A SHORT HISTORY OF VIROLOGY

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When W.W.C. Topley and G.S. Wilson in their famous textbook, as long ago as 1936, prophesied that "the years ahead of us will be the eighteen eighties over again", referring to the great age of bacteriological discovery, they were, like all prophets, risking their reputation. In fact they have been right perhaps even beyond their expectations for at that time both the electron microscope and tissue culture methods were still in their earliest days. Virology has progressed with gigantic strides and it has now not only shed light on previously obscure medical problems but provided the biologist and the geneticist with tools with which to pursue many fundamental studies.

It would be accurate to say that two of the most useful applications of virology were made before viruses as such were known and studied. Jenner's discovery of vaccination as a preventive measure against smallpox has a long and complicated history, starting in 1789 when he tentatively inoculated his firstborn son first with pus from a case of swinepox and then, for 5 times with virulent smallpox, and progressing to 1807 when his methods were widely accepted and the House of Commons voted him a large award as an expression of Britain's gratitude. Pasteur's discovery of the vaccine against hydrophobia, first put to human use in 1885, was the second case in which a dramatic effect was obtained in spite of the fact that the scientific rationale was still deficient in details.

The first person to see viruses was the Scotsman John Brown Buist, who, in 1887, being a bacteriologist in the university of Edinburgh, examined pus from a cowpox lesion. Guarnieri in 1892 described what are now known as the inclusion bodies of smallpox and cowpox. The Frenchman Amedèe Borrel reported seeing the virus of fowlpox in 1904, and in 1906 Paschen described the elementary bodies of cowpox which were the actual virus. All these findings could occur since the cowpox and smallpox viruses are among the larger, being from 150 to 260 millimicrons in size and therefore just come within the powers of resolution of the ordinary light microscope.

Dmitri Ivanowski in 1892 read a paper to the Academy of Sciences in St. Petersburg (which is now Leningrad) on the mosaic disease of the tobacco plant. He did not apparently attribute the disease to an infective agent, but towards the end of the paper he stated that he had found the juice extracted from affected leaves was still infective after filtration through a Chamberland candle. Martinus William Beijerinck, a plant pathologist and bacteriologist (1851-1931) is best known for his extensive studies of bacteria symbiotic on leguminous plants. He worked on tobacco mosaic disease and discovered a filterable infective agent to which he attributed far greater importance than Ivanowski had done, but unfortunately he thought of the agent as a fluid, as a *contagium vivum fluidum* and thereby the value of his discovery escaped him.

In the veterinary world Friedrich Loeffler and Paul Frosch in 1898 discovered

foot-and-mouth disease to be caused by a filterable agent, whilst the first human disease to be definitely attributed to a virus was yellow fever, discovered to be so by Walter Reed and James Carroll in 1901. Once the technique had been developed many other illnesses became attributable to viruses. William Elford of the National Institute for Medical Research of Great Britain by his development of collodion membranes to act as filters round about 1931 not only gave the death blow to any lingering conception of a fluid infective agent, but definitely established the size of the more important viruses then known.

Two of the most interesting discoveries in medical science were the independent ones by Frederick Twort in 1915 and by Felix D'Herelle, first made public in 1917, of bacteriophages. Twort had observed a glassy clearing on a culture slope, proved its transmissible nature and rightly attributed to what he called "an acute infectious disease of the (bacterial) colonies". He also detected the filterable nature of the agent and its specificity. Twort's report duly appeared in a 1915 issue of the "Lancet", and established his priority. When D'Herelle was in Mexico in 1910 at the time of a locust invasion, he had his attention drawn to a diarrhoeic disease from which the insects were suffering. He discovered that a specific microorganism was causing this and on cultures of these he noticed clear spots. D'Herelle used the bacteria to start an epidemic amongst locusts which in 1915 were invading Tunisia and there he again observed the phenomenon, having this time the opportunity to discuss the matter with Charles Nicolle, who supported his idea that a filterable agent might be the cause. This was confirmed when D'Herelle observed the phenomenon once again in connection with cases of dysentery in France in 1915, this time definitely proving the filterability. D'Herelle's complete researches were published in 1921 in a long monograph entitled "The bacteriophage, its role in immunity". Though bacteriophages have not yet come to play the therapeutic role for which their discoverers had hoped they were cast, yet they have assumed an importance almost as great in the study of the intimate structure of living things.

