HEPATITIS B — CLINICAL MANIFESTATIONS AND PROSPECTS FOR ELIMINATION

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SYNOPSIS

Hepatitis B Virus infection is endemic in South East Asia, where an estimated 45 million persons are carriers of the infection. Classical and protean manifestation of the disease have been expanded with the availability of screening reagents which are now able to detect the acute and chronic infection.

The acute viral hepatitis infection is responsible for at least 45% of acute cases of viral hepatitis, and recovery is slow and incomplete. 15 to 33% of such persons develop the chronic carrier state and evidence of viral integration and expression. Chronic sequelae of such infection are earlier morbidity and mortallity in 30-50% over a 5 year period.

Today Liver Cancer is as foremost carrier in the region and up to 80% of these cases are due to chronic HBV. There is good evidence that chronic HBV DNA integration is responsible for the later development of malignant transformation.

Hepatitis B vaccination of susceptibles, public health hygiene and antiviral treatment are strategies for the prevention of HBV and a major cancer of the world today.

INTRODUCTION

In 1950 and early sixties, Viral Hepatitis B (HBV) was known as acute infections hepatitis and acute outbreaks of severe, sometimes fulminant acute hepatitis occurred after transfusion of untested bloods or in renal dialysis units. Early transmission studies showed that HBV-contaminated syringes, needles, acupuncture apparatus or common sharing of needles or vaccination instruments which were poorly cleaned or unsterilised, were responsible for the serious outbreaks of infective hepatitis.

Today, it is now possible to understand the epidemiology and the clinical patterns of Hepatitis B viral infections, both in terms of classical presentations, and less often, the subtle but more serious manifestations of diseases associated with HBV, using diagnostic reagents and molecular probes to detect HBV. HB surface antigen (HBsAg) produced by the virus is non infectious and is the component of HB vaccines. The HBV contains HBV DNA, 'e' Ag, a core, which are infective proteins of ihe virus (See Diagram 1).

Epidemiology

HBV is endemic in many countries of the world with periodic outbreaks of acute infection in young children and adults. It is a public health disease of worldwide dimensions and the World Health Organisation (1,2) has endorsed it as a disease of public health importance because of the extensiveness of the disease, the severity of its morbidity and mortality of illnesses related to its acute and chronic infections.

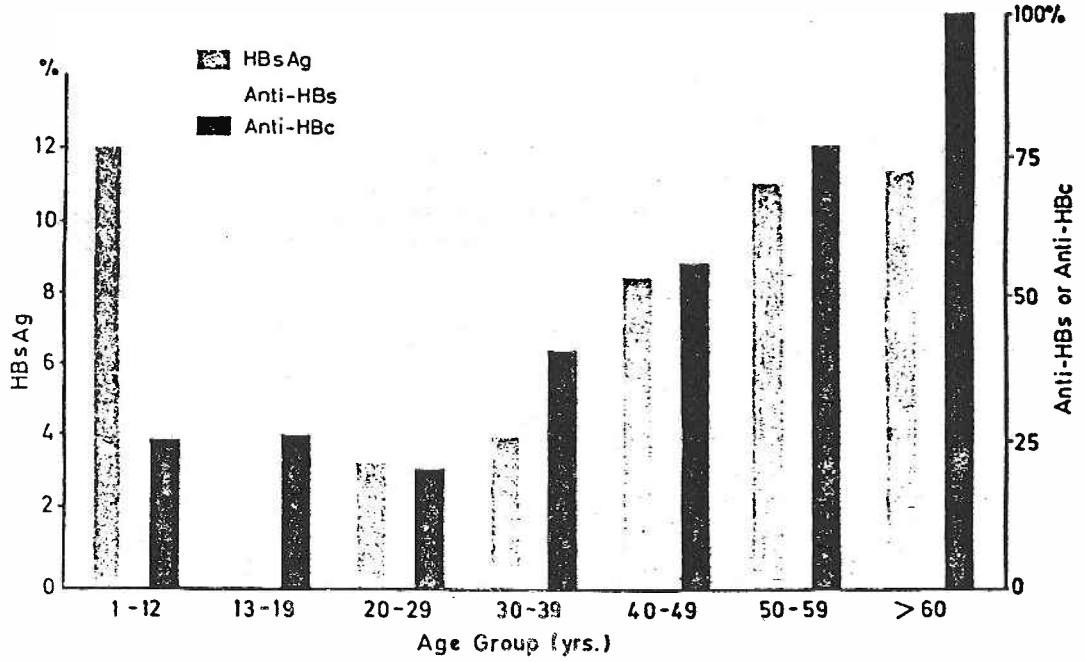
Of the persons who are infected acutely, the majority 70-80% will fully recover. However, longitudinal studies in acute HBV infection have shown that between 30-33% (3) of persons continue to harbour HBV for six months and are carriers of the infection. Follow up of such cases have shown persistent morbidity from the development of chronic active liver disease and cirrhosis. Cirrhotics, who are HBV carriers develop higher risks of developing primary hepatocellular carcinoma (HCC).

