Australia Antigen and the Biology of Hepatitis B

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The discovery of the infectious agent associated with hepatitis B and the elucidation of new mechanisms for its dissemination are the consequences of a series of studies involving many investigators in our laboratory in Philadelphia. The particular directions the work has followed have been a product of the interests and personalities of the investigators, physicians, technicians, students, and others who have come to our laboratory. It has resulted in a complex body of data which crosses the boundaries of several disciplines. I have been fortunate in having as co-workers dedicated and highly motivated scientists. We have had a warm, friendly, and congenial atmosphere and I am grateful to my colleagues for bringing these qualities to their work.

Polymorphism and Inherited Variation

E. B. Ford, the Oxford zoologist, lepidopterist, and geneticist, defined polymorphism as "the occurrence together in the same habitat of two or more (inherited) discontinuous forms of a species, in such proportions, that the rarest of them cannot be maintained merely by recurrent mutation" (*1*). Examples of polymorphism are the red blood cell groups in which the different phenotypes of a system may occur in high frequencies in many populations. This, according to Ford's view, would be unlikely to occur as a consequence of recurrent mutation operating alone to replace a phenotype lost by selection. Another example is the sickle cell hemoglobin system. In this, Hb^S genes may be lost from the population each time a homozygote (who has sickle cell disease) fails to contribute to the next generation because of death before the reproductive age. The heterozygotes (Hb^S/Hb^A) are, however, thought to be differentially maintained in the population because individuals with this phenotype are less likely to succumb to falciparum malaria and consequently survive to contribute genes to the next generation. The theory implies that there are different selective values to the several forms of polymorphisms. This notion has been questioned recently since it has been difficult to demonstrate selective differences for most polymorphisms. Independent of the biological causes for the generation and maintenance of polymorphisms, the concept unifies a large number of interesting biological data. No two people are alike, and polymorphisms probably account for a great deal of variation in humans. There are other interesting implications of polymorphisms. In some instances, the presence of a small amount of a material may be associated with one effect, and the presence of larger amounts of the same material may be associated with a very different effect. One gene for hemoglobin S protects against malaria, while two genes result in the (often) fatal sickle cell disease. Polymorphisms may produce antigenic differences. Antigenic variants of ABO and other red blood cell groups may result in transfusion reactions. Differences in Rh red blood cell groups may cause life-threatening antigenic reactions between a mother and her child late in pregnancy and at the time of birth. Polymorphic antigens may have an effect when one human's tissues interact with those of another in blood transfusion, transplantation, pregnancy, intercourse, and possibly, as we shall see, when human antigens are carried by infectious agents.

Oliver Smithies (who had been a graduate student of A. G. Ogston, my mentor at Oxford) developed the ingenious starch-gel electrophoresis method that allowed the separation of serum proteins on the basis of complex characteristics of their size and shape. With this, he distinguished several electrophoretically different polymorphic serum proteins (haptoglobins, transferrins, and the like). In 1957 and for several years after, in collaboration with Anthony Allison who was then in the Department of Biochemistry in Oxford, we studied these variants in Basque, European, Nigerian, and Alaskan (*2*) populations and found striking variations in gene frequencies. At the same time, I acquired experience and some skill in mounting field studies. Using this and similar techniques in the following years, I studied inherited variants in other populations and regions. These included red blood cell and serum groups in Spanish Basques, in Alaskan and Canadian Indians, and in Eskimos; β-aminoisobutyric acid excretion in Eskimos, Indians, and Micronesians; protein and red blood cell antigens in Greeks, and various variants in North and South American Indians and in U.S. blacks and whites (*3*). We identified several "new" polymorphisms in animals. With Michael Tombs, another of Ogston's pupils, we discovered a polymorphism of alpha lactalbumin in the "Zebu" cattle of the pastoral Fulani of northern Nigeria (*4*). Later, Jacob Robbins and I found a polymorphism of the thyroxine binding prealbumin of *Macaca mulatta* (*5*). From these studies, and those of other investigators, the richness and variety of biochemical and antigenic variation in serum became strikingly apparent.

In the summer of 1960, Allison came to my laboratory at the National Institutes of Health. We decided to test the hypothesis that patients who received large numbers of transfusions might develop antibodies against one or more of the polymorphic serum proteins (either known or unknown) which they themselves had not inherited, but which the blood donors had. We used the technique of double diffusion in agar gel (as developed by Professor Ouchterlony of Göteborg) to see whether precipitating antibodies had formed in the transfused patients which might react with constituents present in the serums of normal persons.

After testing serums from 13 transfused patients (defined as a person who had received 25 units of blood or more), we found a serum that contained a precipitating antibody (*6*). It was a very exciting experience to see these precipitin bands and realize that our prediction had been fulfilled. The antibody developed in the blood of a patient (C. de B., male), who had received many transfusions for

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the treatment of an obscure anemia. He was extremely cooperative and interested in our research and on several occasions came to Maryland from his home in Wisconsin for medical studies and to donate blood.

During the course of the next few months we found that the antibody in C. de B.'s blood reacted with inherited antigenic specificities on the low density lipoproteins. We termed this the Ag system; and it has subsequently been the subject of genetic, clinical, and forensic studies (*7*).

We continued to search for other precipitating systems in the serums of transfused patients on the principle that this approach had resulted in one significant discovery and that a further search would lead to other interesting findings. During my last year at Bethesda, Harvey Alter, a hematologist, came to work with us. We also had been joined by Sam Visnich, a former Navy jet fighter and commercial airlines pilot, who, during a slack period in aviation, came to work in our laboratory as a technician.

In 1963, we had been studying the serums of a group of hemophilia patients from Mt. Sinai Hospital in New York City, which had been sent to us by Richard Rosenfield, the director of the blood bank. Antibodies against the Ag proteins were not common in this group of serums, but one day we saw a precipitin band that was unlike any of the Ag precipitins. It had a different configuration, it did not stain readily with Sudan black (suggesting a low lipid content compared to the Ag precipitin), but it did stain red with azocarmine, indicating that protein was a major component. There was a major difference in the distribution of the serums with which the transfused hemophilia patient reacted. Most of the antiserums to Ag reacted with a large number (usually about 50 to 90 percent of the panel serums), but the serum from the hemophilia patient reacted with only 1 of 24 serums in the panel, and that specimen was from an Australian aborigine (*8*, *9*). We referred to the reactant as Australia antigen, abbreviated Au. The original Australian serums had been sent to us by Robert Kirk. We subsequently went to Western Australia to collect and test a large number of additional serums.

