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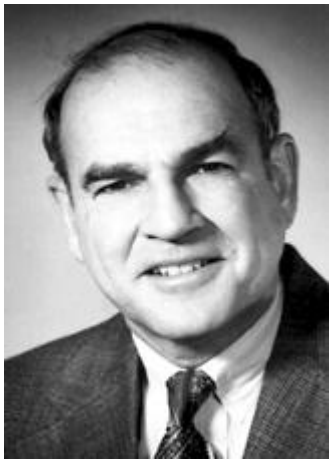
Nobel Prize in Medicines 1976



Baruch S. Blumberg

D. Carleton Gajdusek

The Nobel Prize in Physiology or Medicine 1976 was awarded jointly to Baruch S. Blumberg and D. Carleton Gajdusek "for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases"

The main interest regarding epidemic diseases has concerned different acute diseases at which symptoms appear days to weeks after the individual has been exposed to an infectious agent. Connected with the recovery from disease the infectious agent normally is eliminated from the body. However, certain diseases caused by infectious agents display a deviating pattern both with regard to the time interval between moment of infection and appearance of disease and further concerning the capacity of the body to eliminate the infectious agent. The prize winners of this year have clarified important new mechanisms for the appearance of persistent infections with certain infectious agents and for their spreading and causing of disease. Completely new principles for the behaviour of infectious diseases have been defined by analysis of two different types of diseases.

Baruch Blumberg was trained as a geneticist and studied the variation between certain types of proteins occurring in the blood of different individuals. In connection with

these studies he found the presence of a unique protein in the serum of a patient with hemophilia, who had received several transfusions, in tests against a serum collected from an Australian aborigin. This protein was called Australia antigen and was first suspected to be some kind of serum protein. However, during the years of 1966-68 Blumberg could prove that Australia antigen only appeared in connection with and in some cases after the special form of jaundice caused by infectious agents (hepatitis) which previously had been named inoculation or serum hepatitis. This disease today is called hepatitis B. It was known since about 1940 that there are two forms of hepatitis. Besides hepatitis B there occurs one infectious form, which today is called hepatitis A. Blumberg's discovery of Australia antigen was the starting point for an enormous development over a decade of our knowledge concerning hepatitis B infections. This development is impressive not the least with regard to the fact that the virus causing the disease still today can not be cultivated under laboratory conditions. This is normally assumed to be a prerequisite for the characterization of an infectious agent and the disease process which it may cause. Since his original discovery Blumberg has continued to be the leading figure within the field of hepatitis research. Important new knowledge within this field can be summarized in the following way:

Australia antigen, now called HB_s-antigen (s for surface) has been shown to represent the outmost structure of the virus, which causes hepatitis B infections However, HB_s-antigen normally occurs in serum as a small, independing particle without infectious activity. Hepatitis B virus represents a completely new group of viruses and distinguishes itself distinctly from the infectious agent causing hepatitis A.

Different variants of HB_s-antigen have been shown to occur which has allowed important epidemiological studies. It has been clarified that e g the epidemic occurring among cross country runners in Sweden in the beginning of the 1960ies was caused by a type of hepatitis B virus, which distinguishes itself from the virus which during the last decade has circulated among drug abusers.

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The infectious process in individuals, who have become infected has been shown to take one of several different courses. After either a symptomless infection or the appearance of clear-cut disease 60 to 160 days after infection the virus normally is removed from the organism. However about 10 % of all hospitalized patients in industrialized countries acquire a persistent (chronic) infection. This implies that in the society as a whole about 0.1% of all individuals are carriers of a hepatitis B virus infection. For unknown reasons the corresponding figure for certain developing countries is much higher, about 1 to 15 %. It has been estimated that in the whole world there is more than 100 million people who are chronically infected with hepatitis B virus.

These persons represent an important source for further spreading of the virus. It is known since a long time that transmission of the virus can occur in connection with different medical treatments e g blood transfusions. More recent data show that under certain circumstances also oral and genital transmission may occur and further that a pregnant woman may transmit the infection to her fetus. However, not all individuals who are chronically infected with hepatitis B virus are contagious.

Many carriers do not produce a complete infectious virus. By use of modern techniques it has been possible to distinguish those who are contagious and those who are not. Carriers who have a contagious form of the persistent infection show signs of liver damage, which may occasionally be of a serious nature, whereas other carriers appear healthy.

Today all blood donors are examined to determine a possible occurrence of a persistent hepatitis B virus infection. By elimination of all detectable carriers the frequency of hepatitis caused by blood transfusion has been reduced with at least 25%. The fact that the reduction is not still greater partly is due to that besides hepatitis A and B, there appears to be still another form of hepatitis for which the designation C has been proposed.

Regular gamma globulin efficiently prevents the occurrence of hepatitis A infections, but does not have any effect on hepatitis B virus infections. By the availability of new test methods for hepatitis B virus and antibodies against this virus it is today possible to select

blood donors for preparation of a special gamma globulin containing a high concentration of antibodies against hepetitis B virus. During recent years it has been shown that this type of specific gamma globulin gives an efficient protection against hepatitis B virus infections.

Thus possibilities are now available to eliminate a disease which hitherto has caused considerable problems within many sectors of medical care, e g in kidney dialysis departments and transplantation units.

The occurrence of healthy individuals who produce large quantities of non-infectious hepatitis B virus products has allowed possibilities for the development of a completely new type of vaccine. The production of this vaccine is not based on virus produced in the laboratory but instead on the purification of virus products derived from serum of patients with a persistent hepatitis B virus infection. A vaccine of this kind has been shown to protect against hepatitis B virus infections in chimpanzees and recently also in humans.

