separate fraction with its independent functions and not upon the ratio of the two components.

A large number of patients are now being admitted to the hospital who have general (subcutaneous serous cavity) œdema without evidence of the usual forms of pathology which produce such waterlogging. They do not exhibit any of the clinical symptoms of renal or cardiac involvement or of liver disease. Many of these patients have excessive degree of hypoproteinæmia. The intensity of hypoproteinæmia can be ascertained from the value of total protein. The albumin values can be predicted from the value of total protein by the application of the equation A = 0.762 × total protein — 1.39.

Dietary deficiency is known to cause macrocytic or nutritional anæmia. The fact that anæmia is present indicates that the preceding nutritional disturbance has existed for a fairly long time. In advanced cases, as much as 20 to 25 per cent of globulin protein may be lost resulting in hypoproteinæmia. The albumin fraction of the plasma protein seems to be the necessary replacement item. An accurate estimate of the albumin fraction may be obtained from the value of total protein by the application of the equation A = 0.886 × total protein —1.76, provided other complications do not accompany anæmia.

Protein deficiency occurs in renal conditions in which albuminuria is an important factor. Hypoproteinæmia in these patients is associated with an increase in the value of globulin due to associated infection. The values of albumin can, however, be predicted from the values of total protein by the application of the correlation equation mentioned in the text.

An accurate estimate of the values of albumin and globulin is essential in all patients with elicitable manifestations pointing to tuberculosis, cardiac disease, cirrhosis, myxœdema or a malignant growth and also in all other cases where the clinician suspects that simultaneous occurrence of two different conditions one leading to lowering of albumin and the other to an increase in globulin.

The euglobulin is considerably increased in all patients with cirrhosis of the liver. The increase in euglobulin appears to take place at the expense of the albumin fraction of the plasma proteins. In the hypoproteinæmia accompanying the cirrhosis with ascites, the determinations of euglobulin are valuable as corroborating proofs of the liver cell damage when clinical symptoms definitely point to the liver as the essential seat of the disease. In the investigation of cases of ascites due to chronic malnutrition, the estimation of euglobulin may be also valuable to the clinicians in differentiating cases of purely nutritional deficiency from those where latent liver disease is suspected.

In clinical practice, a single determination of plasma proteins may not prove to be of much value. Repeated determinations often provide valuable information concerning the state of the patient because they reveal the course of the disease through deterioration or improvement.

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CHOLINE DIHYDROGEN CITRATE IN INFANTILE BILIARY CIRRHOSIS

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INFANTILE biliary cirrhosis has been accepted as a separate clinical entity for nearly a decade now. The toll of infants taken by this disease in various parts of India should justify a record and classification of deaths due to this disease under a separate head. But the public health authorities throughout India have not been impressed to the extent desirable to make them understand the necessity for such a record.

The result of this position is that an investigator who wants to investigate the ætiology of this disease lacks the preliminary statistics of its incidence and death rate. Each investigator is left to his own resources and capacity to get the necessary data and do the investigations. Work by me in this direction was published in five articles in the *Indian Medical Journal* (*I.M.J.*, Vol. 33, No. 11, November 1939; *I.M.J.*, Vol. 34, No. 2, February 1940; *I.M.J.*, Vol. 34, No. 3, March 1940; *I.M.J.*, Vol. 34, No. 5, May 1940; *I.M.J.*, Vol. 35, No. 12, December 1941). The sum and substance of those articles is that :—

1. The disease is fairly widespread.
2. The incidence is greater in some parts of Madras Presidency, the Central Provinces, the southern portion of Bengal and Bombay Presidency.
3. The male sex shows a greater proclivity to the disease.
4. The children suffering from it are those fed on rich and fatty diet.
5. The habitual administration of castor oil is likely to be responsible in some cases on account of its being a thick fatty oil capable of damaging the liver cells.
6. The children suffering from this disease are predisposed particularly on account of hyperactivity of some of the endocrine glands.