Globally, it has been estimated that there are 316 million HBV carriers, of which 170 million are in Asia (2). In South East Asia with a population of 450 million persons, the prevalence of HBsAg positive carriers averages 10% in most countries. An estimated 45 million persons are carriers of this infection.

Quiescent infections occur, as evidenced by the increasing number of persons positive to HBV markers (See Table 1) with selective infection in childhood from mother to infant HBV infections, or by cross infections within the family from HBsAg positive carriers. Manifestation of such infections are often inconspicuous. either because the illness is asymptomatic, mild, with fever, flu-like, or mild gastrointestinal upsets. It is now known that 75% of this pool of HBV carriers develop as a result of such low grade horizontal infections and only 25% is accounted by mother to child (or perinatal transmission). Such confirmation have been seen in studies in many South East Asia countries (e.g. HongKong, Thailand, Philippines, Singapore, China, Taiwan and Korea (4). Childhood infections are common in many rural areas where there is mixing of population. Even in the Maori population in New Zealand, (7) increasing horizontal transmission of infection is seen in older children during the schooling period (B. Milne, personal communication, 1986).

HBV prevalence rates vary between population to population under examination. HBsAg positively is higher amongst transvestities (12%) than prostitutes (6%), in spouses of carriers (20% HBsAg positive), in family members of HBsAg and 'e' Ag positive carriers, institutionalised persons and individuals who are in close physical or intimate contact with carriers.

Globally, HBV is endemic in nearly all countries of the Asian Pacific Region, Middle East, Africa, some countries in Eastern Europe, South America and Polynesia. HBsAg positivity carrier rate have been as high as 80% in some adjacent Pacific islands.



