The Nobel prizes (3): Medicine

Antipodean . . .

Carleton Gajdusek's attainments stretch beyond virology. **Cedric Mims** outlines his work and assesses its significance.

CARLETON Gajdusek came into medical virology in the early 1950s and he soon developed a particular interest in the haemorrhagic fevers of the USSR and the Far East. His work on virus infections took him to many other parts of the world including South America, the Middle East and a number of Pacific Islands. Not content merely to investigate the viruses infecting a given population he also made extensive studies of the behaviour, development and language of the people. In all but name he became an anthropologist. During the 1960s he could be counted on to talk with authority not only about the exotic diseases occurring in peoples in remote corners of the earth, but also about aspects of their physical and cultural anthropology. In 1959, at the National Institute of Health in Bethesda, Maryland, he became simultaneously director of a programme for studying child growth and development in primitive cultures and director of the laboratories for slow, latent and temperate virus infections.

It was in 1957, during an expedition to the highlands of New Guinea, that he encountered the disease kuru, and together with Vincent Zigas, the local physician who already knew the disease, he brought kuru to the attention of the rest of the world. Kuru was a chronic neurological condition, progressive and fatal, affecting especially the cerebellum and occurring in a sharply localised area inhabited by the Fore tribe. In these people it was responsible for more than half the total deaths after infancy, and in some villages at least half the women were affected.

Initial thoughts about the role of local genes, local plant or other toxins, were dramatically swept away after Dr Hadlow, of the Rocky Mountain Laboratory, Montana, had pointed out that the brains of patients with kuru bore a histological resemblance to the brains of animals suffering from scrapie. Scrapie, another chronic degenerative neurological condition affecting sheep, was known to be transmissible experimentally from animal to animal, but only after an unusually long incubation period of a year or two. Gajdusek therefore flew refrigerated brains from patients with kuru to the Washington laboratory where in August 1963 his close colleague, Joe Gibbs, injected the brain suspensions into two chimpanzees. Twenty-one and thirty months later the injected animals were seen to sicken with a disease closely similar to kuru and their brains showed almost identical pathological changes.

The disease could be transmitted from chimpanzee to chimpanzee, in whom the average incubation period was 22 months, and in subsequent experiments various other primates were found to be susceptible. All the usual laboratory tests for microorganisms were negative, except for a number of chimpanzee viruses which were recovered and appeared to represent the normal viral flora of the brain. The transmissibility of the agent from animal to animal and its assay ($10^{7.5}$ infectious doses present per gram of brain) firmly established that kuru was caused by an infectious agent. But kuru, being closely similar in its properties to scrapie, was not a conventional virus and to this day its composition and mechanism of replication is unknown. For the first time therefore, a chronic neurological condition of man, in which there were no pathological or other signs of infection, had been shown to be due to a transmissible agent.

'It seems probable that we have still not gathered the full harvest of the discoveries made by Gadjusek'

Throughout this work and during his frequent visits to New Guinea, Gajdusek had both the opportunity and the energy to exercise his anthropological interests. As a result of this he wrote various monographs, produced films and contributed to paediatric journals. The marriage of virology and anthropology bore appropriate fruit when it became clear that the disease kuru in New Guinea was transmitted from person to person by cannibalism. The disappearance of cannibalism in this part of New Guinea has meant that kuru too has now almost disappeared.

Kuru is restricted to a small zone in the highlands of New Guinea, where a total of some 2,000 cases has been reported since its discovery in 1957. But the discoveries about kuru have sparked off a fresh approach to other chronic degenerative neurological conditions of man which are of unknown aetiology, such as amyotrophic lateral sclerosis and parkinsonian dementia. So far one of these conditions, called Creutzfeld Jacob disease, has been shown in Gajdusek's laboratory to be transmissible to primates and caused by a replicating infectious agent similar to kuru. Creutzfeld Jacob disease is rare, but the infectious agent has now been recovered from the brains of patients in five continents of the world. It seems quite likely that the neurological disease is the tip of the iceberg and reflects widespread sub-clinical infection.

AP

Carleton Gajdusek

At about the same time as the discovery of kuru, certain conventional viruses had been shown by others to be responsible for obscure and chronic neurological conditions. Measles virus was recognised as a cause of the rare disease subacute sclerosing panencephalitis, and JC virus, a new human papovavirus, came to be associated with progressive multifocal leucoencephalopathy. Once again the infectious agent was seen to persist in the body and cause a disease after a period of several years.

