POSTGRADUATE MEDICINE

Drs. M. G. Kelly, A. G. Shattock, G. D. Doyle and J.F. Fielding* write on the detection and treatment of drug abuse associated with liver disease which is becoming rampant among adolescents

Drug induced liver disease

INTRAVENOUS drug abuse is an abuse of adolescents with morbidity and even mortality at that age. In contradistinction the morbidity and mortality associated with the abuse of nicotine and alcohol mainly affect those of middle age. Thus the importance of drug abuse associated morbidity and mortality is its impact on those who have not yet experienced adulthood.

The size of the problem is ever increasing. In the month of September this year no fewer than 56 new heroin abusers presented to the Drug Advisory and Treatment Centre.

Drug Abuse associated Liver Disease

The size of the problem: With the rapid growth in the number of intravenous drug abusers comes a corresponding increase in the risk of liver disease amongst such abusers. While it is impossible to

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quantitale the risk on a long term basis there is evidence to suggest that some six tenths of the abusers will develop chronic active hepatitis.

This does not include the increased numbers of close contacts who will also be at risk. Moreover, the calculated risk only applies to those abusers attending the National Drug Advisory and Treatment Centre and may just represent the visible portion (orevenjust the top) of the iceberg as far as the country is concerned.

Antiviral therapy and vaccinations (against hepatitis B virus and when developed against Non A Non B viruses) may alter these risks but will be too late to affect the current problem. If the number of new abusers were but to continue at its present rate (and current evidence is that it is still increasing) then one can expect over 400 cases of chronic liver disease per year of which some 135 would have chronic active hepatitis.

Clearly the size of the problem calls out for urgent action to assist in the prevention, detection and treatment of this appalling psychosocial problem. Whilst there have been many pious utterances of such assistance little help has been forthcoming for the management of intravenous drug abuse associated liver disease.

There is not even an isolation area attached to the National Drug Advisory and Treatment centre for the global management of these patients despite numerous requests for same. Thus health care personnel and close contacts of the patients are put at unnecessary risk of becoming infected by HBV and other viruses. The Department of Health which has consistently limited to provide this isolation area over (he past few years must accept responsibility for such increase risk.

The Diagnosis of Drug Abuse associated Liver Disease: Often this has to be done in conjunction with the psychiatric management of the patient as continuing psychiatric supervision and isolation may be essential to abuse withdrawal. Moreover, irrespective of the biochemical parameters the only way of knowing the state of the abuser's liver is to perform at least one liver biopsy. Only then may one decide if the liver disease is such as to warrant treatment in its own right.

The histological diagnoses vary from normal (very rare), through minor changes, acute hepatitis, chronic persistent hepatitis, chronic active hepatitis to chronic active hepatitis with cirrhosis. Current evidence would suggest that those with HBV associated chronic active hepatitis are at increased risk of long term development of hepatocellular carcinoma.

Treatment of Drug Abuse Associated Liver Disease:

Treatments currently being investigated include the use of an antiviral agent in an effort to lessen the risk of acute hepatitis developing into

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chronic hepatitis and the use of an anti-inflammatory/immunosuppressive agent in an effort to lessen the risk of progression of chronic active hepatitis to chronic active hepatitis with cirrhosis.

The virology of Hepatitis and its serological diagnosis: At least four common types of viruses causing hepatitis are recognised at the present time: Hepatitis A virus, causing "infectious hepatitis", Hepatitis B virus, causing "serum hepatitis" and the more recently recognised Non A, Non B hepatitis. There is considerable evidence that there are at least two forms of Non A Non B hepatitis with different incubation periods. Hepatitis A and B can now be distinguished by serological tests but laboratory tests for Non A Non B hepatitis are still in the research stage.

Although drug abusers just as other members may develop hepatitis. As such infection does not contribute to chronic liver disease and hence the virology of hepatitis A, it will not be discussed in detail in this paper. Suffice to say that one needs to exclude the presence of hepatitis A as a cause of acute hepatitis in those patients who are negative for hepatitis B markers, to enable one to attribute the hepatitis to one of the Non A Non B viruses.

Hepatitis B: The discovery of the association of the "Australian antigen" with hepatitis B in 196S led to the current explosion of research into viral hepatitis. This antigen, now known as hepatitis B

surface antigen (HBsAg), is present in the serum of patients during the late incubation period and the acute phase of serum hepatitis and is usually cleared during convalescence in a variable period of time.

Also appearing in the serum before the onset of symptoms and biochemical changes are the DNA polymerase and the “e” antigen, both associated with the hepatitis B virus and proven markers of infectivity. These markers arc normally “e”antigen beyond 10 weeks is ominous. Simultaneously with or shortly after the disappearance of the “e” antigen, antibody to the “e” antigen appears and is a marker for greatly reduced or non-infectivity, although this is not absolute.

The seroconversion from hepatitis B “e” antigen to anti-HBe within 10 weeks of onset (usually) earlier normally heralds complete recovery. Antibody to core of the virus (anti-HBc) is found from the onset of symptoms and persists, usually for years.

