 53% and females 47%, and their ages ranged from 7 to 72 years. It was originally intended to study as a control a third group in a neighbouring area which had not been exposed to the epidemic, but as the investigation progressed it became obvious that there was no evidence of persistent liver damage in either of the two groups. The idea of a third, control, group was therefore abandoned.

All cases were studied clinically, as follows : we obtained detailed history of the illness during the epidemic and of the clinical state during the period following the epidemic ; each individual was subjected to physical examination by two independent physicians, and the findings were recorded individually.

A battery of liver-function tests were performed on 114 persons who had had hepatitis. These consisted of total serum proteins with albumin and globulin values, total serum cholesterol, total serum bilirubin, thymol and zinc-sulphate-turbidity tests, and alkaline phosphatase and bromsulphalein excretion tests (Wootton, 1964). A biopsy of the liver was taken with the Vim–Silverman needle in 70 of the epidemic cases. The tissue was fixed in neutral buffered formalin, processed routinely, and cut in paraffin ; then stained with haematoxylin and eosin, periodic-acid-Schiff, reticulum and haemosiderin.

This study was begun five years after the epidemic of viral hepatitis. It was possible that some patients with persistent liver disease may have died of liver-cell failure during the intervening period. An attempt was made to ascertain the probable causes of death, among both the patients and members of their families, during this period, by detailed questioning of the relatives and the doctors of the deceased subjects. In this way

the cause of death was traced in five individuals who had hepatitis during the period of epidemic and in 32 of family contacts.

Results

Clinical Assessment.—The results are summarized in Table I. Non-specific digestive symptoms were present in 56 persons who had had hepatitis (epidemic cases) and in 107 family members. The digestive symptoms looked for were anorexia, postprandial distension, diarrhoea, etc. Of these anorexia was the prominent symptom. There was a history of recurrence of jaundice during the intervening period in eight epidemic patients, but none of the family members had jaundice during this period. Jaundice was absent in all persons at the time of examination. In six of these eight persons with recurrent jaundice it was possible to perform the biochemical tests of liver function ; in none were any significant abnormalities detected. An enlarged palpable liver was found in 85 epidemic patients and in 182 family members. The liver edge was sharp in most cases, and the enlargement varied between 1 and 2 cm. below the costal margin. Spleen enlargement was observed in six epidemic patients. It was 2–4 cm. below the costal margin. These six patients did not have any clinical or laboratory evidence of liver derangement or portal hypertension. No case displayed the clinical features of cirrhosis of the liver.

TABLE I.—*Clinical Assessment*

Clinical Features	Cases (304)	Family Members (1,070)
Digestive symptoms	56 (18·4%)	107 (10%)
Recurrence of jaundice	8 (2·6%)	—
Palpable liver	85 (27·9%)	182 (17·0%)
,, spleen	6 (1·9%)	—
Evidence of cirrhosis	—	—

Biochemical Studies.—The results are presented in Table II. In five epidemic cases there was a moderate rise in serum globulins. In two of these the thymol turbidity test was abnormal, the readings being 9 and 16 units respectively. The bromsulphalein excretion test was normal in all except one case, in which the 45-minute excretion was 9%. In all five cases with abnormal biochemical findings the liver biopsy was normal. No biochemical abnormality was found in 109 out of 114 epidemic cases.

TABLE II.—*Biochemical Studies*

Total number	114
No abnormalities	109
Biochemical abnormalities:	
Raised serum of globulins	5
Abnormal flocculation tests	2
Abnormal bromsulphalein retention	1

Liver Biopsy.—Adequate material for histological evaluation was obtained from 65 of the 70 epidemic patients on whom a liver biopsy was performed. No case showed any disturbance of lobular architecture to suggest cirrhosis, nor was there any significant parenchymal damage that could be attributed to persistent hepatitis in the form of active hepatocellular necrosis, inflammatory or active cellular infiltrates, and fibroplasia. In many biopsies the liver cells showed abundant glycogen. Lipofuscin pigment was present in mild to moderate amounts in most of the biopsies, and this was chiefly distributed among cells of the centrilobular zone. Very mild non-specific portal and intralobular infiltrates were present in 25% of cases. Fatty change of moderate severity was observed in six subjects. In no case was there any significant scarring.