We then set out to find out why a precipitin band had developed between the serum of a hemophilia patient from New York and that of an aborigine from Australia. At the outset we had no set views on where this path might lead, although our investigation was guided by our prior experience with the Ag polymorphism. In preparing this "history" of the discovery of antigen Au, I constructed an outline, based on a hypothetico-deductive structure, showing the actual events that led to the discovery of the association of Au with hepatitis. From this it is clear that I could not have planned the investigation at its beginning to find the cause of hepatitis B. This experience does not encourage an approach to basic research that is based exclusively on specific-goal-directed programs for the solution of biological problems.

The next step was to collect information on the distribution of Au and antibody to Au in different human populations and disease groups. We had established a collection of serum and plasma samples, later to develop into the blood collection of the Division of Clinical Research of the Institute for Cancer Research, which now numbers more than 200,000 specimens. The antigen was very stable; blood that had been frozen and stored for 10 years or more still gave strong reactions for Au. There were some instances in which blood had been collected from the same individual for six or more successive years. If the serums were positive on one occasion, they were in general positive on subsequent testings; if negative initially, they were consistently negative. Presence or absence of Au appeared, at least in the early experiments, to be an inherent characteristic of an individual.

We were able to use our stored serums for epidemiological surveys and, in a short time, accumulated a considerable amount of information on the worldwide distribution of Au. It was very rare in apparently normal populations of the United States; only 1 of 1000 serums tested was positive. However, it was quite common in some tropical and Asian populations (for example, 6 percent in Filipinos from Cebu, 1 percent in Japanese, and 5 to 15 percent in certain Pacific Ocean populations). We will come back to a consideration of the hypothesis that was generated from this set of epidemiologic observations after consideration of an interesting disease association discovered at about the same time.

Visnich had been asked to select from our collection the serums of patients who had received transfusions in order to search for more antiserums to Au. He decided, however, to use them both as potential sources of antibody and also in the panels against which antiserums to Au were tested. Included among the transfused serums were specimens from patients with leukemia who had recieved transfusions. A high frequency of Au, rather than antiserums to Au, was found in this group. We subsequently tested patients with other diseases and found Au only in transfused patients.

On the basis of these observations we made several hypotheses. Although they sound like alternative ones, they in fact are not; and, over the course of subsequent years, in a sense, all of them have been supported and are still being tested.

One hypothesis stated that, although Au may be rare in normal populations, individuals who have Au are more likely to develop leukemia than are individuals who do not have the antigen. That is, there is a common susceptibility factor which makes it more likely for certain people both to have Au and to develop leukemia. We also suggested that Au might be related to the infectious agent (virus) which is said to be the cause of leukemia.

A corollary of the susceptibility hypothesis is that individuals who have a high likelihood of developing leukemia would be more likely to have Au. Down's syndrome (Mongolism) patients are more likely to develop leukemia than are other children; estimation of the increased risk vary from 20 to 2000 times that of children without Down's syndrome. I had, in 1964, moved to the Institute for Cancer Research in Philadelphia to start its Division of Clinical Research. While there we tested the serums of Down's syndrome patients resident in a large institution and found that Au was very common in this group (approximately 30 percent were Au positive); the prediction generated by our hypothesis was fulfilled by these observations, a very encouraging finding (*10*). The presence of the antigen in people living closer to Philadelphia also made it possible to study persons with Au more readily. Until this time, all the individuals with Au who had been identified either lived in Australia, or some other distant place, or were sick with leukemia.

Down's syndrome patients were admitted to the Clinical Research Unit (located in our sister institution, Jeanes Hospital) for clinical study. We found again that the presence or absence of Au seemed to be a consistent feature of an individual. If Au was present on initial testing, then it was present on subsequent testing; if absent initially, it was not found later. In early 1966 one of our Down's syndrome patients, James Bair, who had originally been negative, was found to have Au on a second test. Since this was an aberrant finding we admitted him to the Clinical Research Unit. There was no obvious change in his clinical status. Because he apparently had devel-

oped a "new" protein, and since many proteins are produced in the liver we did a series of "liver chemistry" tests. These showed that between the first testing (negative for Au) and the subsequent testing (positive for Au) this patient (J.B.) had developed a form of chronic anicteric hepatitis.

On 28 June 1966, the day of J.B.'s admission to the Clinical Research Unit, my colleague, Alton Sutnick, wrote the following dramatic note in the patient's chart.

> SGOT [serum glutamic oxaloacetic transaminase] slightly elevated! Prothrombin time low! We may have an indication of [the reason for] his conversion to Au+.

His prediction proved correct. The diagnosis of hepatitis was clinically confirmed by liver biopsy on 20 July 1966, and we now began to test the hypothesis that Au was associated with hepatitis (*11*). First, we compared the transaminase (SGPT, serum glutamic pyruvic transaminase) levels in males with Down's syndrome who had Au and those who did not. The SGPT levels were slightly but significantly higher in the Au(+) individuals. Second, we asked clinicians in Pennsylvania to send us blood samples from patients with acute hepatitis. W. Thomas London and others in our laboratory soon found that many hepatitis patients had Au in their blood early in their disease, but the antigen usually disappeared from their blood, after a few days or weeks. Another dramatic incident occurred which added to our urgency in determining the nature of the relation of Au to hepatitis. Barbara Werner (now Dr.) was the first technician in our laboratory in Philadelphia. She had been working on the isolation of Au by extensions of the methods developed by Alter and Blumberg during the earlier work in Bethesda. Early in April of 1967 she noticed that she was not in her usual good state of health. She was well aware of our observations that Au was related to hepatitis and, one evening, tested her own serum for the presence of Au. The following morning a faint but distinct line appeared, the first case of viral hepatitis diagnosed by the Au test. She subsequently developed icteric hepatitis and, fortunately, went on to a complete recovery.

