In the view of most observers, the nitrogen measurement gives a more abundant primitive atmosphere. The Viking lander measured an enrichment of nitrogen-15 over nitrogen-14 that appears to be due to differential escape of the lighter isotope, caused by a photochemical process suggested 4 years ago by Michael McElroy at Harvard University. When the preferential escape of nitrogen-14 is related to the total amount of nitrogen outgassed, it points to a dense early atmosphere—especially if much of the nitrogen released long ago was trapped in nitrite and nitrate minerals. At a maximum, the nitrogen measurement indicates that the carbon dioxide atmosphere could have reached a pressure as great as the earth's (1 bar), and the water could have covered the planet to a depth of 200 meters, if all of both volatiles were released at once.

Thus, where the presumed water might be found and where the extra carbon dioxide is hidden are not idle questions. "It is clear that Mars must have an inventory of volatiles at least 20 times greater than what is presently observed in the atmosphere and the polar caps," says Fanale. The discovery of a large deposit of frozen carbon dioxide somewhere on the planet cannot yet be ruled out, but Fanale proposes that the most likely place to find the extra carbon dioxide is in the regolith, which may extend down to 1 km below the surface in his view. Carbon dioxide could be absorbed onto this material, which at present martian temperatures could function as a cold trap. In such a repository, the carbon dioxide could participate in a cycle of atmospheric changes that would increase the pressure during warm periods by a sort of feedback mechanism—warmth would release carbon dioxide, which would increase both pressure and temperature. The principal evidence for such a fluctuating climate on Mars is the layered appearance of the permanent polar cap.

A regolith model of bimodal climate oscillation would change more sluggishly than if the balance of the carbon dioxide were stored during cold periods in a solid chunk somewhere near the poles—as most often discussed before Viking. But a climate oscillation based on the regolith could nevertheless be operative if surface temperature increases persisted over a 100,000-year period, according to Fanale. This period is typical for the sources of heating that have been suggested as drivers for the postulated atmospheric instability. Among the heating phenomena that have been proposed are changes in the inclination of the planetary axis of rotation (obliquity) and changes of the intrinsic dynamics of the sun. Periodic tilting of the rotation axis, followed by a return to the "normal" position, would effectively increase the solar flux on Mars, particularly in polar regions. Periodic fluctuations of the intrinsic brightness of the sun, predicted by some solar models, would of course change the amount of heating by sunlight on all the planets.

The atmospheric evolution of a planet is a very complex process, and apparently one that only yields to careful, subtle analysis. Prior to Viking, the earth was the only example. Now geochemists have two planets to test atmospheric evolution, and dynamicists have two planets to test models of weather and climate. All observers agree that the Viking measurements have given atmospheric modelers exactly the levers they need for a consistent formulation of the outgassing of the planet. In a few months or a year, predicts Ichtiaque Rasool of NASA, the measurements of argon, krypton, xenon, and nitrogen will make the theories on the size of the primitive atmosphere converge to a consensus.

—WILLIAM D. METZ

# The 1976 Nobel Prize for Physiology or Medicine

During the week of 11 October the World Health Organization convened in Geneva a committee on viral hepatitis for the third time in 4 years. The rapid succession of meetings and reports is indicative of the progress being made in an important field of public health which had lain fallow for many years. In spite of intensive research efforts since World War II on the part of a few investigators supported almost totally by the U.S. Army Medical Research and Development Command through its committee on liver diseases, significant advances in hepatitis began only after the revelation that a recently discovered antigenic substance in blood, named Australia antigen, was specifically related to one form of liver infection, so-called serum hepatitis. Those of us in Geneva preparing the third WHO Technical Report on Viral Hepatitis were deeply pleased to learn that Baruch Blumberg had been awarded a share of the Nobel Prize for Physiology or Medicine for his discovery of the Australia antigen. Without knowledge of this antigen, productive meetings such as ours could not be taking place.

Baruch Blumberg, of the Institute for Cancer Research in Philadelphia, was awarded the prize "for his discovery concerning new mechanisms for the origin and dissemination of infectious diseases." His discovery of the Australia antigen ultimately became a major breakthrough in hepatitis research, for it permitted intensive study of the disease and of the nature of the viral agent, even though the virus itself has yet to be grown in culture in significant amounts.

