Growing Points in Medicine

Success and Failure in Human Virus Diseases* I—Aetiology

SIR CHARLES STUART-HARRIS

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The past thirty years have brought many changes in the practice of medicine, particularly in the prevention and treatment of disorders due to infectious agents. During the same period there has been a rich harvest of basic knowledge concerning viruses, and some of this has been applied to the prevention of virus disease in the community. Although these developments in the laboratory study of viruses—in knowledge concerning their molecular structure, mode of multiplication, and biochemistry—have been spectacular, it is unlikely that what has been termed “the golden age of virology” is yet at an end.

Progress in the study of infectious disease has usually begun with the identification of aetiological agents, and in the case of virus diseases of man and animals the new techniques introduced in the past 30 years have proved outstandingly successful. Yet with each new technique success has been tempered with failure, and there still remain aetiological problems in human disease to this day.

Studies of Aetiology

The traditional methods used for the study of viruses in the laboratory before 1940 depended on the attempted transmission of the virus from man to animals with the production of lesions which could be studied histologically and used as a source of virus for passage. Long before the days of electron-microscopy the viruses of herpes, smallpox, yellow fever, poliomyelitis, rabies, and influenza were studied in this way and concepts were derived concerning the pathogenesis of virus diseases which were little different from those applied to bacteria. When the fertile hen's egg was introduced as a basic culture medium sterile virus preparations, often remarkably free from animal protein, became available for serological use and for the preparation of vaccines. Yet it is doubtful whether viruses which were previously unknown because of negative experiments in animal transmission were recovered through the use of the chick embryo. Nevertheless, the convenience of the embryo as a laboratory tool played an enormous part in increasing knowledge of human influenza, mumps, and measles.

From 1949 onwards, when Enders and his team first cultivated poliovirus in tissue cultures growing in test-tubes,¹ the virologist has adopted cell cultures as the standard medium

for isolating viruses, for studying their antigens and the antibodies formulated against these by the infected host, and for preparing vaccines. The harvest of viruses from human specimens by using tissue culture cultivation has been very large. We have passed through the lush days of growing poliovirus and other enteroviruses, of adenoviruses and the various myxoviruses of the respiratory tract to the present day. Highly technical and difficult procedures are now required for growing common cold rhinoviruses, Tyrrell's coronaviruses,² and the cell-associated viruses of infectious mononucleosis, varicella, and zoster. A big disappointment, which may soon be remedied, is the repeated failure to cultivate the hepatitis viruses.

Let us begin with the exanthemas.

Rubella

Once rubella virus was found to be capable of multiplication in tissue cultures it proved to be a relatively easy virus to isolate from the throat swabs of patients with classical rubella. The principal lesson for the clinician has, however, come from the study of congenital rubella acquired by the fetus and persisting as a chronic infection with sequelae manifest during infancy and childhood. The expanded rubella syndrome includes low birth weight, congenital heart disease, bone lesions, hepatosplenomegaly, thrombocytopenic purpura, microcephaly, deafness, and cerebral palsy.³ It far exceeds the original description by Gregg⁴ as babies with cataract and cardiac lesions. The fact that infected neonates continue to excrete rubella virus and are infectious to susceptible contacts, including nurses, has also been a surprise. Another has been the ability of rubella-infected mothers without any clinical signs of illness to pass the virus on to their fetuses.

The risk of contraction of rubella infection by the fetus depends on the stage of pregnancy. It is greatest in the first month and diminishes steadily during the first three months of pregnancy. Published estimates of the risk vary widely, but are as high as 50 to 60% in the first month, then becoming sharply reduced to perhaps 5% or less after the 12th week.^{5,6} Alongside this risk must be placed the fact that at least 70% of women of child-bearing age have antibodies to the virus and are presumed to be immune. This has been found to be the case in widely separated countries all over the world,⁶ and in Britain and the U.S.A. the figure is 80%. In those women who are seronegative and who, if pregnant, are exposed to contact infection, serological studies help to decide whether they have become infected. It is difficult to prevent infection by antibody. The recent study by the Public Health Laboratory Service Working Party on Rubella on the use of immunoglobulin in the form of normal gammaglobulin was disappointing.⁷ Even high doses of globulin given at the time of reporting to the practitioner, which is often several days

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University of Sheffield

SIR CHARLES STUART-HARRIS, M.D., F.R.C.P., Professor of Medicine

after contact, failed to prevent subsequent infection of the mother. The only way to improve results seems to be speedier reporting of contact by the mother who has been at risk. The preparation of gammaglobulin from rubella convalescents also seems worthy of trial. I will refer to the question of immunization with rubella vaccine in Part IV of the lecture.