By the end of 1966 we had found that Au was associated with acute viral hepatitis. In our published report (*10*) we said:

> Most of the disease associations could be explained by the association of Au(1) with a virus, as suggested in our previous publications. The discovery of the frequent occurrence of Au(1) in patients with virus hepatitis raises the possibility that the agent present in some cases of this disease may be Australia antigen or be responsible for its presence. The presence of Australia antigen in the thalassemia and hemophilia patients could be due to virus introduced by transfusions.

That is, we made the hypothesis that Au was (or was closely related to) the etiologic agent of "viral" hepatitis, and we immediately set about to test it. Our original publication did not elicit wide acceptance; there had been many previous reports of the identification of the causative agent of hepatitis and our claims were naturally greeted with caution. Indeed, an additional paper on Australia antigen and acute viral hepatitis (*11*) which extended our findings published in 1967 was initially rejected for publication on the grounds that we were proposing another "candidate virus" and there were already many of these.

Confirmation of our findings and the first definitive evidence on the relation of Au to posttransfusion hepatitis came soon. Kazuo Okochi, then at the University of Tokyo, had followed a line of inquiry very similar to ours. He had started with the investigation of antiserum to Ag (lipoprotein), and we had corresponded on this subject. Okochi then found an antiserum in a patient with chronic myelogenous leukemia which was different from the precipitins in antiserum to Ag. He also found that it was associated with liver damage. During my several field trips to Japan, I had lectured on Australia antigen. Okochi sent the unusual antiserum to us to compare with antiserum to Australia antigen; we found that they were identical. He confirmed our finding of the association of Au with hepatitis and then proceeded to do the first definitive study of transfusion. He found that Au could be transmitted by transfusion and that it led to the development of hepatitis in some of the people who received it, and that some transfused patients developed antibody to Au (*12, 13*). The Au-hepatitis association was also confirmed in 1968 by Alberto Vierucci (*14*) who had worked in our laboratory and Alfred Prince (*15*).

We had made some preliminary observations in Philadelphia in collaboration with John Senior of the University of Pennsylvania on the transfusion of donor blood which was found to contain Au. We then developed a protocol for a controlled, long-term study to determine whether donor bloods which had Au were more likely to transmit hepatitis than those which did not. In 1969 we heard from Okochi that he had already embarked on similar transfusion studies. In June of that year he visited our laboratory in Philadelphia and showed us his data. These, in his (and our) opinion, demonstrated with a high probability that donor blood containing Australia antigen was much more likely to transmit hepatitis than donor blood which did not contain the antigen. [Similar studies were later done by Dr. David Gocke (*16*) in the United States and the same conclusions were reached.] We immediately stopped the experimental study and established the practice of excluding donor bloods with Australia antigens in the hospitals where we were testing donor units. This was a dramatic example of how technical information may completely change an ethical problem. Before Okochi's data had become available it was a moral necessity to determine the consequences of transfusing blood containing Australia antigen; and it had to be done in a controlled and convincing manner since major changes in blood transfusion practice were consequent on the findings. As soon as the conclusion of Okochi's well-controlled studies were known to us, it became untenable to administer donor blood containing Australia antigen. *Autres temps, autres moeurs.*

It was, however, possible to do a study to evaluate the efficacy of Au screening on posttransfusion hepatitis with the use of historical controls. Senior and his colleagues had completed an analysis of posttransfusion hepatitis in Philadelphia General Hospital before the advent of screening and found an 18 percent frequency of posttransfusion hepatitis. In the fall of 1969, we started testing all donor blood and excluding Au positive donors. Senior and others undertook a similar follow-up study 1 year after the screening program was in progress. They found that the frequency of posttransfusion hepatitis had been reduced to 6 percent, a striking improvement (*17*).

The practical application of our initially esoteric finding had come about only 2 years after the publication of our paper on the association between Au and hepatitis (*10*). In retrospect, one of the major factors contributing to the rapid application of the findings was the simplicity of the immunodiffusion test. Another was our program of distributing reagents containing antigen and antibody to all investigators who requested them. We did this until this function was assumed by the National Institutes of Health.

After the confirmation of the association of hepatitis with Australia antigen, a large number of studies were published, and, in a relatively short time the routine use of the test in blood banks became essentially universal in the United States and many other countries. It has been es-

timated that the annual saving resulting from the prevention of posttransfusion hepatitis amounts to about half a billion dollars in the United States.

Virology

Virological methods (that is, tissue culture, animal inoculation, and others) had been used for many years prior to our work to search for hepatitis virus, but had not been very productive. Our initial discoveries were based primarily on epidemiologic, clinical, and serological observations. Here, I will try to review the early virology work from our laboratory [Robinson and Lutwick have reviewed much of the recent work (*18*)].

Bayer *et al.* (*19*), using the isolation techniques initially introduced by Alter and Blumberg (*20*), examined isolated Au with the electron microscope. They found particles about 20 millimeters in diameter which were aggregated by antiserum to Au. There were also sausage-like particles of the same diameter, but much elongated (Figs. 1 and 2). Subsequently Dane, Cameron, and Briggs identified a larger particle about 42 mm in diameter with an electron-opaque core of about 27 mm (*21*). It is probable that this represents the whole virus particle. Both the 20-mm and 42-mm particles contain Australia antigen on their surfaces and this is now termed hepatitis B surface antigen (HBsAg). The surface antigen can be removed from Dane particles by the action of detergents to reveal the core which has its own antigen, hepatitis B core antigen (HBcAg). Antibodies to both these antigens (anti-HBs, anti-HBc) can be detected in human blood. The surface antigen can be detected in the peripheral blood by the methods we initially introduced and by more sensitive methods that have since been developed. Anti-HBs is often found in the peripheral blood after infection and may persist for many years. It may also be detected in people who have not had clinical hepatitis. Anti-HBc is usually associated with the carrier state (that is, persistent HBsAg in the blood) but may occur without it. HBcAg itself has not been identified in the peripheral blood. Anti-HBc is also found commonly during the active phase of acute hepatitis, before the development of anti-HBs but in general does not persist as long as anti-HBs.