The development of virology has run concurrently with developments in technique. What had made the work difficult was the smallness of the microorganisms which set them beyond the reach of ordinary microscopes and the impossibility of growing them away from living cells and it was as these obstacles were overcome that progress was made, researchers being driven by the impellent necessity to find ways of preventing some of the most widespread and dangerous diseases, mainly yellow fever, influenza and poliomyelitis.

Yellow fever became an illness of direct interest to a country highly organised scientifically with the involvement of the United States of America in Cuba in the last years of the nineteenth century. It was the American investigators Reed, Carroll, Agramonte and Lazear who, acting on the theory of Carlos J. Finlay of Havana established the fact that yellow fever was transmitted by special mosquitoes and discovered in 1901 that the illness could be produced in human volunteers by bacteria-free filtrates of serum from patients. This was not fully established until Adrian Stokes, Bauer and Hudson succeeded in infecting a *Macacus rhesus* monkey in the Gold Coast as late as 1927. The terrible illness took toll of many of those who investigated it. Stokes died in 1927 in Nigeria, Hideyo Noguchi in Accra in 1928, William Young at 40 a few months later, Paul Lewis aged 50 in 1929 in Brazil and

Theodore Hayne at 32 in 1930 in Nigeria. The construction of the Panama Canal through what was a yellow fever zone started, for the second time in 1906, and fully completed in 1920, put the entomological findings to a severe test. The Rockefeller foundation, founded in 1913, made the study of yellow fever its special objective and since 1916 has spend over fourteen million dollars in research on it. In 1929 Sellards of the Harvard Medical School carried to America a monkey liver infected with yellow fever from a Syrian patient in Dakar. Sellards's partner was Max Theiler, of Swiss origin, who had been born in South Africa, had graduated in medicine in London and studied at the London School of Hygiene. Theiler discovered that mice could be infected if inoculated intracerebrally and that whilst mouse passage heightened the virus' virulence for that species it lessened it for monkeys. Theiler himself contracted an infection and had only a mild attack, prhaps because the virus had been attenuated by passage. Theiler also discovered the neutralisation test as applied to mice for yellow fever, using serum from human laboratory infections. The French faced with the stern necessity of safeguarding the people in their equatorial possessions against yellow fever, promptly adopted the use of the modified Dakar virus by inoculation in the skin and administered the mouse brain cultures to fiftysix million persons between 1939 and 1953.

Theiler was concerned with developing a more secure vaccine. He cultivated the Asibi strain — later known as 17D — on a Maitland type of tissue culture. consisting for the first passages of whole chicken embryos and for the next, to avoid neurotropicity, of chicken embryos without their central nervous system. In November 1936 Theiler, Smith and Lloyd tested the virus which had now been attenuated on thmmselves and on Dr. Thomas Francis Jr., all four having immunity against yellow fever through previous accidental infections. They had some reaction and developed a rise of antibodies. It was next tested on 8 persons with no previous immunity. In March 1937 it was announced that a yellow fever vaccine for an extended trial was available. Theiler later adopted the egg membrance method of culture. Between 1940 and 1947 the Rockefeller Foundation had produced over 28 million doses of vaccine distributing them gratis, and thus a great pestilential disease was effectively halted: the millions which old John D. had made out of that oil which his father had once peddled as a cureall had been put to excellent medical use after all.