Age specific prevalence of HBV markers in Singapore

Table 1

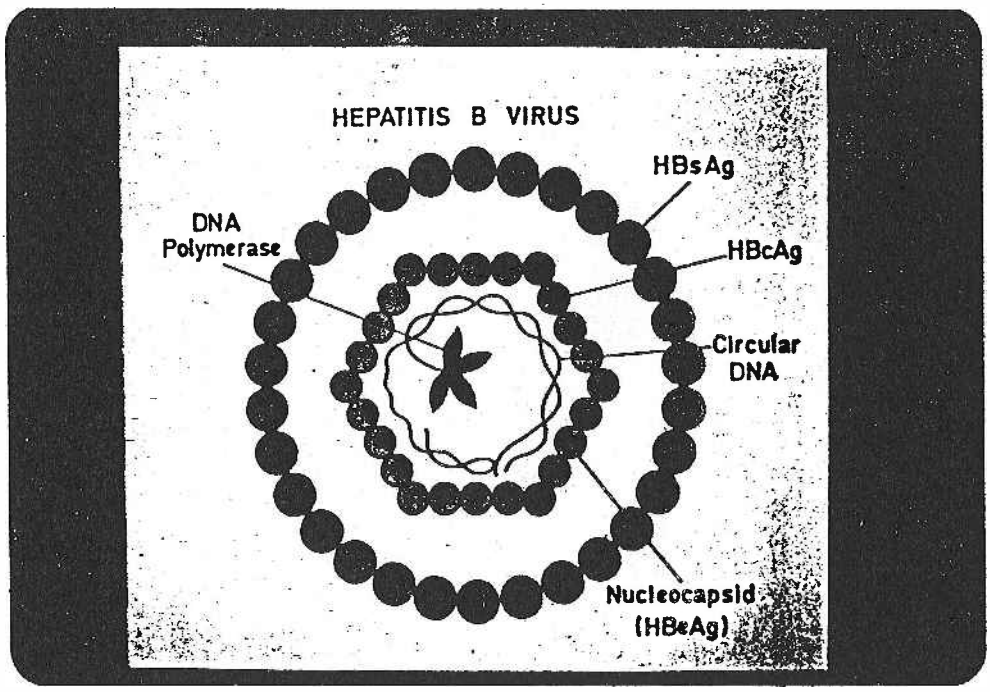


Diagram 1

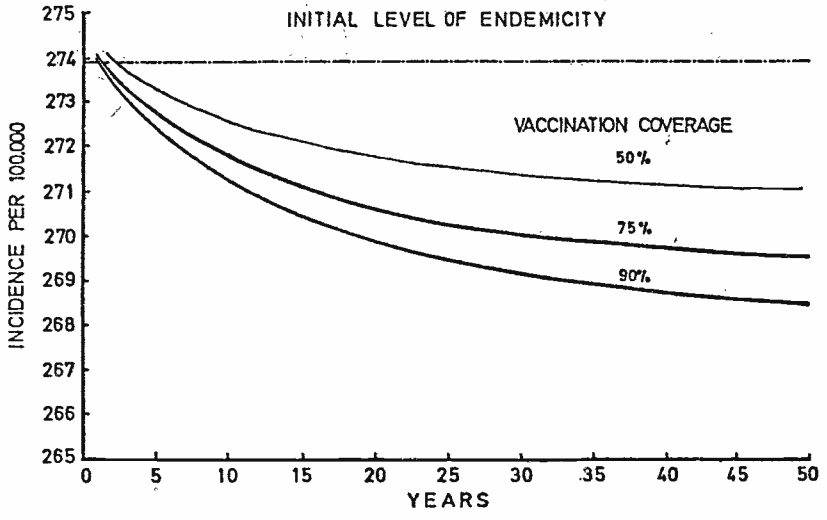
Transmissions

HBV is transmitted (i) through transfusion or parentral administration of HBsAg-contaminated blood and its products, (ii) contaminated needles, syringes and skin pricking instruments, (iii) from the shared household items, such as towels, razors, handkerchieves, clothings, toothbrushes, combs, bedding, (iv) from the HBV infected wounds, bruises, ulcers, nosebleeds or carriers, (v) from bed bugs, body lice and other blood sucking insect vectors. (vi) from HBsAg positive mothers to child at delivery.

Perinatal transmission

HBsAg positive/ 'e' Ag positive mothers transmit the infection in over 90% to their newbornchild, regardless of the race, or sex. HBV virus unlike rubella virus, is a large virus and does not cross the placenta. It does not produce congenital malformations like rubella nor does it infect the foetus unless there have been breaks in the maternal-foetal barrier. In most prospective studies, including our recently completed Singapore studies (5), intrauterine carriers develop in 6 to 10% of perinatal infections and are not preventable by immunoprophylaxis. However, amniocentesis, prolonged labour and other obstetrical manipulations may encourage the development of intrauterine infection and such procedures should be avoided if possible.

However, HBsAg positive/'e' Ag negative mothers transmit the infection to only 8% of their newborns. This difference, is because of the low frequency of viral HBVDNA in the maternal sera of HBsAg positive/ 'e' Ag' negative mothers which is in contrast with the high levels seen in HBsAg positive/'e' Ag positive mothers.



SIMULATED EFFECT OF CONTINUOUS SINGLE IMMUNIZATION OF NEWBORN OF POSITIVE MOTHERS ON INCIDENCE OF HEPATITIS B

Figure 1: shows continuous immunisation of newborns of Hepatitis B carrier mothers will not reduce the carrier rate significantly.