DNA has been isolated from the cores of Dane particles and is associated with a specific DNA polymerase. Robinson and Lutwick have shown that the DNA is in the form of double-stranded rings (*18*). Jesse Summers, Anna O'Connell, and Irving Millman of our institute have confirmed these findings and provided a model for the molecule, which appears to have double- and single-stranded regions (Fig. 3) (*22*).

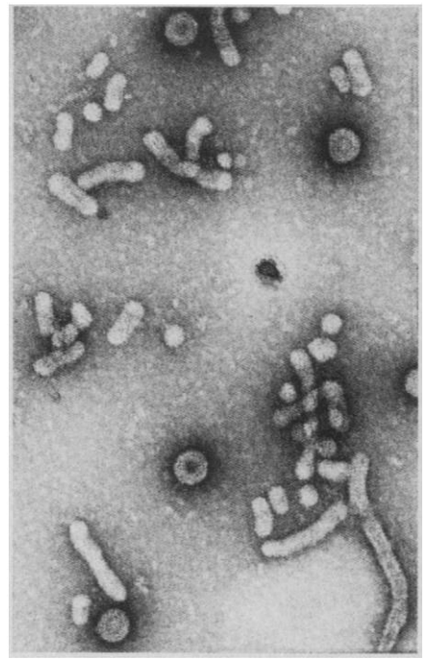

Fig. 1. Electron micrograph showing the several kinds of particles associated with hepatitis B virus (see Fig. 2). Magnification, × 90,000. [Electron micrograph prepared by E. Halpern and L. K. Weng]

By means of immunofluorescent and electron microscope studies, hepatitis B core particles have been identified in the nuclei of liver cells of infected patients; HBsAg is found in the cytoplasm. It is thought that assembly of the large particles occurs in the cytoplasm and that large and small particles (surface antigen only) emerge from the cells and eventually find their way to the peripheral blood.

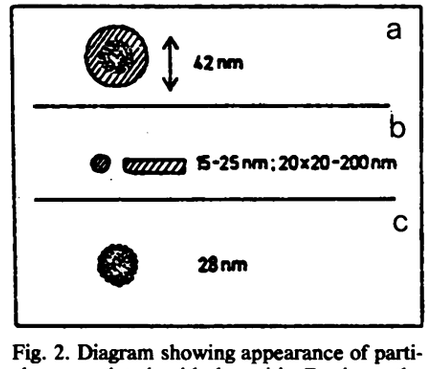

Fig. 2. Diagram showing appearance of particles associated with hepatitis B virus, the large or Dane particle (a), the small surface antigen particle, and the sausage-shaped particle (b), and the core of the Dane particle (c). [Adapted from E. Lycke, *Lakartidningen* 73, 3743 (1976)]

Vaccine Against Hepatitis B

In 1968 we were informed by the federal government, which provided most of the funds for our work, that they would like to see applications of the basic research they had funded for many years. It occurred to us that the existence of the carrier state provided an unusual method for the production of a vaccine. We presumed that the very large amounts of HBsAg present in the blood could be separated from any infectious particles and used as an antigen for eliciting the production of antibodies. The antibodies in turn would protect against infection with the virus. Irving Millman and I applied separation techniques for isolating and purifying the surface antigen and proposed using this material as a vaccine. To our knowledge, this was a unique approach to the production of a vaccine; that is, obtaining the immunizing antigen directly from the blood of human carriers of the virus. In October 1969, acting on behalf of the Institute for Cancer Research, we filed an application for a patent for the production of a vaccine. This patent was subsequently (January 1972) granted in the United States and other countries (*23*).

There are observations in nature which indicate that antibody against the surface antigen is protective. In their early studies, Okochi and Murakami observed that transfused patients with antibody were much less likely to develop hepatitis than those without it (*13*). In a long-term study, London *et al.* (*24*) has shown that patients on a renal dialysis unit, and the staff who served them, were much less likely to develop hepatitis if they had antibody than if they did not (Fig. 4). Lustbader has used these data to develop a statistical method for rapidly evaluating the vaccine (*25*).

There have now been several animal and human studies of the vaccine, and the results are promising (*26*). It should be possible to determine the value of the vaccine within the next few years.

Variation in Response to Infection with Hepatitis B

A physician is primarily interested in how a virus interacts with humans to cause disease. But this is only part of the world of the virus. Our introduction to studies on hepatitis B was not through patients with the disease, but rather through asymptomatic carriers and infected individuals who developed antibody. Therefore, many of our investigations have been of infected but apparent-

ly healthy people. There are a variety of responses to infection:

1) Development of acute hepatitis proceeding to complete recovery. Transient appearance of HBsAg and anti-HBc. Subsequent appearance of anti-HBs which may be persistent.

2) Development of acute hepatitis proceeding to chronic hepatitis. HBsAg and associated anti-HBc are usually persistent.

3) Chronic hepatitis with symptoms and findings of chronic liver disease not preceded by an episode of acute hepatitis. HBsAg and anti-HBc are persistent.

4) Carrier state. Persistent HBsAg and anti-HBc. Carrier is asymptomatic but may have slight biochemical abnormalities of the liver.

5) Development of persistent anti-HBs without detectable HBsAg or symptoms.

6) Persistent HBsAg in patients with an underlying disease often associated with immune abnormalities, that is, Down's syndrome, lepromatous leprosy, chronic renal disease, leukemia, primary hepatic carcinoma. Usually associated with anicteric hepatitis.

7) Formation of complexes of antigen and antibody. These may be associated with certain "immune" diseases such as periarteritis nodosa.