Deaths.—As stated earlier, an attempt was made to record the number of deaths and their probable causes during the period between the epidemic and the follow-up study. Five of the epidemic patients had died since the epidemic, but in

none of them could the terminal state be attributed to liver disease. In two the death was clearly due to accidents, and in the remaining three it was unrelated to liver diseases. A similar inquiry among family members showed that 32 persons had died since the epidemic. The causes again appeared to be unrelated to liver failure. Most of the deaths were among children below the age of 10, and those around 40 years. One death in the age group 18 to 30 years was due to drowning.

Comments

The main objective of this inquiry was to find out whether after apparent clinical recovery from an attack of acute infectious hepatitis a proportion of cases progressively develop liver damage leading to cirrhosis over the years, and to measure approximately the magnitude of the problem if it does exist.

The massive epidemic of infectious hepatitis that occurred in 1955–6 was unique. The present study began five years after the epidemic subsided and was completed two years later.

There is no evidence that the clinical features of subacute or chronic liver disease exist among the patients who had suffered from infectious hepatitis. There seems to be a somewhat higher prevalence of symptomatology related to liver disease in the form of non-specific digestive symptoms, particularly anorexia, among those who had had a clinical attack of hepatitis than among the family members. The significance of this is not apparent.

Liver-function tests and liver biopsies have likewise not shown any significant evidence of persistent liver damage. Such abnormalities of liver structure as have been found in the liver biopsy are believed to be too vague and non-specific to be of real significance. They are similar to those ordinarily met with in any necropsy series in which liver disease is not a primary cause of death. Our inability to discover deaths due to liver-cell failure among the patients who had died during the intervening period is another pointer in the same direction. Among the family contacts there would be expected to be some cases of anicteric hepatitis, since they were exposed to the same environmental influences as the cases of hepatitis at the time of the epidemic. In them, too, there was no evidence of persistent liver disease. Our results are in line with other prospective studies where carefully planned and controlled observations were carried out to find the incidence of long-term sequelae (Zieve, Hill, Nesbitt, and Zieve, 1953 ; Neefe, Gambescia, Kurtz, Smith, Beebe, Jablon, Reinhold, and Williams, 1953 ; Cullinan, King, and Rivers, 1958 ; Chalmers, 1961 ; Nefzger and Chalmers, 1963). These reports deal with adult males enlisted in the Army. Our material belongs to the general population of Delhi of both sexes. The standard of living and nutrition are much lower than those of American and British Army personnel. Our findings are contrary to the observations made by some European and Japanese workers in their retrospective studies (Bjørneboe, 1957 ; Kosaka, 1964).

Cirrhosis of the liver is frequently seen in hospital practice in India. Alcohol is an insignificant factor in its causation (Ramalingaswami, Wig, and Sama, 1962). Protein malnutrition is unlikely to be of major importance. In the absence of more definite evidence, viral hepatitis is widely believed to be a significant causal factor. While we do not deny that a very small fraction of cases of viral hepatitis may go on to cirrhosis, in the majority of cases of cirrhosis it is difficult to establish reasonable evidence of a previous attack of viral hepatitis. The results of the present study show that we must continue to search for factors other than viral hepatitis as a cause of such cases of cirrhosis in adults in this part of the world.

Summary

An explosive outbreak of infectious hepatitis occurred in the city of Delhi in 1955–6. This paper deals with a follow-up study of 304 persons who had acute hepatitis during the epidemic and of 1,070 persons who were their family contacts. The interval between the epidemic and the follow-up was five years.

The study consisted of clinical assessment in all patients and of biochemical and liver biopsy studies in a proportion of them. Biochemical studies included the determination of total serum protein, serum albumin and globulin, thymol turbidity, zinc-sulphate turbidity, alkaline phosphatase, bilirubin, and brom-sulphalein excretion.

Except for the presence of an enlarged palpable liver in 27.9% and of non-specific digestive symptoms in 18.4% of the epidemic cases, no clinical evidence of persistent liver damage was observed.

There were no cases of cirrhosis nor any with significant scarring of the liver among the 65 liver biopsies. In a small number of cases non-specific alterations of doubtful significance were disclosed by the liver biopsies.

In 109 out of 114 individuals studied biochemically there was no evidence of any biochemical abnormality indicating liver disease. In those cases that did show minor biochemical abnormalities the liver biopsies were within normal limits.

In the group that was studied there was no evidence of persistent liver damage following the epidemic of infectious hepatitis.