It is against this background that Gajdusek's work on kuru must be assessed. It is now firmly established that chronic diseases of man, especially neurological diseases, can arise as a result of the slow but relentless multiplication of certain infectious agents, sometimes referred to as "slow viruses", which cause disease many years after initial infection. The possible incubation period with kuru, for instance, is between 10 and 15 years. Much of the recent excitement in multiple sclerosis research arises from observations based

on this concept. It represents a great step forward in our understanding of disease and it seems probable that we have still not gathered the full harvest of the discoveries made by Gajdusek. These discoveries, moreover, may well prove to be of more than mere biological interest, because traditionally microbiology has moved from the recognition of an infectious aetiology to the development of a vaccine and thus to the prevention of the disease.

The agents responsible for kuru, Creutzfeld Jacob disease and scrapie pose major problems for the investigator. All assays and tests depend on the lengthy incubation period in experimental animals and it may take more than a year to learn the result of a single experiment. Other microbiologists would have shied away but Gajdusek's insight, patience and persistence have ensured that the infectious origin of kuru was discovered and the disease given an important place in our understanding. He has been the pioneer and the central authority in this area of biomedical research. His encyclopaedic memory, his familiarity with strange places and primitive peoples have generated many legends. He is the sort of man one might have expected to win a Nobel prize and at the same time it is both a surprise and a pleasure to find such a gentle and likeable man behind the legends. □

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A **Special Correspondent** describes the discovery made by Baruch Blumberg, 'one of the success stories of the century'

SURPRISE, suspense and success are the three indispensable ingredients cin a good detective story, and none of them is absent from the events which led up to the discovery and evaluation of Australia antigen, now usually known as hepatitis B antigen, or HB antigen.

The story starts nearly 20 years ago, when Dr Baruch Blumberg, one of the recipients of the 1976 Nobel Prize for Medicine, was at work on proteins in the blood. It is well known that humans show individual variation in the antigens, or blood group substances, on their red blood cells. Blumberg set out to detect and compare comparable substances in the plasma as opposed to those on the cells. Using as antisera specimens from patients who had received many transfusions, a reacting antigen was found in an Australian aborigine.

The surprises began when this was found to be widely, if unevenly, distributed in human blood throughout the world. The United States, where Dr Blumberg was working, was in fact relatively free from it, although a survey of patients revealed that cases of leukaemia, Down's syndrome (mongolism) and hepatitis figured among those who were positive. The question began to be asked: was this in fact not a simple protein antigen but a human leukaemia virus?

The possibility of being able to detect and study such a virus opened wide horizons—but it was now that the suspense began, because it quickly became unlikely that it was, in fact, a leukaemia virus. A common factor in leukaemia and Down's syndrome is altered cellular immunity; in addition, patients with leukaemia have many transfusions with a concomitant opportunity for acquiring hepatitis, and children with Down's syndrome (at least, those of them in institutions) are notoriously prone to hepatitis.

It was about this time that hepatitis B infection, acquired from transfused blood, broke upon the haemodialysis trade. The transmission of hepatitis B virus, undetectable by any means except the production of the disease in a patient, had always been a problem in blood transfusion and the use of blood products, but the disasters which overtook staff and patients in dialysis units had made it doubly urgent to find a means of recognition, a serological marker for the presence of the agent.

It is now well known how, during the late 1960s, it became clear that Australia antigen was such a marker—but was it, in fact, the hepatitis B virus? When examined by negative staining it did, so to speak, come to life, and at least some of the particles could be seen to be acceptable as virus. By now it has been possible to purify these particles, and to determine that they have double-stranded DNA and a DNA polymerase, and in fact to do many things with them except grow them in a laboratory system.

Many medical microbiologists must have hoped that this would give a clue to growing hepatitis B virus in a cell culture system, but so far they have been disappointed. However, this has not prevented the use of HB antigen to study the natural history of hepatitis B virus, to detect carriers, and, to detect antibodies in human serum, and this is where the third ingredient, a successful conclusion, comes in.

As a corollary, it is possible to prevent many cases of hepatitis B (post-transfusion and otherwise) and hence to make haemodialysis, blood transfusion, and the use of blood products infinitely safer. Unfortunately, there is still no conventional small laboratory animal, but the chimpanzee serves as a possible, if expensive, source and host. Even a vaccine has been prepared from HB-antigen-positive human blood, and even though its worth has yet to be assessed, there is little doubt about the effectiveness of the passive immunity conferred by the injection of concentrated, purified, specific anti-HB immunoglobulin.

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Baruch Blumberg

Although the final evaluation of HB antigen involved, in the end, many laboratories, the work all springs from the researches of one principal and primary investigator. Even if, by hindsight, the connection between the molecular genetics of polymorphism and the prevention of hepatitis B in haemodialysis units all over the world seems to involve a series of knight's moves in chess, the consequences of Blumberg's discovery, judged as a piece of preventive medicine, must rank as one of the success stories of the century. Perhaps in this respect it is as near as any previous award to Alfred Nobel's desire to reward those whose discoveries have been of benefit to mankind. □