Though these points give us an idea of the predisposing causes of the disease the exciting cause has not been found to be definite. Bacteriological investigations made repeatedly by various observers have brought forth nothing except that in some cases *B. coli* have been found to grow in the cultures of urine of patients suffering from the disease. But the theory of the organisms being responsible for the causation of cirrhosis, etc., is not acceptable to many. In the absence of specific extraneous causes endogenous toxins and non-specific proteins have been thought of. But these again do not account for all the cases. The conclusion, therefore, is that in children predisposed to this disease cirrhosis is easily brought about by any one or a combination of a number of cases.

The pathological findings in the structure of the liver in this disease have been as follows :

1. Varying degrees of necrosis of the liver cells uniformly distributed throughout the organ.
2. An avascular non-inflammatory œdematous connective tissue network enclosing in its meshes small islands of hepatic parenchyma of unequal sizes and in varying degrees of degeneration.
3. An obliterative lesion of the terminal and some of the bigger divisions of the hepatic venous tree without appreciable changes in the portal venous and biliary trees.
4. Areas showing disorganization of the reticulum of the sinusoidal capillary bed mostly around the hepatic venous terminals.
5. An unsuccessful attempt at regeneration of the hepatic parenchyma as evidenced by the small size of the rounded lobules of the liver cells distributed throughout the organ.

The treatment has naturally to remove the cause. Most of the preventable causes can be tackled but the cirrhosis itself has been found to be difficult to counteract.

For diminishing the tendency of the liver to produce the enormous amount of fibrous tissue at the expense of the liver cells, in the absence of any suitable drug, various methods of empirical treatment in the form of administration of vitamins, calcium, iron and such other things have been tried with little or no effect. A few cases which are on the border line of health and disease get well but in typical cases of cirrhosis this sort of empirical treatment is of no avail.

This fact of a lack of a suitable drug to treat the disease made me turn to other countries to find out how they were dealing with cases of this type. A searching enquiry both into the literature and the incidence of this disease in countries like America has shown that though cirrhosis of the adult variety is fairly common, the clinical entity as observed by us in cases of infantile biliary cirrhosis in India is not found there. Nevertheless I thought it would be to our advantage if we can know whether the clinicians there were able to treat successfully at least cases of cirrhosis of the adult type. With this aspect in view, I contacted Eli Lilly and Company who were kind enough to send me samples of choline dihydrogen citrate tablets which were found to be useful in cases of cirrhosis of adults.

I have been administering this drug to all children suspected to be suffering from this disease. Altogether 102 cases were tried. 75 of these were children under 2 years, 16 of them between 2 and 3 years and 11 under 1 year. 62 of them were early cases with only slight enlargement of the liver, and palpable spleen, slight anæmia, phosphates in urine, irritable temper and a slight diminution of weight. All these cases recovered within two weeks of the administration of the drug. Three to four tablets a day were given. Injections of liver extract with vitamin B were given in older children. Liver began to diminish in size. Children began to put on weight. Activity became normal and irritability gave place to cheerfulness. Rice diet has been found to be agreeable to most of the children except a few young ones who were on milk diet. Excess of fat was avoided in all these cases.

13 cases came after ascites had set in; 4 of these only recovered, in whom there was just a small quantity of fluid. The other cases in which ascites was marked ended fatally.

17 cases came with other intercurrent ailments, complicating the cirrhosis. All these cases recovered. In most of the cases ascariasis

infection was present. Malaria, kala-azar, etc., were also noted in some cases.

Three cases came in an advanced state of the disease and all of them ended fatally in spite of treatment.

Thus it will be seen that in a total of 102 cases carefully selected for treatment with choline dihydrogen citrate 79 recovered, though some of them are still taking the drug. It may also be noticed that the drug is of great value in early cases where the damage to the liver cells has not been much and where recovery is easy and possible without much difficulty.

