Indian J Pediat 47 : 525-529, 1980

EDITORIAL COMMENTARY

Research needs in liver diseases in India

N.C. Nayak, M.D., F.A.M.S.

Success in the understanding and practice of scientific medicine has its beginning in the appreciation of the needs in research and of proper approaches for their fulfilment. In any area of biomedical research these latter require specific attention to the following in a sequential manner : (1) identification of the problem, (2) planning of strategy, (3) designing of study, (4) standardization of methods and technology, (5) collection of data on time schedule, (6) computation and interpretation of data, (7) planning of further study. Determination of priority area in research would, however, depend on the magnitude of a problem, both in terms of frequency of occurrence and severity with regard to morbidity as well as mortality.

Compared to the adult, the liver in infants and children is a larger organ, comprising approximately 5% of body weight (in contrast to 2% in adults). Besides inherited and inborn errors of metabolism involving protein, carbohydrates, lipids, and minerals, this organ is constantly subjected to a variety of insults. Thus hepatic disorders are common in the child. During the last decades, several techniques have developed which allow in-depth study of many biological problems. Tools are now available for detailed investigations of problems by transmission or scanning electron microscopy, for examination of structure through biochemical or histochemical studies on a battery of enzymes, by electron probing for trace metals, by application of methods that identify immunological markers on different types of cells including the liver cells, lymphocytes etc, by purification of various components through cell fractionation, chromatography and electrophoretic techniques and by *in vitro* culture methods. Several agents that are capable of injuring the liver and producing disease have been identified and markers for certain types of injury and for associated factors have been recognised, though several still remain to be investigated. Some of the facets in the panorama of liver disorders in children in India that need urgent attention are : (1) hepatitis virus infections, (2) toxic liver injury and various types of cirrhosis, (3) Indian childhood cirrhosis, (4) biliary atresia and neonatal hepatitis syndromes, (5) portal hypertension due to non-cirrhotic causes, (6) alpha-l-anti-trypsin deficiency, and (7) the problem of nutritional liver disease. I will briefly discuss the lacunae in our knowledge and the research needs in each one of these areas.

From the Department of Pathology, All India Institute of Medical Sciences, New Delhi, 110029

Reprint request:- Dr. N.C. Nayak, Professor and Head, Department of Pathology.

Hepatitis virus infections

Knowledge on this subject has advan-

ced very rapidly over the last decade. We now possess information on various aspects of the biology and means of transmission of these agents as well as on the different types of clinical manifestations and sequelae resulting from infections by them. Virus-A, infecting largely through the feco-oral route produces both epidemic type of acute hepatitis but does not appear to either lead to chronic disease of any sort or induce a carrier state. Viruses B and non-A non-B on the other hand infect principally through the parentral route, produce both acute as well as chronic hepatitis and have distinct carrier states, some times extending over many years. The B virus is also significantly associated with cirrhosis and primary liver cancer in the adult. While all these categories of viruses exhibit horizontal transmission, the B virus is known to be transmitted vertically as well, resulting in viremia and subsequent infection of the liver in the newborn and young infant. Recent data indicates that carrier rates for the B virus is high among young children in some countries while it is low in others. In case of virus A infection before childhood is over, almost one hundred per cent individuals acquire immunity as revealed by specific antibodies of the IgG and IgM class in the serum.

It is necessary that mapping of infection rates and of the spectrum of clinical and sub-clinical manifestations of all the hepatitis virus infections be gathered for children in various areas of our country. The magnitude of vertical transmission of hepatitis B virus, the evolution of its infection in the newborn and its effects need to be investigated. The sero conversion, in terms of appearance of hepatitis B virus surface antigen as well as appearance of the various antibodies and other antigens must be determined. It has been claimed in a few studies that infection in very early childhood or infancy may make an individual susceptible to development of chronic liver disease including cancer at a later age. Thus long term follow-up of children born to hepatitis B carrier mothers by monitoring the various viral markers in the serum would provide very useful information. The magnitude of the problem of acute and chronic hepatitis as induced by the different hepatitis viruses also needs clarification. It would be very important to know whether chronic hepatitis of the active or persistent variety occurs and if so with what frequency in infants and children of various ages. The problem of non-A non-B hepatitis in the pediatric age group must also be investigated since this virus is also transmitted, like the hepatitis B virus, through the parentral route and knowledge on this agent is just gathering momentum. The natural history of acute and possibly chronic hepatitis produced by this group of viruses in children need to be looked at. Also, the combined effects of hepatitis infection and nutritional liver disorders are worth examining.