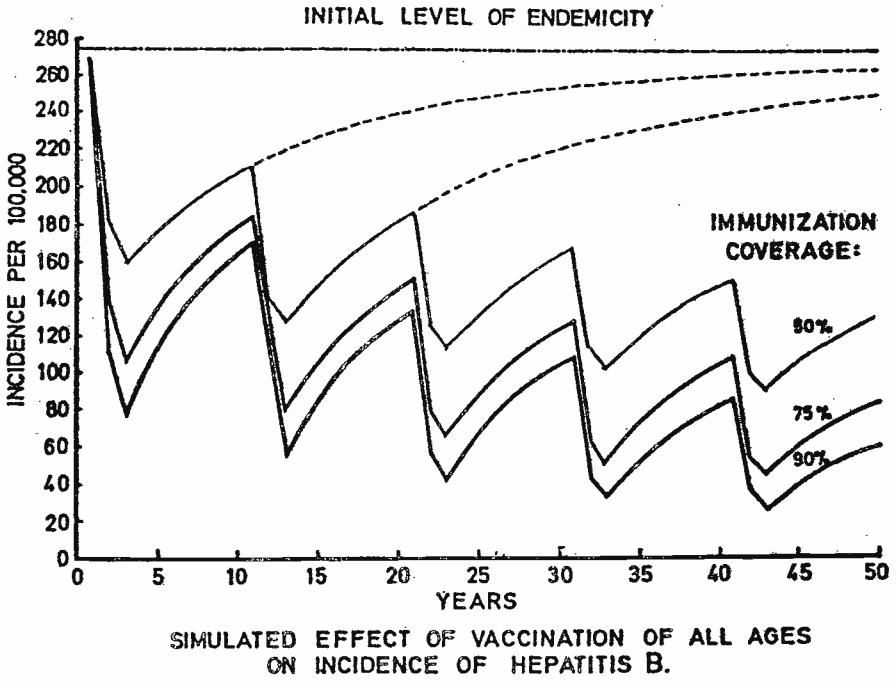


Figure 2: shows that immunisation of at least 90% of the whole susceptible population is required to control HBV and this vigilance has to be maintained over 50 years. Laxity in immunisation programmes would lead to loss of herd immunity and recrudescence of previous infection rates.

Clinical Features

The classical illness of acute HBV is a 'flu' like illness with joint pains, abdominal discomfort, nausea, jaundice, malaise and the passing of dark coloured urine. The incubation period is between 15—150 days after acquiring the infection and the time taken to full and complete recovery is often three to six months.

Infrequent complications include rapid progressive immune complex glomerulonephritis, systemic lupus erythematosus, polyarteritis nodosa, infantile papular aerodermatitis, essential mixed cryoglobulinaemia, Guillain-Barre Syndrome, brachial neuritis, polymyalgia rheumatica and the rapid deterioration seen in patients undergoing immunosuppressive/cytotoxic or irradiation therapy (6).

HBV is also related to chronic active hepatitis, cirrhosis, fulminant hepatic failure and primary hepatocellular carcinoma. More recently, delta antigen, a parasitic RNA virus of HBsAg has been found to produce a more severe hepatitis with gross structural hepatic damage than HBV alone. Delta antigen infection occurs both as a superinfection and as a coinfection in HBsAvg positive carriers. Fortunately, its mode of transmission is parenteral and this infection can be prevented by hepatitis B immunisation. Delta Ag infection has been associated with mortality rates of 15—20% in several villages in Colombia and Venezuela. It has now made its presence in several countries in S.E. Asia and the Western Pacific Region.

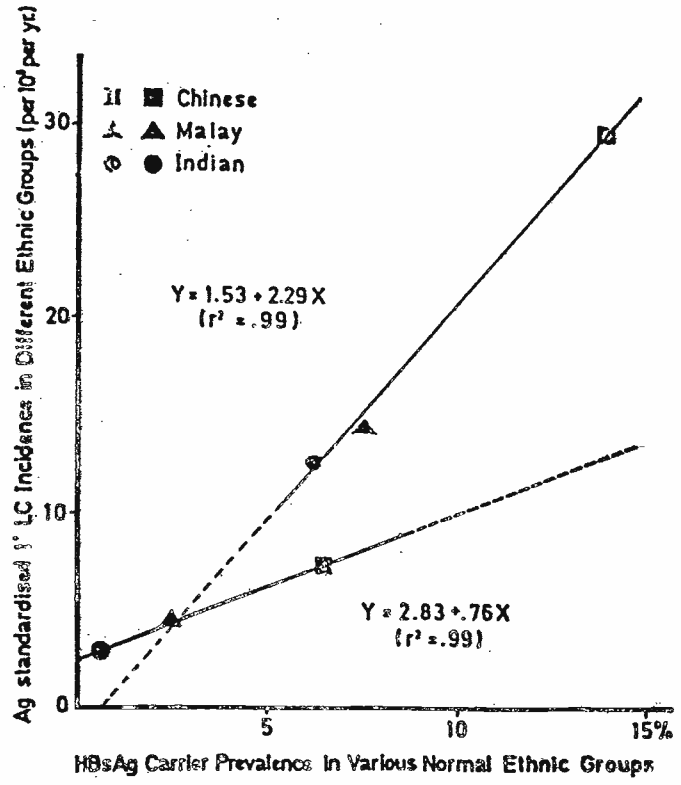
Primary Liver Cancer

Primary Hepatocellular Carcinoma is the most common Liver Cancer in the Far East and is the eight commonest cancer in the world. It is also the leading cancer in many countries in S.E. Asia and the Western Pacific Region. It affects all ethnic groups from Chinese, Malays and Indians (See Table II) to Caucasian, Maoris, Polynesians, Philippines, Japanese, Koreans, Thais and others. It has affected both the famous and the poor equally.