Finally, often considerably later than the clearance of HBsAg, the antibody to the surface antigen (anti-HBs) appears. Anti-HBs is the antibody which confers immunity and is the antibody which is elicited following vaccination.

How do all these different antigens of he pat it is B relate to each other? The virus, often called the Dane panicle after its discoverer Dr. David Dane of the Middlesex Hospital, is unusual, many would say extraordinary.

It consists of a “core” structure containing DNA, part of which is only single-stranded, plus core antigen and DNA polymerase. One of the components of the core antigen complex is the “e” antigen.

The core structure is surrounded by a layer of the surface antigen acting as a protective coat. However during multiplication of the virus in the hepatocytes large quantities of the surface antigen and “e” antigen are produced surplus to the requirements for just building new virus particles.

This surplus surface antigen and “e” antigen appear in the blood. However the “e” antigen is only produced during the replication of the virus itself, whereas the surface antigen is often continued to be produced even in the absence of viral replication.

The mechanisms and reason for the production of surplus HBsAg and “e” antigen are still unknown although the advantage to the virus of having surplus proteins to “mop up” antibodies to surface antigen are obvious. The surplus surface antigen appears as very numerous small particles approximately half the size of the virus and also as tubules of various lengths. It is the small particles of surface antigen that are isolated, purified and inactivated and used in the manufacture of the currently available vaccine. Variations in the proteins of the surface

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antigens are responsible for the epidemiologically useful subtypes of HbsAg, but there are no known differences in virulence between subtypes.

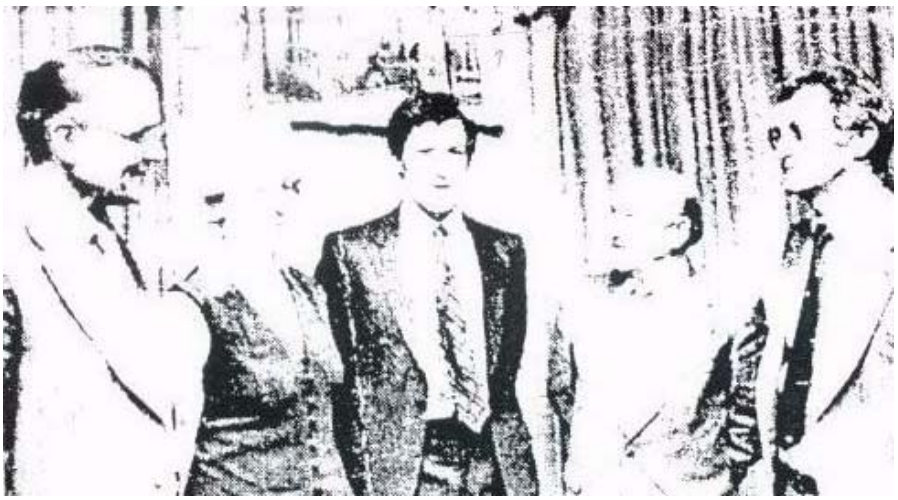
South antibody and cell-mediated immunity are involved in clearing the virus and antigens from the system. Chronic hepatitis B with continuing HgsAg antigenaemia may develop in some cases, possibly due to the absence of certain antibodies, but the exact mechanism is unknown.

Chronic carriage of HBsAg may persist long after liver damage has resolved and biochemistry returned to normal. Such cases are relatively common and mainly non-infectious and often only discovered because of blood donation.

Others may have progressive liver disease due to abnormal cell mediated immune reactions, and may eventually progress to cirrhosis. Carriers are more common among males and more likely to occur if the infection is acquired during birth or in childhood.

It is estimated from surveys carried out world wide that there are over 175 million hepatitis B carriers in the world, the incidence varying from less than one per thousand in the western world to more than 10% in tropical

(*Contd. on page 32*)



At a meeting on recent advances in Cardiac Radiology-Lower Osmolality, Contrast Media and Coronary Angioplasty were: Dr. G. Gearty, Dr. Patricia Morton, Dr. R. C. Cumberland, Sheffield, guest speaker, Mr. P. Gray, May and Baker Ltd., and Mr. P. Dunne, M. & B.

Dr. B. Murphy, Dr. M. Scott, Mr. P. Denieffe, M. & B., Dr. J. Gately, Ms. Mary Murphy, and Dr. J. Molloy.

countries and the Far East. In • Ireland* the carrier rate is approximately one per 2000 persons.

Usefulness of tests for monitoring hepatitis B: One of the first uses of tests for HBsAg was, and stilt is, for screening blood donors. This has eliminated most cases of post-transfusion hepatitis B although, because t-o lest is sufficiently sensitive to detect all donors with the lowest level of circulating virus, a few cases caused by hepatitis B do still occur.

The most sensitive tests for its detection are radio-immuno - assay (EIA, ELISA) and some types of passive haemagglutination. These tests are employed by blood banks world wide for their donor screening.