Family Studies

In our first major paper on Australia antigen (*9*) we described family clustering of Au in a Samaritan family from Israel that had been studied by the anthropologist Batsheva Bonne. From it we inferred the hypothesis that the persistent presence of Au was inherited as a simple autosomal recessive trait. The genetic hypothesis has proved to be very useful not in the sense that it is necessarily "true" [exceptions to the simple hypothesis were noted by us and others very soon (*27*)], but because it has generated many interesting studies on the family distributions of responses to infection with hepatitis B. We suggested that hepatitis virus may have several modes of transmission. It can be transmitted horizontally from person to person similar to the transmission of "conventional" infectious agents. This is seen in the transmission of hepatitis B virus (HBV) by transfusion. Other forms of direct and indirect horizontal transmission exist; for example, by sputum, by the fecal-oral route, and, perhaps, by hematophagous insects (see below). It has even been reported that it has been spread by

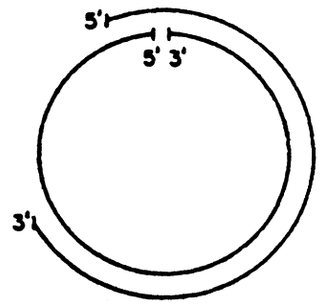

Fig. 3. Structure of the DNA extracted from Dane particles proposed by Summers *et al.* (*22*). The position of the gaps in the single strands and the location of the 5′ and 3′ ends are shown.

computer cards (*28*), an extraordinary example of adaptation by this ingenious agent! HBV may also be transmitted vertically. If the genetic hypothesis were sustained, then it would imply that the capacity to become persistently infected is controlled (at least in part) as a Mendelian trait. The data are also consistent with the notion that the agent could be transmitted with the genetic material; that the virus could enter the nucleus of its host and in subsequent generations act as a Mendelian trait. The data also suggest a maternal effect. A reanalysis of our family data showed that in many populations more of the offspring were persistent carriers when the mother was a carrier than when the father was a carrier. Many investigators have now shown that women who have acute type B hepatitis just before or during delivery or women who are carriers can transmit HBV to their offspring, who then also become carriers. This may be a major method for the development of carriers in some regions, for example, Japan. Interestingly, this mechanism does not appear to operate in all populations. This

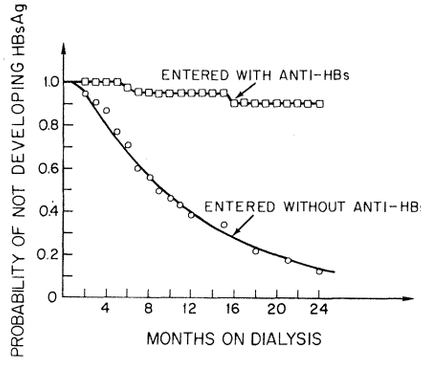

Fig. 4. Probability of not developing HBsAg for patients admitted to a renal dialysis unit with and without anti-HBs. The patients with anti-HBs are relatively well protected while those without antibody are very likely to develop infection. [Adapted from Lustbader *et al.* (*25*)]

suggests that some aspects of delivery and parent-child interaction, differing in different cultures, as well as biological characteristics may affect transmission.

The family is an essential human social unit. It is also of major importance in the dissemination of disease. A large part of our current work is directed to an understanding of how the social and genetic relations within a family affect the spread of hepatitis virus.

Host Responses to Human Antigens and HBV: Kidney Transplantations

London, Jean Drew, Edward Lustbader, and others in our laboratory have undertaken an extensive study of the patients in a large renal dialysis unit in Philadelphia (*24*, *29*, *30*). The renal patients can be characterized on the basis of their responses to infection with hepatitis B. Patients who develop antibody to HBsAg are significantly more likely to reject transplanted kidneys that are not completely matched for HLA antigens than patients who become carriers of HBsAg (Fig. 5) (*30*). Since many of the patients became exposed to hepatitis B while on renal dialysis, their response to infection can be determined prior to transplantation. In this patient population there is a significant correlation between development of anti-HBs and the subsequent development of antibodies to HLA after transplantation. We have also found a correlation between the development of antibody to HLA and anti-HBs in transfused hemophilia patients and in pregnant women. Hence, there appears to be a correlation between the response to infection with HBV and the immunologic response to polymorphic human antigens in tissue transplants. Further, from preliminary studies, it appears that donor kidneys from males are much more likely to be rejected by patients with anti-HBs than by patients without anti-HBs. These differences were not observed when the kidneys were from female donors. London is now extending his observations to other transplants, in particular, bone marrow, to determine whether a similar relation exists.

Sex of Offspring and Fertility of Infected Parents

In many areas of the world, including many tropical regions (for example, the Mediterranean, Africa, southeast Asia, and Oceania) the frequency of HBsAg carriers is very high. In these regions,

most of the inhabitants will eventually become infected with HBV and respond in one of the several ways already described. Our family studies and the mother-child studies show that there is a maternal effect. Jana Hesser (then a graduate student in anthropology working in our laboratory) and Ioanna Economidou, Stephanos Hadziyannis, and our other Greek colleagues collected information on the sex of the offspring of parents in a Greek town in southern Macedonia. In this community the probability of infection with HBV is very high and a majority of the parents had evidence of infection, that is, detectable HBsAg or anti-HBs (or both) in their blood. It was found that if either parent was a carrier of HBsAg there were significantly more male offspring than in other matings (*31*). Using the Greek data and additional data from Mali in West Africa in subsequent studies, London, Drew, and Veronique Barrois (a postdoctoral trainee from Paris) have found that there is a deficiency of male offspring when parents have anti-HBs and that this may be a consequence of differential male mortality during the period in utero (*32*). This had led London and his colleagues to test the hypothesis that anti-HBs has specificities in common with Hy or other histocompatibility antigens determined by genes on the Y chromosome. If these observations are supported by additional studies, then HBV may have a significant effect on the composition of populations in places where it is common, which includes the most populous regions of the world. The ratio of males to females in a population has a profound effect on population size as well as on the sociology of the population. This connection of anti-HBs with sex selection may also explain why there is a greater likelihood of rejection of male kidneys by renal patients with anti-HBs, and indicate how kidneys can be better selected for transplantation. Pregnancy and transplantation of organs have certain immunologic features in common. Rejection of male kidneys and "rejection" of the male fetus may be mediated by similar biological effects.