Blumberg's work leading to this discovery began as a consequence of his interest in inherited polymorphisms of blood. He and a co-worker, A. C. Allison, hypothesized that patients receiving multiple transfusions would receive some serum proteins of a phenotype different from their own and would respond by producing antibodies. With the simple two-dimensional micro-Ouchterlony immunodiffusion technique, serums from multiply transfused patients were tested against a panel of serums from donors living in different geographic areas. One serum from a transfused patient possessed a precipitin (antibody) for some of the serums in the panel. This antiserum reacted with substances that seemed to comprise a system of inherited antigenic low-density $\beta$-lipoproteins.

Blumberg then began a search for additional antigen systems, and in 1963 two serums from multiply transfused American hemophiliac patients yielded a single precipitin line with only 1 of 24 serums in a test panel. The antigen in this one serum contained at most only a relatively small amount of lipid, which distinguished it from the serum $\beta$-lipoproteins. Since the reacting serum was obtained from an Australian aborigine, Blumberg named it Australia antigen. Subsequent studies by him and others revealed that it was relatively rare in healthy persons living in North American and West European communities but that it was frequently present in the blood of those living in many parts of Africa and Asia.

Since the Australia antigen was often found in the blood of leukemic patients, Blumberg first suggested that its presence might be of value in the early diagnosis of their disease. However, while studying a number of serums Blumberg and his colleagues found evidence that linked the antigen to viral hepatitis. Other investigators, notably A. M. Prince at

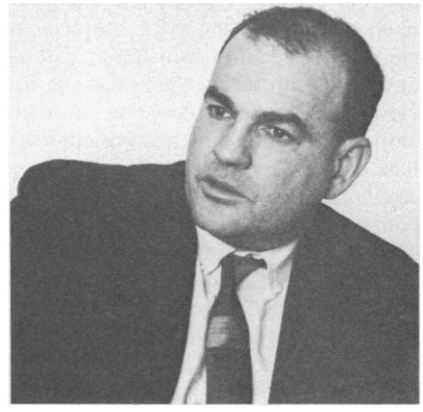
the New York Blood Center and K. Okochi at the Tokyo University Hospital, confirmed and extended these observations which established beyond doubt the close relationship between the antigen and serum hepatitis, a form of hepatitis characterized by a long incubation period. These observations were quickly corroborated by laboratories throughout the world, and a new era in hepatitis research began.

What was once called Australia antigen is now recognized as the surface antigen of the 42-nanometer double-shelled hepatitis B virus, which also contains a small DNA molecule and a DNA polymerase in its core. The surface antigen, now termed HBsAg, exists as a separate 20-nm sphere or in a filamentous form, and can be conventiently measured by highly sensitive and specific tests.

Hepatitis B virus poses an enormous public health problem. In the United States alone there are about 1 million carriers, and in the world about 100 million. Not only does the virus cause hepatitis type B, but evidence is accumulating that points to its role in primary carcinoma of the liver. Elimination of hepatitis B infection by vaccination, should that prove possible, might also reduce the occurrence of hepatocellular carcinoma. Such evidence of protection by a vaccine could come sooner than anticipated for any other type of cancer, since in areas of high HBsAg prevalence primary hepatoma is one of the leading causes of death.

The protective effect of postinfection antibodies to hepatitis B surface antigen for neutralizing hepatitis B virus has been established by a series of cooperative studies sponsored by the National Institutes of Health. This finding suggests that a vaccine capable of stimulating the body to produce such antibodies would be effective. Hitherto, all virus vaccines have been prepared from virus stocks that have been cultivated in tissue culture (for example, poliovirus in human or monkey cell cultures) or in suitable animal systems (for example, influenza in embryonated hen's eggs). Since hepatitus B virus has not yet yielded to tissue culture techniques, investigators have turned to carriers of HBsAg as a source of immunogen for vaccines. This is a departure for development of a viral vaccine, and must be approached with great care and adequate safeguards to be certain that some undesirable material, such as a piece of infectious nucleic acid, or a tissue antigen that might cause a harmful immunopathologic reaction in the liver or kidney, is not present in the vaccine.

In view of the above considerations, it has not yet been established whether the vaccine should be prepared from whole HBsAg or from its fractionated and purified antigenic components. Biochemical studies on purified material have revealed that HBsAg contains seven polypeptide subunits with molecular weights between 19,000 and 120,000. A carbohydrate moiety is associated with at least three of these polypeptides. In addition, two glycosphingolipids have been extracted which are structurally similar to the fucosylglycolipids, or blood group glycolipids. The glycoproteins and glycolipids are of particular interest since it has been reported that carbohydrate is associated with the antigenic activity of HBsAg.