Up to 80% of Liver Cancer is caused by chronic HBV carriage. The HBVDNA is now detectable in liver and peripheral leucocytes of liver cancer patients. Locally in Singapore, all three ethnic groups are afflicted with HCC. Males have a higher carrier rate for HBV than females by a ratio of 4:1 and this is the same ratio for HCC seen in males and females.

Chronic HBV carriage by other animal HBV viruses have produced identical HCC in woodchucks, ground squirrel, Peking duck and the prairie dog. On epidemiological evidence such as those based on prospective and case control studies, as well as morphological studies in animals, there is no doubt that chronic HBV infection and HBV integration is a major cause of liver cancer seen in the world today. The need for prevention and eventual elimination of HBV infections is therefore an urgent health issue today.

Table 2



Relationship between incidence of HBsAg and primary liver cancer among different ethnic groups. (LC = liver cancer)

Hepatitis B prevention

From epidemiological information on the methods of transmission, the following stages can be taken to protect persons exposed to risk of infection.

(1) Hepatitis BV immunoprophylaxis
(2) Hygiene education
(3) Treatment of HBsAg positive/'e' Ag positive carriers.

Relative risk of Liver Cancer

Using the attributable risk formula of $AR = \frac{P(R-1)}{PR+1-P}$ when P is the proportion of population at risk from HBV and R is the relative risk of Liver Cancer, it can be calculated (based upon an average prevalence of HBsAg positive in the population of 8% and assumed modest risk of HCC in carriers of 20), the attributable risk of a carrier developing liver cancer and dying is 60%, i.e. 60% of lives can be saved by elimination of HBV carriage by immunisation or other means.

(1) Hepatitis B immunoprophylaxis

High risk susceptibles: These are persons who have no serological evidence of exposure (such as neonates born to HBsAg positive carrier mothers and seronegative hospital staff exposed to needle stick injuries).

For adults exposed to needle stick injuries immunisation should be both by passive and active immunuisation. For adults, 5 mls of Hepatitis B immunoglobulin (HBIG) (of a titre of anti-HBs of at least 200 IU/ml) should be given within 24 hours of exposure. This should be followed by B-Hepavac, MSD, 10µg stat and at one and six months subsequently, in all those under 40 yrs of age. For those over 40 yrs of age 20µg doses may be needed. For those whose anti-HBs are not detectable, further boosters may be needed if exposure risk is present. For infants under 1 yr: Neonates born to HBsAg positive/'e' positive mothers should be given HBIG 0.5 mls i.m. at delivery followed by 5µg B-Hepavac MSD in another limb. Subsequent doses would be given at one, two and six months. In infants born to HBsAg positive/'e' positive mothers, the vaccination is efficacious in 100% when the child is HBsAg seronegative at 24 hrs, but the efficacy falls to 88% (5), when the child is already infected at 24 hrs. About 20—25% of newborn children to HBsAg positive/'e' Ag positive mothers have detectable HBsAg in their venous blood at 24 hrs.

5ug doses of B-Hepavac MDS given to normal infants and other children born to HBsAg positive/'e' negative mothers were 100% effective in protection against HBV.

Since B-Hepavac (MSD) contains antigen derived from pure 'S' Ag gene (and no pre-S element), the requirement for having a pre-S Ag is not an issue since 100% protective efficacy is already achieved with the 'S' Ag fragment alone from B-Hepavac MSD.

Similarly in the clinical trials (8), in which the Hepatitis B Vaccine was used extensively no vaccine recipient, who had developed an anti-HBs response, has developed acute viral hepatitis or changes elevations in SGPT levels. This would indicate that the vaccine was efficacious in preventing both hepatic damage, the infection and the chronic carrier state.

Vaccine dosage, schedules and route of administration

The manufacturers have recommended that the route of administration, to achieve the optimal response should be intramuscular. However, reduced responses (by as much as 64% seroconversion) have been seen when the vaccine was given subcutaneously, e.g. into the

gluteal region (9). Subcutaneous injection by automatic jet gun have achieved 85% seroconversions.