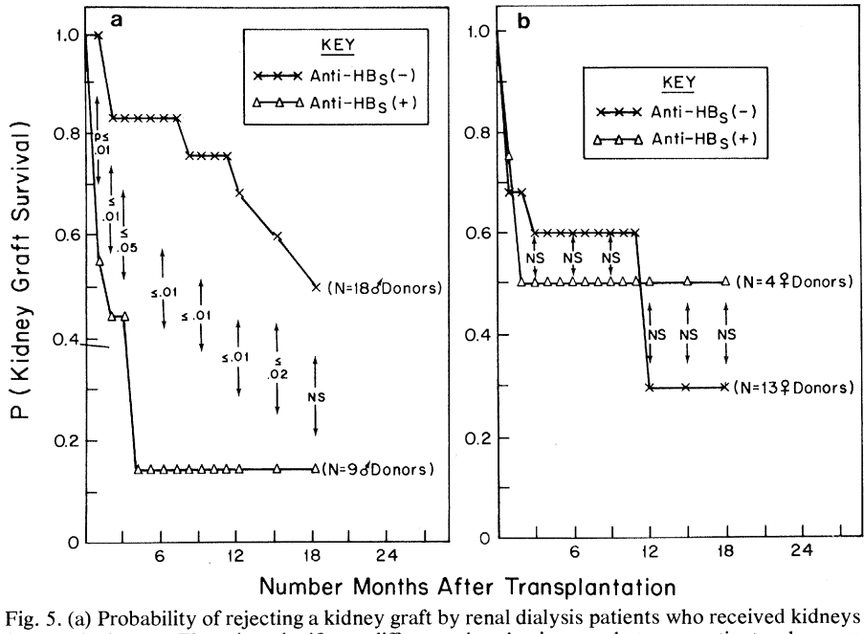

Fig. 5. (a) Probability of rejecting a kidney graft by renal dialysis patients who received kidneys from male donors. There is a significant difference in rejection rate between patients who were carriers and those who developed anti-HBs (*30*). (b). Probability of rejecting a kidney graft by renal dialysis patients who received kidneys from female donors. There is no difference in the rejection rates between the two groups of patients (*30*).

Table 1. Frequency of HBsAg, anti-HBc, and anti-HBs in primary hepatic carcinoma (PHC) and controls in Senegal and in Mali, West Africa. Abbreviations: RIA, radioimmunossay; *P* is the two-tailed probability obtained from Fisher's Exact Test. [Adapted from Larouzé *et al.* (*37*)]

Test	Patient				Control				
	Number tested	+	−	Percent positive	Number tested	−	+	Percent positive	*P*
				Senegal PHC					
HBsAg RIA	39	31	8	79.4	53	6	47	11.3	4×10^{-11}
Anti-HBc	39	35	4	89.7	58	16	42	27.6	1×10^{-9}
Anti-HBs	39	8	31	20.5	58	26	32	44.8	0.02
Total exposed	39	37	2	94.8	58	38	20	65.1	8×10^{-4}
				Mali PHC					
HBsAg RIA	21	10	11	47.6	38	2	36	5.2	4×10^{-4}
Anti-HBc	20	15	5	75.0	40	10	30	25.0	5×10^{-4}
Anti-HBs	21	8	13	38.0	40	17	23	42.5	0.95
Total exposed	21	19	2	90.4	40	25	15	62.0	0.02

Primary Hepatic Carcinoma

The project with which we are most concerned at present is (i) the relation of hepatitis B to primary hepatic carcinoma (PHC), and (ii) methods for the prevention of the disease. PHC is the most common cancer in men in many parts of Africa and Asia. For many years investigators in Africa including Payet *et al.* (*33*), Davies (*34*), and Steiner *et al.* (*35*) have suggested that hepatitis could be the cause of PHC. With the availability of sensitive tests for Australia antigen it became possible to test this hypothesis; it has now been established that there is a striking association of hepatitis B with PHC (*36, 37*) (Table 1). In our studies in Senegal and Mali we found that essentially all the patients had been infected with HBV and that most had evidence of current infection (presence of HBsAg or anti-HBc, or both). Ohbayashi and his colleagues (*38*) had reported several families of patients with PHC in which the mothers were carriers. In our study in Senegal (*39*), Bernard Larouzé and others found that a significantly larger number of mothers of PHC patients were carriers of HBsAg compared with controls, and that none of the fathers of the cases had anti-HBs. In control families, on the other hand, 48 percent of the fathers developed antibody (Table 2). The hypothesis we have made is that, in some families, children will be infected by their mothers, either in utero, at the time of birth, or shortly afterward during the period when there is intimate contact between mother and children. In some cases, the infected child will proceed through several stages to the development of PHC. At each stage, only a fraction of the infected individuals will proceed to the next stage, and this will depend on other factors in the host and

in the environment. The stages include retention of the antigen (carrier state), development of chronic hepatitis, development of cirrhosis and finally, development of PHC (Fig. 6). We are currently testing this hypothesis in prospective studies in West Africa (*37*). If it is true, then prevention of PHC could be achieved by preventing infection with HBV, and the vaccine we have introduced, in association with appropriate public health measures, could reduce the amount of infection. This might also involve the use of γ-globulin in the newborn children of carrier mothers, and such studies are now being conducted by Beasley and his colleagues in Taipei. We are now considering the appropriate strategies that might be used to control hepatitis infection and, perhaps, cancer of the liver.

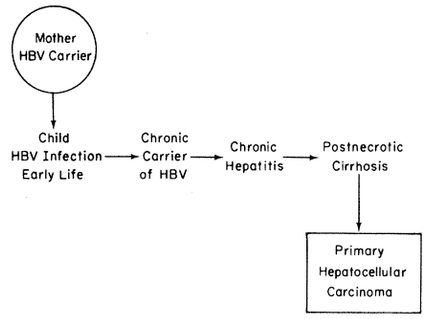

Fig. 6. Scheme for the pathogenesis of primary hepatic carcinoma, showing the sequence of stages leading to PHC.