The history of influenza so far is as interesting as that of yellow fever though not yet so successful. Attention has remained focussed on the illness since 1918-19 when a pandemic, the greatest in history, attacked some five hundred million people killing, through its pulmonary complications, twentyone million. An influenza epidemic amongst swine also appeared first in 1918 in Western Illinois, U.S.A., the disease running roughly parallel to that in man, although it persisted in swine after the human epidemic had died out. The epidemiology of swine influenza was studied by Shope and some very complex cycles were discovered involving the swine lungworm and the earthworm.

The discovery of the influenza virus was made in 1933 at the National Institute for Medical Research at Hampstead by Wilson Smith, Christopher Andrews and Sir Patrick Laidlaw, largely consequent on the discovery of a suitable experimental animal the ferret, which had come into use in studies on canine distemper. The

etiological connexion of the ferret-passaged virus was clinched when an infected ferret sneezed in Dr. Wilson Smith's face and infected him with influenza, furnishing the first strain of human influenza to be definitely isolated, which was appropriately labelled W.S. Later this strain was successfully passed to anaesthetised mice by intranasal inoculation. Another well-known strain, the PR8 strain was isolated by Francis from Porto Rico cases and served to produced the first vaccines.

Laidlaw formulated the theory that the virus of swine influenza was the human 1918 virus adapted to swine. British and American workers found antibodies against swine influenza to be generally present in the blood of adults even if they had had no contact with swine and absent from the blood of persons born after 1920. In 1941 George Hirst discovered that the influenza virus agglutinates chicken red blood cells and that there was also specific agglutination inhibition by antibodies. It became evident that the antibodies present in a person's serum showed which virus had infected him in his early years.

The World Health Organisation in 1948 instituted the World Influenza Centre located quite fittingly at the National Institute in Hampstead.

A new type of A virus appeared first in a place near Kweichow in China in February 1957. It spread to Hong Kong where 10% of the population was affected. First samples were obtained by the 406 Medical General Laboratory of the American Forces at Zama in Japan, sent to the Walter Reed Medical Centre at Washington and identified as a new type, the Asian type. Antibodies against it could only be found in survivors from the 1889-92 epidemic. It was mild but highly infectious.

The millenial history of poliomyelitis as a clinical entity has now, following its study as a virus disease, reached a dramatic climax and one may reasonably hope it will reach a happy conclusion. Landsteiner and Popper in 1909 succeded in infecting monkeys and Flexner and Lewis showed that the illness could also be produced by filtrates, thus proving its viral etiology. Until about 1396 the view had prevailed that the poliomyelitis virus was exclusively neurotropic and an important landmark was the discovery by Paul and Sabin that the virus was commonly found in the faeces. In 1939 Charles Armstrong of the U.S. Public Health service found the virus to be transmissible to the cottonrat, and Jungeblat and Sanders that the rat-adapted strain could be passed to white mice.

The most interesting developments have been those associated with the attempts to produce a prophylactic since this illness could not be dealt with by non-specific hygienic measures. These attempts were closely linked with unusual circumstances. Franklin Delano Roosevelt had suffered from a paralytic form of poliomyelitis and when he later became president of the United States of America, at the suggestion of the well-known researcher and medical publicist Paul de Kruif, he founded in 1938, the National Foundation for Infantile Paralysis, with at its head for the first three years De Kruif himself and Mr. Basil O'Connor, an ex-president of the American Red Cross Society. De Kruif eventually withdrew leaving the leadership to O'Connor. O'Connor, an Irish-Catholic lawyer with a Harvard training had a dynamic and inspiring personality and was it seems completely resolved that he would give the medical profession no peace till it had given him and the world the means of preventing poliomyelitis. He organised the collection of funds, especial-

ly through the "March of Dimes" campaign about 1945 and was in a position to finance research very strongly.