The ease with which the drug can be administered and the absence of ill-effects are the special advantages of the drug. The only trouble met with is occasional diarrhœa. The drug is then stopped. It can be again administered as soon as the intestinal irritability subsides.

OBSERVATIONS ON AN OUTBREAK OF KALA-AZAR IN CALCUTTA

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ABOUT a quarter of a century ago, Knowles, Napier and Das Gupta (1923) showed that kala-azar was prevalent in an endemic form in certain areas of Calcutta, inhabited mainly by poorer classes of Anglo-Indians, Indian Christians and Mohammedans. In spite of the fact that large numbers of imported cases resided in other areas of the town very few or no cases of kala-azar occurred amongst the permanent residents of these apparently non-endemic areas. They concluded that the conditions requisite for the transmission of kala-azar from one patient to another were at their best (or worst) as far as Calcutta was concerned in that endemic area of the city. It is interesting to recall that the investigations and experiments carried out mainly by the workers of the School of Tropical Medicine, Calcutta, the Kala-azar Commission of India and other kala-azar research units of the Indian Research Fund Association that followed this observation during the next two decades led first to the incrimination of the sand-fly, *Phlebotomus argentipes*, as the vector of kala-azar, and finally the solution of the kala-azar transmission problem, when Swaminath, Shortt and Anderson (1942) succeeded in transmitting the disease to human volunteers by the bite of the sand-fly.

The data that formed the basis of this pioneer epidemiological investigation were collected by Napier at the kala-azar clinic of the Calcutta School of Tropical Medicine. This clinic was opened at the beginning of 1921 and during the first year the attendance increased month by month and a steady level was reached in a year or two. This was the first out-patients' clinic for kala-azar in Calcutta at the time of its inception. Though other out-patients' clinics were started in the city during the next few years, the attendance of the patients at this clinic has been quite considerable on account of its popularity and suspected cases of kala-azar from different parts of the city as well as those imported from different parts of Bengal and the neighbouring provinces attend for diagnosis and treatment. The clinical and epidemiological data relating to the *indigenous* kala-azar cases may thus properly be regarded as pertaining to a representative statistical sample of the kala-azar cases in the city.

During the years following the Bengal famine of 1943, it was found that steadily increasing numbers of cases of kala-azar and those with grave complications were being encountered at the kala-azar clinic of the School of Tropical Medicine, Calcutta. A study of the epidemiological and clinical data collected during the routine investigation of the patients attending the clinic or admitted into the Carmichael Hospital for Tropical Diseases was undertaken. In this paper it is proposed to present the results of this study under three principal headings, (*a*) the trends of incidence of kala-azar in Calcutta, (*b*) the distribution of the disease in Calcutta, and (*c*) the variation in the clinical picture of kala-azar seen during the period following the famine and then to discuss these findings and consider the epidemiological factors concerned with the outbreak of kala-azar in Calcutta.

The trends of incidence of kala-azar in Calcutta

As indicated previously the figures relating to the indigenous kala-azar cases attending the clinic at the School of Tropical Medicine, that form a representative sample of the kala-azar affected population of Calcutta, have been utilized for the study of the trends of incidence of the disease in the city. It has been found out that about half of the total number of kala-azar cases attending the clinic are indigenous cases (*see* table I and chart 1). From these two, *i.e.* the chart 1 and the table I, the trends of incidence are readily ascertained.

It will be seen that there was a peak of incidence in the year 1923 and the number of cases remained practically steady for the next two years, and then gradually the number of cases decreased till a more or less steady inter-epidemic level was reached and maintained from 1930 to 1943. The low figure in 1942 was due to partial evacuation of the population on account of the war scare. The next wave of increased incidence commenced with a rise in the number of cases in 1944; by 1945 the rise was well marked and in 1946 a high peak was reached. This rise of the number of cases of kala-azar is even more strikingly shown by the chart showing the number of new cases of kala-azar per month since 1943 (*see* chart 2). The rise was gradual but steady from 1944 till