Transmission by Insects

HBsAg has been detected by several investigators including Prince *et al.* (*40*), Smith *et al.* (*41*), Muniz and Micks (*42*), and others in mosquitoes collected in the field in areas where HBsAg is common in the human population. In 1971, we collected mosquitoes in Uganda and Ethiopia and found Au antigen in individual mosquitoes (*43*). In more extensive studies in Senegal, we found a field infection rate of about 1 in 100 for *Anopheles gambiae* and also identified the antigen in several other species of mosquitoes (*44*). It is not known whether HBV replicates in mosquitoes, but it has been reported that it can be detected in mosquitoes many weeks after feeding and it has been found in a mosquito egg. Feeding experiments have been conducted with the North American bedbug (*Amex lectulorius*); these studies show that this insect can also carry the antigen (*45*). William Wills, in our laboratory, has found a very high infection rate ($\sim$ 60 percent) in the tropical bedbug *Cimex hemipterus* collected from the beds of individuals known to be carriers of hepatitis B (*46*). Bedbugs could transfer blood (and the virus) from one occupant of a bed to another. If it is in fact a vector of hepatitis, then it could provide a frequent nonvenereal (and unromantic) form of connubial spread. It may also provide a means for transmission from mother (or father) to young children who may share the parents' bed in early life; and this would be related to the child-rearing practices of a community.

Insect transmission may be important in the program for the control of hepatitis B infection and for the prevention of chronic liver disease and primary hepatic carcinoma. An understanding of the role of insects in the spread of infection, particularly its transmission from mother to children, would help in designing effective strategies for control.

Hepatitis B as a Polymorphism

The original discovery of hepatitis B resulted from the study of serum antigen polymorphisms. Its identification as an infectious agent does not diminish the value of this concept. It is useful to view infection with HBV not only as a "conventional" infection but also as a transfusion or transplantation reaction; our studies on renal transplantation are an example of this.

HBV appears to have only a small amount of nucleic acid, probably only sufficient to code for a few proteins. Much of the coat (and possibly other portions of the virus) could be produced by the genes of the host. Millman and his colleagues found that the surface antigen contains material with antigenic specificities in common with serum proteins including IgG, transferrin, albumin, beta-lipoprotein, and others (*47*). If this is true, then the antigenic makeup of the virus would be, at least in part, a consequence of the antigenic characteristics of the host from whence it came; and this, as suggested by our sex studies, may include male antigens. In our discussion of the "Icron" concept (a name we introduced which is an acronym on the Institute for Cancer Research) (*48*), we pointed out that the responses of the putative host to HBV may be dictated in part by the nature of the "match" between the antigens of the host and virus (that is, the virus acts as if it were a polymorphic human antigen). London *et al.* (*49*) and Werner and London (*50*) have described this in a review of these concepts. If person A is infected with HBV particles that contain proteins antigenically very similar to his own, then he will have little immunologic response and will tend to develop a persistent infection with the virus. On the other hand, if the proteins of the agent are antigenically different from his, he will develop an immune response to the virus (that is, anti-HBs) and will have a transient infection. During the course of infection in person A, new particles will be synthesized

Table 2. Frequency of HBsAg, anti-HBc, and anti-HBs in patients with primary hepatic carcinoma (PHC) and controls, and in the parents of patients and controls. The studies were conducted in Dakar, Senegal, West Africa. Abbreviations: ID, HBsAg by immunodiffusion; RIA, HBsAg by radioimmunossay. [Adapted from Larouzé *et al.* (*39*)]

Item	*N*	+	%+	*N*	+	%+	*P*
	Primary hepatic carcinoma (PHC)			*Controls*			
HBsAg(+)ID	28	9	32.1	28	5	17.9	0.35
HBsAg(+)RIA	28	22	78.6	28	16	57.1	0.15
Anti-HBc(+)	28	25	89.2	28	18	64.3	0.05
Anti-HBs(+)	28	7	25.0	28	18	64.3	6×10^{-3}
HBsAg(+), anti-HBc(+), or anti-HBs(+)*	28	27	96.4	28	26	92.9	0.99
	Mothers of PHC			*Mothers of controls*			
HBsAg(+) ID	28	15	53.6	28	3	10.7	1×10^{-3}
HBsAg(+) RIA	28	20	71.4	28	4	14.3	3×10^{-5}
Anti-HBc(+)	28	20	71.4	28	9	32.1	6.9×10^{-3}
Anti-HBs(+)	28	3	10.7	28	15	53.6	1×10^{-3}
HBsAg(+), anti-HBc(+), or anti-HBs(+)*	28	21	75.0	28	19	67.9	0.76
	Fathers of PHC			*Fathers of controls*			
HBsAg(+) ID	27	2	7.4	27	3	11.1	0.99
HBsAg(+) RIA	27	5	18.5	27	5	18.5	1.00
Anti-HBc(+)	27	5	18.5	27	8	29.6	0.52
Anti-HBs(+)	27	0	0	27	13	48.1	3×10^{-5}
HBsAg(+), anti-HBc(+), or anti-HBs(+)*	27	5	18.5	27	18	66.6	7×10^{-6}

*Any evidence of infection with HBV.

which contain antigenic characteristics of A. In turn, person A can infect person B and the same alternatives present themselves. If the relevant proteins of B are antigenically similar to the antigens of A and the antigens of the HBV produced by A, then B could develop a persistent infection. If they are different, then antibody can form, as described above. (A derivative of this hypothesis is that inflammatory disease of the liver is associated with the immune response to the infectious agent rather than solely with replication of the agent.) A further possibility is that the virus has complex antigens; that some may match the host and some may not and that both persistent infection and development of antibodies may occur. The persistent antigens and the antibody in the same individual would have different specificities, and this occurrence has been described (*51*).

This view of the agent as an Icron introduces an interesting element into the epidemiology of infectious agents in which not only the host and virus are factors, but also the previous host or hosts of the agent. If, in fact, the agent does replicate in insects (see above), the antigenic characteristics of previous human hosts may be affected by transmission through another species. This in turn might have an effect on the response of the next host.

Bioethics and the Carrier State

During the course of our work a number of bioethical questions have arisen (*52*). Experience has shown that these bioethical considerations cannot be separated from "science," that answers cannot be provided on a "purely scientific" ground, and that our technical knowledge is inseparably intertwined with bioethical concerns.