Toxic liver injury and cirrhosis

Unlike in the western countries, hepatic injury induced by biological toxins, particularly of the pyrrolizidine group from plants and of fungal origin like aflatoxin B1 appear to pose some problem in our country. These hepatotoxic agents not only induce liver cell

damage but also are capable of producing vascular abnormalities leading to further cellular injury, The magnitude and extent of these disorders need to be assessed, and their long term effects carefully evaluated. It is now known that certain toxic injuries of the liver are self perpetuating even after withdrawl of the initial injuring agent. The mechanism of such progressive injury is likely to be immunologically mediated, in which case afflictions during childhood may pass on to chronic liver disorders like cirrhosis in adulthood. It is necessary that detailed immunological and morphological studies are undertaken on liver diseases with definite toxic etiology. It has been known from experimental studies that certain varieties of toxic liver injuries induced by chemicals can either be augmented or reduced in severity with modifications of the enzyme profile of the hepatocyte. Protein deficiency, in fact, seems to protect against several forms of toxic liver injury. In case this is also true with injuries induced by biological toxins, in a relatively undernourished population like ours who are particularly prone to damage by toxins coming through food, the hepatocytic injury is likely to be less severe. These facets need careful investigation since they have important clinical and therapeutic significance.

With the availability of techniques by which foot prints of etiologic agents producing acute and chronic liver injury can be identified, attempts at classifying cirrosis mainly on the etiological basis is coming into vogue. Morphologic categorisation of changes in the liver in different forms of cirrhosis provide additional information that might help in epidemiological aspects of cirrhosis and suggest an etiological basis of the disease. The adult cirrhosis is generally sequel of continuing injury associated with hepatitis virus infections, toxic damage to the liver or chronic alcohol ingestion. Information on the varieties and the etiological associations in cirrhosis of childhood, on the other hand, is inadequate. While it is true that some special types of cirrhosis do occur in infancy and in the early childhood, cirrhosis in the older child has generally remained unexplored. Also, the relationship of the childhood cirrhosis to cirrhosis in adults is almost totally unknown. It is time that these areas are investigated with the use of various techniques that are available now to determine associated abnormalities, infections and the like.

Indian childhood cirrhosis

This syndrome is not only very frequent in our country but seems to be almost exclusively a problem of our own. The disease is unique and is frequently fatal, having thus attracted attention of investigators beginning with the initial description by Dr. Sen from Calcutta almost a century back. Several aspects of this disease have been clarified and certain new informations are available now though the central question of etiopathogenesis of the disease continues to remain an enigma. The role of hepatitis and other viruses causing liver injury, the contribution and precise significance of the role of inheritance, trace metal patterns with particular reference to hepatic copper and copper binding proteins, hepatotoxic agents in the environ-

ment and metabolic abnormalities, all these need further probing. It is essential that initial stages of the disease, before the process crosses the point of no return, must be clearly identified, possibly through studies on asymptomatic siblings and children in susceptible families. A peculiar predilection not only of certain castes but also of certain religions in our country to this disease merits more elaborate investigation. The disease seems to be relatively infrequent in the Muslim as well as in the sikh population even when children in the families in the same area are highly susceptible to the disease. The fact that the disease shows a distinct familial predilection and that it is of unusual occurrence among otherwise susceptible groups of Indian people settled abroad, make it possible that there is a complex interaction between subtle genetic inheritance and environmental factors. Investigation of this aspect of the problem needs thoughtful planning on the lines of studies made on certain other problems like lung cancer, where siblings and twins separately settled in different countries of the world with varying socio-economic situations have been examined. Since no adequate therapy for the disease is available yet, empirical treatment schedules may be tried to see if some benefits are made available to patients who come with advanced disease. On the other hand knowledge on earlier stages of the disease and of possible etiopathogenesis would help in attempting cures during early stages or even in prevention.