Measles

Laboratory success in the recovery of measles virus preceded that with rubella virus by some years. Consequently attention has moved from an interest in the disease towards its attempted control by immunization. The disease produced by measles virus was well characterized before the virus was isolated, and there have been few clinical developments of interest to the practitioner. The relationship of the virus to the central nervous system has perhaps been the most intriguing finding. The occurrence of encephalitis during or after an attack of measles has of course, long been known though its precise pathogenesis has remained obscure.

Recently a most surprising development has linked measles virus with Van Bogaert's disease—subacute sclerosing (or inclusion) panencephalitis. This rare, fatal neurological disorder characterized by chronic mental changes progressing to dementia, paralysis, and extrapyramidal signs with myoclonic or athetoid movements has been recognized in the past by its distinctive morbidity. In addition to gross softening and sclerosis of the cortex and elsewhere, there are characteristic type A intranuclear and cytoplasmic inclusions in both neurones and glial cells. It was shown by Connolly *et al.*⁸ that brain tissue from such patients stained specifically when treated with a fluorescent antibody conjugate capable of detecting measles antigen. Later workers have shown that brain nuclei contain particles resembling a myxovirus, and recently Horta-Barbosa *et al.*⁹ and Payne *et al.*¹⁰ succeeded in isolating strains of measles virus from cell cultures derived from brain biopsies of patients with subacute sclerosing panencephalitis.

The presumption is that in subacute sclerosing panencephalitis measles virus has somehow become introduced and locked into the brain, where it persists in spite of plentiful

antibodies in both serum and C.S.F. As infection by measles virus may have occurred some years before the onset of subacute sclerosing panencephalitis, Burnet¹¹ has postulated that the disease illustrates a form of immunological tolerance. He suggested that measles virus attacks the thymus in these rare cases, lodges in thymus lymphocytes, and prevents their participation in immunological elimination of the virus elsewhere. It is possible that subacute sclerosing panencephalitis may follow measles vaccination, perhaps because of the modified virulence of the vaccine virus. Some cases have occurred both in the U.S.A.¹⁰ and in Britain in which the illness followed measles vaccination. Viruses recovered from such patients may have been derived from the vaccine, but of this there is no proof. A distinguished group of virologists in the U.S.A.¹² considers that in addition to measles another virus, so far characterized only by the electronmicroscope, is required to produce the full brain syndrome. But it is accepted that subacute sclerosing panencephalitis is an example of chronic virus infection of the brain. Other examples are cytomegalovirus infection of neonates, and slow viruses, such as those causing scrapie in sheep and Aleutian mink disease. Kuru and other chronic human encephalopathies may prove to be viral in aetiology.

(Part II will be published next week)

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Contemporary Themes

Immigrant Mother and Her Child*

F. N. BAMFORD

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Summary

The health risks of 1,164 immigrant Asian mothers and their babies in Bradford were compared with those of an indige-

nous group from obstetric data collected between 1965 and 1969. The average number of children for families in each group in 1969 were 3.31 and 2.33, respectively; 43.9% of 2,206 Asian mothers delivered in 1968-9 had less than a one-year interval between pregnancies. In 1965 the perinatal mortality rates for the two groups were 48.6 and 26.6, respectively, whereas in 1969 the corresponding figures were 26.8 and 25.5, respectively. Though the risks to maternal and child health of Asians are greater, Asian families are more stable and their children have a more secure upbringing than non-Asian children. However, Asian children need increased environmental stimulus in early childhood to prevent educational disadvantages at a later age.

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School Health Service, Bradford 1

F. N. BAMFORD, M.D., D.P.H., Principal Medical Officer