It has been recognized that hepatitis B may be transmitted by means other than transfusion, that is, by contact, fecal-oral spread, insects, and the like. With the introduction of the screening test, many carriers were identified. It is estimated that there are 1 million such carriers in the United States and more than 100 million in the world. This has led to a situation that may be unique in medicine. Although some carriers may be able to transmit hepatitis by means other than blood transfusion, this is probably not true for many (or most) carriers. There are studies which show that spread of infection from carriers in health care occupations to patients may not be common. At present there is no satisfactory method of identifying the infectious carriers although it appears that carriers with "e" antigen, an unusual antigen originally described by Magnius (*53*), are much more likely to transmit disease. Despite this, carriers have had professional and social difficulties. Health care personnel who are carriers have been told that they must leave their jobs. In some cases, carriers have changed their pattern of social behavior because of the fear that they might spread disease to people with whom they come in contact. What appeared to be happening was the development of a class of individuals stigmatized by the knowledge that some member of the "class" could transmit hepatitis.

The bioethical problems raised from the studies of hepatitis carriers can be viewed as a conflict between public health interests and individual liberty. When the risk to the public is clear, and the restrictions on personal liberties are small, there is little problem in arriving at appropriate regulations. For example, the transfusion of blood containing hepatitis B antigen is a disadvantage to the patient recipient and it has been stopped. The denial of the right to donate blood is not a great infringement of personal activity, and the individuals concerned and society have agreed to accept this moderate restriction. The problems raised by person-to-person transmission are more difficult. The extent of the hazard to the public is not clear, since it is not (now) possible to distinguish carriers who transmit disease from those who do not. On the other hand, if all carriers are treated as infectious, the hazards imposed on the carrier may be enormous, that is, loss of job and ability to continue in the same profession, restriction of social and family contacts, and others. What is clear is that for a very large number of carriers, the risk of transmitting hepatitis by person-to-person contact must be very small. All members of the carrier class should not be stigmatized because some can transmit hepatitis.

On a broader level, the ethical issue is raised as to the extent to which biological knowledge about individuals should impinge on daily lives. Is it appropriate to regulate the risks inherent in people living together and interacting with each other? An issue has been raised with respect to hepatitis because the test can be easily done and because millions of people are tested as part of blood donor programs. As a consequence of these tests, this particular group of carriers has been identified. There are carriers of other agents, some of them potentially more hazardous (such as staphylococcus or typhoid), and these carriers are not routinely tested and therefore not placed at a disadvantage.

It is hoped that many of these problems can be resolved by continued research into the nature of the hepatitis carrier state, and that carriers who have already been identified will not be jeopardized during this period when necessary information is not available.

A characteristic of many large-scale public health control programs is the emergence of problems that were not anticipated prior to the institution of the program. For example, the control of malaria has in many areas resulted in a markedly decreased infant mortality with a large increase in population. When this has not been accompanied by a concomitant increase in food production, the nourishment and well-being of the population have actually decreased.

With the availability of the serologic and environmental tests for hepatitis B, it is now possible to begin the design of control measures for this disease. If the hepatitis B vaccine is found to be effective, then it may also be of value in preventing the development of the carrier state. We are now attempting to investigate the biology of the hepatitis B agent to learn whether some of the consequences of control can be known before the program begins. An example already discussed is the possible effect of HBV infection on sex ratio. The role of the virus in the life of the insects in which it is found is not known, but may be profound; and there may be other effects on the ecology that are not now obvious.

We hope to continue the study of these broad problems to be as well prepared as possible when and if attempts are made to eliminate or decrease the frequency of the hepatitis B virus.

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NEWS AND COMMENT

Bakke Case: Question of Special Minority Admissions Programs

The preliminaries are ending for what many observers regard as the most important Supreme Court test of the principles of minority education since the 1954 Brown *v.* Board of Education decision, which ordered school desegregation. At issue is the special admissions program for minority students at the medical school of the University of California at Davis and, by implication, all preferential admissions programs for minorities in higher education.

In the current case, The Regents of the University of California *v.* Allan Bakke, the university is appealing a California state supreme court decision in favor of Bakke, who claimed that he was excluded from the Davis medical school because of a special minority admissions program that is constitutionally invalid. The specific complaint was that the program violates the equal protection clause of the Fourteenth Amendment.

The broad issue is that of "reverse discrimination," that is, of preferential treatment of minority students to compensate for the effects of past discrimination. (The groups usually included in this category are Blacks, Mexican-Americans, mainland Puerto Ricans, and Native Americans.)

Opponents of the special admissions programs argue that such programs amount to racial quotas and that they are illegal, unjust to those excluded, stigmatizing to those they assist, and racially divisive. Most of these opponents argue that the objectives of the special admissions programs are worthy but should be achieved by other means.

So intense has been the interest in the Bakke case that the Supreme Court, after docketing the case this spring, extended the usual period for the filing of friend-of-the-court briefs. More than 40 of the amicus curiae briefs had been submitted by the early-June deadline for briefs in support of the petitioner (the university). Briefs supporting the respondent (Bakke) will be accepted for 30 days after the deadline. The total number of briefs is expected finally to exceed the largest number in living memory—more than 50 in the case of Brown *v.* Board of Education.

The immediate context of the Bakke case is the effort of predominantly white professional schools to increase enrollment of minority students since the Civil Rights Act of 1964 prohibited discrimination on the basis of race, color, national origin, and sex in both public and private institutions of higher education. In the late 1960's, professional schools, which had low enrollments of minority students, almost universally instituted "affirmative action" programs to increase the number and percentage of students from minorities identified as suffering heaviest discrimination in the past.

Although such programs were implemented across the board at both the undergraduate and graduate levels, they were most conspicuous in the professional schools because of an unprecedented increase in competition for places. This was particularly true of medical and law schools and, to a lesser degree, of engineering schools. According to data published in a recent study of minority medical education* by Charles E. Odegaard, enrollment of selected minorities rose from 854 in 1968–69 to 4524 in 1975–76. In percentage terms, minority representation rose from 2.4 to 8.1

**Minorities in Medical Education* (Josiah Macy, Jr. Foundation, New York, 1977), $4.