Carleton Gajdusek has studied a unique group of diseases in the brain. These studies were initiated to clarify the origin of a remarkable disease which in high frequency attacked a neolithic people living in the highlands of New Guinea. The disease is called Kuru and appeared, when it was discovered in the middle of the 1950ies, mainly in women and children. From the time of appearance of the first symptoms there is a progressive destruction of brain tissue which within 6 to 12 months leads to the death of the patient. There are no features of this disease which indicate that it may be caused by an infectious agent. The patients do not have fever and there are no signs of inflammation. Gajdusek performed a careful analysis of different characteristic symptoms occuring during the disease and its epidemiological distribution. He also managed to get access to brain material from deceased patients which allowed detailed microscopical analysis. Various hypotheses postulating that the disease might be of hereditofamiliar natur or that it was caused by some unique intoxication - alternatively lack of some essential nutritional - had to be rejected after careful analyses. Attempts were also made to transmit the disease to small experimental animals which however gave negative results.

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The realization that the changes in the brain of patients with Kuru shared certain features with the unique infectious disease in sheep named Scrapie caused Gajdusek to expend his attempts to transmit the possible infectious agents also to larger experimental animals. By inoculation of chimpanzees with brain material from Kuru patients Gajdusek in 1965 unexpectedly managed to obtain a disease in these animals which was identical to Kuru in man. The time between inoculation of animals and the occurrence of the first symptoms was one and half to three years. This finding implied the occurrence of infectious agents of previously unknown nature in man. During the last decade several important observations concerning infectious agents of this kind have been made. However, the accumulation of this knowledge has been rather cumbersome partly due to the fact that these infectious agents, like in the case of hepatitis B, as yet have not been cultivated in laboratory systems. Further, studies in experimental animals have been limited by the restricted availability of the special animals needed and the slow development of the disease. The following important observations may be mentioned.

The background to the epidemiology of Kuru has been clarified. Among 35,000 persons in the group of people where the disease occurred more than 3,000 patients have died over a period of two decades. The situation allowing the transmission of the infectious agent has been shown to be the form of ritual cannibalism which until 1959 was practiced in this group of people. In connection with preparation of a deceased relative as an object for a funeral meal women and children were exposed to the infectious agent. Since the ritual cannibalism ceased to occur after 1959 Kuru has not appeared in children born after this year. Several cases of Kuru, however, still occur today which indicates that the time interval between exposure to the infectious agent and the appearance of disease may span over several decades. It is to be expected that within one generation Kuru as a disease has disappeared.

The fact that a disease like Kuru, which is not connected with fever or any inflammatory reaction, was caused by an infectious agent prompted an analysis of several other progressively destructive processes in the central nervous system. The interest was

first focused on a disease named Creutzfeldt-Jakob's disease. This disease is uncommon (about one case per million individuals) but occurs all over the world. Also from patients with this disease could an infectious agent be isolated in chimpanzees in 1968. Recently this infectious agent has been transmitted also to cat and to hamster. The time interval between inoculation of experimental animals and appearance of symptoms generally exceeds one year. Ten percent of all cases of Creutzfeldt-Jakob's disease have a hereditary background. Also from these cases can an infectious agent be isolated. The finding that a hereditary disease had an infectious origin was completely new and unexpected.

The possibility that further diseases in the brain e g different forms of presenile dementia, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis possibly may be caused by infectious agents is the subject of continuous studies.

Besides the two diseases in man discussed above similar infections have been identified in sheep - Scrapie - and further in mink. With a common designation these diseases are called spongioform encephalopathies because of the vesiculation that occurs in brain cells showing pathologic changes. Attempts have been made to compare the infectious agent causing these different diseases. It has been shown that all four infectious agents may cause disease in certain species of old and new world monkeys. The possibility that the four infectious agents are very similar or even identical has been discussed.

The natural ways of transmission of these infectious agents have only been partly clarified. The possibility for transmission in connection with ritual cannibalism obviously is unique. Medical personnel in their professional activities may however get into contact with possibly infected brain material. Further a possible transmission in connection with corneal transplantation has been discussed. In the hereditary form of Creutzfeldt-Jakob's disease there appears to be a direct transmission from parents to the offspring. This, however, does not appear to be the case in Kuru. Other possible ways of transmission might be between species via certain types of food.

The infectious agents causing spongioform encephalopathies display unique features. With regard to their resistance against physical and chemical treatments they

clearly distinguish themselves from viruses as conventionally defined. Heating, treatment with ultraviolet light or alkylating agents which destroy the infectious property of conventional viruses allow the survival of the infectious agents causing Kuru and related diseases. Since it still remains to purify and chemically characterize the latter infectious agents the background to the high resistance of these agents remains unknown, but it is obvious that one is dealing with a completely new type of infectious agents. This is also obvious from the fact that no defence of the type encountered in connection with conventional virus infections can be demonstrated in patients with Kuru or Creutzfeldt-Jakob's disease. There is no production of antibodies and no appearance of interferon has been identified.

Even if much knowledge remains to accumulate concerning slow infections in the brain of the type described it is clear today that these infections are caused by agents of a completely new type, which initiate a pathologic process of hitherto unknown kind. This implies that the definitions of diseases, which may potentially be of infectious origin have to be markedly widened.

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/1976/press.html