Backed by a grant from the N.F.I.P. John Enders, Fred Robbins, and Tom Weller in 1947 set to work on virus diseases in the Jimmy Fund Building attached to the Children's Hospital at Harvard Medical School in the celebrated, colonnaded and imposing Lanwood Quadrangle. Their immediate objective was the cultivation of the mumps virus in tissue culture mainly on Maitland lines. They adopted a system of changing the medium rather than subculturing on the new cells and started the use of antibiotics to prevent infection. Weller was using skin and muscle human embryo tissue for culture of the chicken-pox virus. Having some flasks left over he inoculated them with poliomyelitis virus and found it survived and multiplied. Poliomyelitis could therefore be grown in cells other than nerve cells and it could be grown in vitro. It was also grown in intestinal cells. The first announcement was made in "Science" for the 28th. January 1949 and at last the road was opened for the preparation of vaccines, and O'Connor announced that the Foundation had fifteen million dollars available for such purposes.

Many workers had tried their hand at vaccines before this, using monkey nervous tissue, notably Maurice Brodie using a formal killed virus and John Kolmer with an attenuated living virus. Both were tried out in 1935 somewhat ineffectively and inconclusively: their safety was, to say the least, suspect, and no more was heard of them. Brodie died in 1939 at the age of thirty under rather tragic circumstances. Fundamental work on poliomyelitis included the discovery in 1949 by Bodian, Howe and Mountain at Johns Hopkins of the three types of virus, and in 1952 by Bodian and Horstman independently of the viraemic phase of the illness. The National Foundation had a "Typing Committee" which included Sabin and Salk, which finished its work in 1951 and became the "Immunization Committee". Many accepted the financial backing of the foundation for research, including Salk and Sabin, and O'Connor felt it his duty to see that not a day should be wasted in developing an effective vaccine and in making it available to the public.

Jonas Salk had graduated from New York University in 1939, gone in 1942 to the University of Michigan at Ann Arbor on a fellowship from the National Foundation, and, in 1947 to the University of Pittsburgh School of Medicine. Being director of the Virus Research Laboratory he was in an excellent situation for developing a poliomyelitis vaccine to which he devoted all his attention. He decided on the use of a formalin-killed virus and the problem mainly was the necessity of making absolutely certain that no single particle of virus survived the treatment. In fact the preparation of every batch of vaccine was a research project by itself. Once sterility was ascertained, once the safety factor had been assured, the remaining problem was that of testing the vaccine's efficiency. This was first done on survivors of the illness in whom it was possible to note a rise in viral antibody titre, then on persons who had no natural antibodies. In May 1953 Salk vaccinated himself, his wife and his three young children. Others, first some hundreds and then some thousands were vaccinated, but in the last resort the effectiveness of this vaccine had to be assessed by a comparison of incidence in protected and in unprotected groups and numbers had to be enormous to give information of any

value. Thomas Francis of the University of Michigan was prevailed upon to devise and supervise such a test and eventually to assess its results. This he did, insisting on his own terms for conducting the vast experiment. The number of children involved was over a million and eight hundred thousand. Never before had any prophylactic measure been studied quite so scientifically, and never before probably had there been so much at stake. The result obviously could not be expressed in some few short phrases nor in a few percentage figures, but the gist of the Francis report was that Salk's vaccine was a safe and effective way of preventing the illness, especially its paralytic form. The Francis report was published on the 12th April 1955, which, purely by coincidence but a lucky one none the less, happened to be the tenth anniversary of the death of Franklin Roosevelt, who had inspired the great undertaking. Both Salk and Francis were careful to conduct the enquiry in a spirit of scientific detachment, but the event was such that it attracted the attention of the public at large and chiefly of the press who made of it front page news with the largest possible types. After a fortnight it became apparent that a tragedy was to mar the completeness of this success, when a batch of vaccine was found to have been incompletely treated and 77 cases of poliomyelitis were produced with 11 deaths. This was the sort of accident which everybody had been so careful to guard against. It soon became certain that this was due to a fault in the preparation of the special batch, but there had been nothing wrong with the method itself. Since then millions of doses of vaccine have been used without any untoward result and surely a large number of cases of poliomyelitis must have been prevented.