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Early Dietary Management of Sugar Intolerance in Infancy

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Infants who show intolerance of one or more sugars are being increasingly recognized. Though such a condition may be congenital, sugar intolerances secondary to a variety of enteric conditions present a far greater problem—for example, secondary to coeliac disease (Plotkin and Isselbacher, 1964), enteric infection (Careddu, Giovannini and Cevini, 1963), giardiasis (Durand, 1964), sprue (Santini, Aviles, and Sheehy, 1960), kwashiorkor (Bowie, Brinkman, and Hansen, 1965), and cystic fibrosis (Cozzetto, 1963).

As early as 1911 Finkelstein and Meyer advised the reduction of milk sugar in the dietary treatment of infants with gastro-intestinal disturbances. Intolerance to carbohydrates, both temporarily following acute diarrhoea and persistently associated with chronic intestinal disease, was described by Howland (1921), who advised carbohydrate restriction for infants with either severe or prolonged diarrhoea.

Successful treatment by the removal of the offending sugars from the diet has recently been described by a number of workers—for example, Anderson, Kerry, and Townley (1965), Lifshitz, Klotz, and Holman (1965), Burke, Kerry, and Anderson, (1965), and Arthur, Clayton, Cottom, Seakins, and Platt (1966).

The purpose of this paper is to describe the practical details in the management of infants requiring diets free of certain sugars.

Preparations Used Instead of Cow's Milk or Breast Milk

The following preparations have been used satisfactorily:

1. Galactomin No. 17 (Trufood): a low-lactose, full-fat food with liquid glucose as the carbohydrate. (Low-lactose milk food made by Cow and Gate is similar.)

2. Reduced-fat Galactomin (manufactured for our use by Trufood): a low-lactose, reduced-fat food with liquid glucose as the carbohydrate.†

3. Reduced-fat, fructose-formula Galactomin (manufactured for our use by Trufood): a low-lactose, low-fat food with fructose as the carbohydrate.

4. Lactase-treated breast milk: prepared in the diet kitchen of the hospital. Lactase splits lactose to glucose and galactose.

The amount of lactose remaining in these preparations is insignificant, and they may be considered " lactose-free."

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† Reduced-fat Galactomin and reduced-fat, fructose-formula Galactomin are now available commercially from Trufood Ltd.

Details of preparations 1, 2, and 3 are given in Table I. Lactase-treated breast milk is made in the following manner, the procedure being an adaptation of that described by the Royal Netherlands Fermentation Industries Ltd. (personal communication, 1963). 1 g. lactase (T. J. Sas & Son, Ltd.) is added, as a powder, to each litre of breast milk. The mixture is incubated in a water-bath at 35° C. for two hours and is shaken occasionally. A further 1 g. of lactase per litre of milk is then added and the incubation continued similarly for a further two hours. A sample is then removed for culture. The mixture is brought to the boil, and then boiled for 20 minutes. A further sample is taken for culture. The milk is then deep-frozen at −15° C.

TABLE I.—*Composition of Synthetic Milks*

	Protein (g.)	Fat* (g.)	Carbohydrate (g. Form)	Phosphorus (mg.)	Calcium (mg.)	Sodium (mg.)	Potassium (mg.)	Calories
1. Galactomin No. 17..	6·3	6·3	14·2 liquid glucose†	136	204	30	129	143
2. Reduced-fat Galactomin	6·2	4·1	16·5 liquid glucose	136	204	30	129	131
3. Reduced-fat, fructose-formula Galactomin‡ ..	6·2	4·1	16·5 fructose	136	204	30	129	131

All quantities are in g. or mg./oz. dry powder, which is normally reconstituted as a 1-in-8 dilution.
* Fat = Blend of unhydrogenated coconut and maize oils.
† Liquid glucose is a mixture of dextrin, maltose, and dextrose.
‡ This milk is manufactured as a dry mix, and is not spray-dried.

It has been our experience that in secondary lactose intolerance there is generally intolerance of sucrose too. As the infant is often too ill for a series of diagnostic tests, we remove sucrose routinely as well as lactose from the diet. We therefore do not usually use Velactin (Wander) or Nutramigen (Mead Johnson), as both preparations contain added sucrose, though only a trace of lactose.

Since infants are particularly susceptible to deprivation of vitamins (Mann, Wilson, and Clayton, 1965), it is essential that adequate supplements be given with the preparations listed in Table I and with lactase-treated breast milk. A recommended supplement is three tablets of Ketovite plus 5 ml. of Ketovite supplement liquid (Paines & Byrne) daily. These preparations are lactose- and sucrose-free. Supplements containing vitamins A, D, C, and the commoner ones of group B are *not* adequate.