Baruch Blumberg

Today, type B hepatitis remains an important public health problem, as evidence continues to mount that the type B virus is spread not only by parenteral route but by the oral route as well. Transmission of hepatitis B virus is either direct (physical contact between infectious and susceptible persons, as in household contacts) or indirect (when the virus is transmitted by contaminated material such as in transfusion of contaminated blood or in self-injection of drugs with contaminated needles).

Most recently particular attention is being paid to another antigen related to hepatitis B, HBeAg, first recognized in 1972 by L. O. Magnius and J. A. Espmark at the National Bacteriological Laboratory, Stockholm. Its importance lies in the growing realization that the presence of HBeAg in the blood of an HBsAg carrier indicates that the blood is highly infectious. On the other hand, HBsAg carriers who also possess antibodies against HBeAg are much less infectious. This is of particular importance in current attempts to produce a vaccine against hepatitis B from blood containing HBsAg.

As an outgrowth of Blumberg's discovery, the incidence of hepatitis B in transfused patients has been greatly reduced, the direct result of the expanded testing of donor blood for HBsAg. A small number of hepatitis B cases still results from transfusion of contaminated blood that was not adequately tested. However, currently the most frequent cause of transfusion hepatitis is believed to be another virus, presumably a type C hepatitis virus, since both hepatitis A and B viruses can be ruled out by sensitive tests for detecting these viruses and their antibodies. (Perhaps one of the other antigens discovered by Blumberg but not yet fully studied may lead to the control of the newly postulated hepatitis C virus.)

The above account of the pathways opened up by one man's discovery of a new antigen from a remote part of the world is ample proof—if any is needed—of the benefits that accrue to a society which is willing, hopefully through its elected representatives, to support creative scientists.

Baruch Blumberg has lived up to his name, which in Hebrew means "blessed." Through his vision and his labor, blessings in the form of better health will be brought to many of us.

JOSEPH L. MELNICK
*Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas 77030*

The late Joe Smadel would have been pleased to learn of the decision of the Nobel Committee of the Karolinska Institute to award part of the 1976 Prize for Physiology or Medicine to Daniel Carleton Gajdusek, for it was Smadel who first recognized Gajdusek's potential brilliance and helped secure his first job at the National Institutes of Health. Smadel, an associate director at NIH, attempted to focus Gajdusek's diverse interests, immense scientific knowledge, and considerable energy into a single area of pursuit. While no one has yet been able to accomplish this, Smadel's early efforts have apparently been somewhat successful.

Carleton Gajdusek is a man of many facets: virologist, anthropologist, linguist, comparative child behaviorist, and world traveler. He speaks six languages and numerous native dialects. Born 53 years ago in Yonkers, New York, Gajdusek earned degrees from the University of Rochester and Harvard Medical School before undertaking postdoctoral studies at the California Institute of Technology, Harvard University, Walter Reed Army Institute of Research, Pasteur Institute (Teheran), and the Walter and Eliza Hall Institute in Melbourne. It

was while working on immune mechanisms with Sir Macfarlane Burnet at the Hall Institute that Gajdusek had his first opportunity to travel to New Guinea and commence the investigations which would eventually lead to Stockholm.

In New Guinea Gajdusek met Vin Zigas, District Medical Officer of the Public Health Department in Port Moresby. Two years earlier Zigas had found a neurologic disorder in a tribe of cannibals which was killing 1 percent of the population each year. This disease, called kuru, interested Gajdusek to such an extent that he spent the next 10 months living among these natives, bartering axes and tobacco for bodies of kuru victims from which he removed tissues for pathologic, microbiologic, and toxicologic examination. During this time, Gajdusek made numerous journeys into the Eastern Highlands to study the people, their habits, and the geographic distribution of kuru. He kept detailed notes on all of these epidemiologic patrols, and it is a passage from one of these diaries, recorded on 6 September 1957, at a rest house in a village known as Uvai, which gives the greatest insight into Gajdusek's character and also into his concern for the people he was studying (Gajdusek has since adopted or taken as wards 16 boys from New Guinea and other Pacific islands, and he says he will use his Nobel Prize money to help educate them):