For normal adults below the age of 40 yrs of a 10μg dose given at 0, 1 and 6 months appears to be as effective as the 20μg doses and achieve approximately 90% seroconversion one month after the third dose. For subjects who are older a large dose or extra doses may be required as their responses are weaker. Occasionally, a 5 g dose may be explored intradermally in the non or slow responders. Patients with uraemia would require at least 40 g doses. Intradermal doses of 2μg have been successfully given to adult Caucasian subjects (10), but the overall response was 85% in twelve persons vaccinated. There was no response in two older subjects over 45 years of age. 5μg doses given intradermally have also been responsive in our local experience, in some older recipients who had not responded to three standard 10μg doses. Intradermal inoculatios have produced mainly painless nodules and few side effects. The antibody levels after two intradermal doses have been identical to intramuscular injection, but the booster third dose produces a much higher antibody titre which is 10 times greater than by the intradermal route (Zoulek and Dienhardt, personal communication).

The anti-HBs is against both the predominant "a" subtype as well as "d" antigens present in HBV in the Asia Pacific region. In Singapore, the subtypes are adr (40%), adw (45%), ayr (5%), ayw (1%). In our experience in Singapore, anti-HBs seroconversions are seen in 90% of vaccines below the age of 40 yrs. Titres greater than 20 mill/ml anti-HBs are seen in 85% of the responders. This titre is sufficient for standard protection.

Seroconversion of 85—90% were also seen in recipients of a schedule given at 0, 1, 2 months, but the duration of antibody persistence is about 18 months in this group.

Low titre responders tend to lose their antibody status more quickly. They and non-responders are susceptible to needle stick infection and should be given prophylactic HBIG if infected.

Extent of Immunisation

Extrapolation from the control of other infectious diseases, such as smallpox and polio, show that compulsory immunisation for at least 95% of the susceptible population is necessary before the disease can be effectively controlled. The same principle may also be applied to the control of Viral Hepatitis B. Based upon an epidemiological model of Singapore with a prevalence of HBsAg of 8%, at least 95% coverage of the whole susceptible population is needed to significantly reduced the carrier rate.

However, a reduction of carriers by a factor of 2 would also reduce significantly HBV. The strategy would therefore be the uese of vaccines for susceptibles, antiviral therapy to eliminate 'e' Ag carriers and health hygiene.

Before compulsory vaccination can be introduced, safe, pure, effective and low cost vaccines must be available. Until then, vaccines can only be given on priority bases to the most susceptibles.

(2) Hygiene education

Apart from immunisation of at risk persons, such as members of families where carriers exist, hospital staff, young males (especially servicemen and those working in institutional and social practices, where there are opportunities for close physical or intimate contact with carriers and where there are common sharing of items, (such as towels, razors etc.) is occurring, the public should be made aware of the importance of good hygiene practices and the need for immunisation.

(3) Antiviral therapy for carriers

There are reasons why strategies to eliminate the carrier state is important. These are:

(a) to prevent the spread of the infection to other susceptible populations.

(b) to prevent the development of the acute and chronic sequelae of HBV infections (such as delta superinfection or coinfection, cirrhosis, hepatic failure, liver cancer).

Early treatment rather than late is important, since conversion from 'e' Ag to 'e' Ag negativity is associated with more areas of HBV integration in the liver and more extensive histological changes. Various treatment strategies are currently being explored in many centres. There is no doubt that the present data indicate that antiviral therapy for chronic hepatitis B carriers would soon be standard treatment protocols (11,12). Already, there are strong evidences that prolonged treatment of combinations of agents are superior to single agents alone, in elimination HBV DNA which is a useful index of Dane particles present in the area of carriers. This test is more valuable than measuring HBsAg, since the presence of HBsAg may also indicate expression of integrated HBV, and not only viral replications. Such ongoing treatment programmes are already taking place in our department in Singapore. Where the natural course of HBsAg positive and 'e' Ag positive carrier is for HBV DNA polymerase elevations to persist for at least a year in 90% of carriers, we have already seen remarkable elimination of HBV DNA within 16 weeks in 5/5 (100%) of chronic HBsAg positive, 'e' Ag positive carriers, treated in our Unit. Further exploration of suitable combination strategies using Alpha or Beta intereferons, Prednisolone and Adenine Arabinoside or Acyclovir are presently being undertaken in our department.

It is with this optimism that, perhaps with unified effort from the medical practitioners, the National Authorities, and the advances made in antiviral and vaccine programmes can we dare to hope towards a more reduced rate of Liver Cancer and the other complications of HBV by the year 2000.

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