Biliary atresia-neonatal hepatitis syndromes

An important area in infantile liver disease which continues to remain in the dark regarding proper evaluation of etiopathogenesis, spectrum of manifestations and management is the group of syndromes referred to as the so-called 'biliary atresia', the neonatal hepatitis and choledochal cyst. It appears that these conditions are not so rare in our country as it was earlier believed to be. Several infants are brought to the hospitals every year but generally nothing can be done to them with regard to relief of the obstructive jaundice and the liver quickly progresses into a stage of secondary biliary cirrhosis. It is currently believed that the three conditions are inter-related and result from an inflammatory disease of the biliary passages rather than from congenital malformations. Detailed investigative work to determine the frequency of occurrence of these diseases, their possible inter-relationships, the natural history of each of them and the role of any known or as yet unknown infective agents are urgent necessities. Clarifications on these points would help in outlining proper therapeutic and surgical management in these infants and children. In-time treatment is likely to prevent progressive liver damage and help the liver to regenerate back to normal. It is possible that in these conditions too there exists complex interplay between certain metabolic deficiencies, acquired or inherited, and viral or other infections.

Portal hypertension

Portal hypertension and consequences thereof continue to remain an important gastrointestinal problem in children of our country. In the majority of these patients. thrombotic occlusion or other

abnormalities of the extrahepatic portal venous system appear to be the major cause. In a proportion, particularly among older children the entity of non-cirrhotic portal fibrosis constitutes a proportion of portal hypertension not associated with cirrhosis. The latter condition, frequently encountered among adults, has been suggested to be related to narrowing and occlusion of major intrahepatic branches of the portal vein possibly resulting from thrombotic episodes in long past. It is thus possible that the initial events occur in early periods of life and that whether it is an extrahepatic or an intrahepatic vascular lesion, these constitute different areas of the same spectrum of diseases. It is important that some studies be undertaken to investigate the phenomena of intra-vascular coagulation and of phlebitic injury in children from susceptible groups.

Alpha-1-anti trypsin deficiency

This metabolic abnormality results in improper secretion of the protein into blood leading to its low concentration in the serum and accumulation in the liver cells. These in turn are associated, often after prolonged interval, with pulmonary diseases or chronic liver injury and cirrhosis. From time to time some of the hepatic disorders in childhood have been ascribed to this metabolic deficiency. However, confirmation of these views are still lacking, particularly in patients, and need further study in the pediatric age group. Also, while it is true that various phenotypic manifestations of this inherited disorder can be seen in children with abnormal amounts of the protein in the liver and serum, their exact role in the etiology of pediatric liver diseases are not well established.

Nutritional liver diseases

In the past nutritional liver injury ascribed to deficiency of proteins and calories had been often blamed to be precursors of chronic liver diseases in adulthood. Several clinical and experimental studies have indicated that this may not be true and in fact very severe protein deficiency is likely to be associated with poor collagen formation, a process converse to what happens in cirrhosis and chronic hepatitis. Some recent data on adults, however, indicate that resections of large parts of small intestine for various conditions may result in abnormal nutritional states which predispose the liver to injury very similar to what is seen in the alcoholic or the socalled 'nutritional' liver disease. It is possible that combination of a variety of nutritional deficits and of intestinal bacterial infections might produce substances which are toxic to the liver. In this connection then abnormalities in nutritional inputs which is common in a country like ours should be given a fresh look regarding their role in hepatic injuries of various types. It may be necessary to set up proper experimental studies and also well monitored investigations in the infant and child to resolve some of these issues.