> I came into the Fore on March 14th for a brief visit. Kuru has now kept me in so-called "uncontrolled" regions for almost half a year, much of which time I have been out on patrol. I have abandoned my French and Russian authors; my correspondence, which has fallen to naught but the voluminous scientific exchange about Kuru and our three Kuru papers, has afforded me little time to follow world news, literature or home events for these six months. I am a bit shocked when I consider how little all this bothers me and how little is my anxiety to leave. I know full well that I shall be walking the streets of Paris, Rome, London and New York and Washington again and that from these places the New Guinea jungles and the "savages" are but remote museum pieces or subjects for arty cine films and literature—hardly the humans with whom I now live and sleep. To me they are, as were my friends of New Britain, among the warmest and closest friends I have had. I respect, admire and love them, and know that once I part from them, I may never see them or hear from them again. I am in no hurry. Kuru work, at any rate for the first field stage, is nearly done, and I must be on my way—long and devious though it may be.

While Gajdusek's New Guinea exploits were heroic and may never be quite equaled again, it is the unusual nature of kuru which continued to pique his interest and that of microbiologists all over the world. On returning to the United States in 1958, Gajdusek became

Daniel Carleton Gajdusek

a visiting scientist at NIH, and he and Zigas published the results of their considerable efforts. While extensive, these studies were unsuccessful in discovering a probable cause. Then, in 1959, William Hadlow of the Rocky Mountain Laboratory wrote a letter to *Lancet* in which he recognized pathologic similarities between kuru and a disease of sheep known as scrapie. Scrapie was known to be caused by a filterable agent that was transmissible to sheep but produced disease only after very long incubation periods of 1 year or greater. Five years earlier, an Icelandic veterinarian, Bjorn Sigurdsson, had labeled this type of diseases "slow virus infections" and set forth a number of criteria describing them. Because of scrapie's transmissibility, Hadlow suggested that brain suspensions from natives dead of kuru be inoculated into subhuman primates and that these animals be observed for an extended period of time. Gajdusek and his associates then succeeded in transmitting kuru to chimpanzees in 1963; they did the same for a second kuru-like condition, Creutzfeldt-Jakob disease, in 1968.

The transmission of Creutzfeldt-Jakob disease to subhuman primates demonstrated for the first time that a degenerative brain disease of man could result from a slow virus infection and that these diseases are not geographically limited artifacts of primative populations but can be found worldwide. From his position as chief of the Laboratory of Central Nervous System Studies in the National Insitute of Neurological and Communicative Disorders and Stroke, Gajdusek has championed the idea that although Creutzfeldt-Jakob disease is rare, killing an estimated 200 individuals a year in the United States, we may only be seeing the tip of the iceberg and that more common illnesses such as Alzheimer's disease, Pick's disease, Parkinsonism dementia, and Huntington's chorea may be caused by similar slow-acting agents.

However, this hypothesis is difficult to prove because these unusual neuropathic agents produce no specific antibody responses in their hosts, which makes comparative serologic studies impossible. This is further complicated by the fact that these agents have never been positively visualized and can only be detected by their ability to produce disease in susceptible animals after long incubation periods. Thus, standard diagnostic tests for more conventional viruses cannot be used. The failure to physically, chemically, or structurally identify these agents has been a most perplexing and exciting problem. All evidence suggests that scrapie and related agents are new forms of a replicating, biologically active microorganism heretofore unknown to animal virologists.

Equally as fascinating is the unorthodox way in which these agents interact with their hosts. Why are there no inflammatory or specific immune responses to these slowly progressive, lethal infections? Each experiment seems to raise more questions than it answers. Alan Dickinson of the Animal Breeding Research Organization in Edinburgh has convincingly shown that there exist many different subpopulations of scrapie agent and it is this finding which raises the two most compelling questions of all. Are there also subpopulations of the Creutzfeldt-Jakob disease agent capable of producing diverse pathologic reactions in humans, thereby substantiating Gajdusek's hypothesis?

One cannot write of Carleton Gajdusek without mention of his longtime colleague Clarence J. Gibbs, Jr. Their accomplishments on experimental studies of slow virus diseases are inseparable. While Gajdusek has been the driving force, it is Gibbs who provides the even keel necessary for implementation of protocols and execution of day-to-day detail needed for the continued productivity of any laboratory. Gajdusek would be the first to acknowledge Gibbs' invaluable contributions to their program.

The field of slow virus diseases caused by unconventional agents has come out of the shadows and the sunlight feels good. Waiting for long incubation periods and experiments that never seem to end will be a little more tolerable now, thanks to the honor bestowed on a unique individual.

RICHARD F. MARSH
*Department of Veterinary Science, University of Wisconsin, Madison 53706*