Extra sensitive versions of these tests, together with a battery of tests for other markers, are available at the Virus Reference Laboratory, U.C.D., for the serological diagnosis, confirmation and for monitoring the recovery of patients with hepatitis B infection. (It is noteworthy that Ireland has made a valuable contribution to diagnostic hepatitis technology in that staff at the Virus Reference Laboratory at U.C.D. were among the first to work on the "e" antigen and this led to the development of a sensitive enzyme-immuno-assay for the detection of the prognostically significant "e" antigen and antibody).

Patients' sera found positive for hepatitis B surface antigen are automatically tested for the "e" antigen and antibody, so that specific requests for the latter are unnecessary. Tests with hepatitis B and there is some debate as to whether blood donors should be tested for this antibody, in addition

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to the HBsAg test, although the economics of this operation would appear to make it unjustified at present. IgM specific anti-HBc tests have recently been developed in some laboratories and will become useful for diagnosis during the "window period" when the HBsAg has cleared but anti-HBs may not be detectable.

Prophylaxis of Hepatitis B: Two approaches are now possible in the prbphylaxis of hepatitis B: Hepatitis B specific hyperimmune gamma-globuin (HBIG) and vaccination. The former is a preparation made from anti-HBs rich plasma and is very useful in the prevention (or modification) of hepatitis B in needlestick and other accidental exposure and in babies born to mothers in the acute stage of hepatitis B; To be of maximum effect in the latter it has been shown essential to administer HBIG has passed all clinical trials, where it was found safe, very effective and without side-effects. It has been used in over 13,000 persons in "high risk" groups. These include renal dialysis patients and staff, homosexuals, drug addicts, laboratory and some categories of hospital staff, and others. For the first time ever a vaccine has been produced before the virus was propagated de novo in tissue culture!

Non-A, Non-B Viral Hepatitis: At present the definition of this type of hepatitis is hepatitis of viral origin where hepatitis A, B, cytomegalovirus and Epstein-Barr virus infection have been excluded. Leptospirosis and toxoplasmosis may also need to be tested for.

There are at least two types of Non-A, Non-B viruses based on incubation periods and chimpanzee transmission experiments. Further more an 'epidemic' type has been described in several areas, principally in India. It is the commonest type of post-transfusion hepatitis in the United Slates and causes

a sizeable proportion of sporadic acute hepatitis in many, if not most countries for which data are available.

In Ireland this figure is estimated from data published by A.G.S. to be 50%. However there are many sub-clinical causes; other characteristics useful in its study are the frequent appearance of multiple peaks of the transaminases and unique histological findings in chimpanzee studies.

It is increasingly clear that the DNA polymerase and the "e" antigen, both associated with the hepatitis B virus and proven markers of infectivity. These markers are normally cleared in early convalescence limiting chronic liver disease. Serological tests are under development but are presently plagued by non-specificity problems.

The Delta Agent: The delta agent is normally found only in association with hepatitis B although it is a putative Non-A, Non-B virus. Currently delta is hypothesised as being a defective RNA virus relying on hepatitis B for some of its function, including possibly the 'loan' of HBaAg as coat material.

It was discovered by Dr. Mario Rizzetto in Italy, where it is more common, particularly in persons with repeated parenteral invasion such as drug addicts. Unfortunately work on delta is hampered by the lack of liver derived antigen for serological tests, so that very few laboratories indeed can work on this agent.

The Department of Medical Microbiology at U.C.D. has recently developed the first ELISA technique using delta antigen extracted from serum, and this will enable other laboratories to study various

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populations for the delta agent and its effects. It is claimed that delta infection is found more frequently associated , with chronic carriers of HBsAg and those with chronic hepatitis. The cause and,' effect relationship are quite unclear, and certainly not proven.

The Future: Prevention is better than cure and so the main thrust through policing and education must be the reduction and ideally the elimination of intravenous drug abuse. In the interim proper facilities must be made available for the management of these patients by the psychiatrist and physician together with the required backup haematological, biochemical, serological and immunological teams. As far as possible this team must be on the same site.

The abuser with suspected or known virus associated liver disease must be isolated and all health care personnel attending these patients must be offered Hepatitis B vaccine. This is probably simpler than testing 10 determine those who do or do not require such vaccination as screening is not without cost and no risk has ensued from vaccinating those with previous HBV infection.

It must be remembered that such vaccination will not intiluence the outcome of disease. Vaccinations against Non-A, Non-B viruses must also be offered when available. Until HBV vaccination becomes available HBIG must be available for those accidentally exposed to HBV infection. Babies of acutely HBV infected mothers probably do best by getting both HBIG and HB vaccine.

Treatments aimed at lessening the risk of acute hepatitis progressing to chronic hepatitis and of chronic active hepatitis progressing to chronic active hepatitis with cirrhosis must

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*References relating to statements in this paper are available on request.

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Dr. E. Bresnihan, Dr. J. Kelleher, Dr. J. Masterson, Dr. M. Molloy and Mr. S. Martin, M. & B.