Meanwhile Albert Sabin at Cincinnati and Hilary Koprowski at Philadelphia were working on a vaccine with live but attenuated viruses. Sabin since 1955 has succeeded in producing attenuated strains of viruses of each type, and since 1957 his vaccine has been tried first on monkeys and chimpanzees, then on Dr. Sabin, his wife and children (doing something which is no less heroic because it has become almost traditional amongst researchers) then on a few hundred volunteers mainly from penitentiaries and subsequently on several million people in Russia and elsewhere. Sabin maintains that live vaccine by mouth produces a local and cellular intestinal resistance which prevents the passage of poliomyelitis virus, and he hopes that the vaccine virus will ultimately lead to the extinction of the pathogenic strains. The great problem in this and in the case of any live vaccine is the question of any possible reversion of the attenuated viruses to virulence. There does not appear to be any evidence that this has happened or is likely to happen. On the contrary there can be little doubt that the widespread use of Sabin's vaccine has effectively nipped in the bud epidemics in Singapore, in Hull and in Malta. Even there the results are not beyond questioning by statistical rules but workers in the field who saw the vaccine's effectiveness would be persuaded with the greatest difficulty if at all to refrain from using a measure so potent for good.

In 1947, working at the New York State Health department laboratory in Albany, by the use of new born mice, Gilbert Daledorf discovered the Coxsackie group of viruses, so called after a village with under three thousand inhabitants in the Hudson River Valley where the first patients came from. This discovery shed a great deal of light on polio-like cases. ECHO (enteric cytopathogenic human orphan) viruses, of which there are at least twenty types, were first identified in Ender's

laboratory. These too could produce fever, and muscular pain, and were sometimes responsible for cases which, before they were known, would have been diagnosed as non-paralytic poliomyelitis. At the laboratory of Infectious Diseases in the National Institute of Infectious Diseases of the American Public Health Service in Bethesda, near Washington, the first virus of the adenovirus group was discovered, the whole group numbering over twentyfour types. Wallace P. Rowe and Robert Huebner cultivated it from adenoidal tissue removed at operations. One type, type 3, causing conjunctivitis, pharyngitis and fever was first isolated from Huebner himself and later from a laboratory technician and from a pediatrician, the latter, at least, having contracted the infection through his work.

Measles had in 1911 been proved by Joseph Goldberger, who had also discovered the cause of pellagra, to be a virus disease. In 1938 Harry Plotz, then working at the Paris Pasteur Institute cultivated the virus on chicken embryos. In 1939 G.W. Rake of the Squibb Institute for Medical Research and Morris Shaffer grew it on egg membranes. In 1953 Enders and T.C. Peebles grew the Edmonston strain (so called after a patient David Edmonston) on monkey and on human kidney cells. Samuel L. Katz and Enders himself in 1957 succeeded in attenuating the virus by prolonged passage and by its use in protecting monkeys. Tests on children so far can, at least, be considered promising and it appears likely that measles also will soon be under specific prophylactic control.

By an admirable process of exchange, virology has benefited enormously from pure research in other sciences such as biochemistry and optics and in its turn has contributed to the development of such sciences as genetics. As far back as 1935 William H. Stanley a chemist working in a laboratory of plant pathology of the Rockefeller Institute, succeeded in obtaining the virus of tobacco mosaic disease in crystalline form, and showed that it was an organism if within a cell and a chemical particle when out of it. Stanley first believed the virus particle to be a protein, but Bawden and Pirie of Cambridge found it to contain phosphorus through its content of ribonucleic acid, being a nucleoprotein with 94% of proten and 6% of nucleic acid. Tobacco mosaic virus has a molecular weight ranging from 40 to 50 million, being heavier than any known protein. In 1955 Carlton E. Schweldt and F.L. Schaffer succeeded in crystallising the poliomyelitis virus, obtaining just one crystal out of nine hundred litres of liquid monkey kidney tissue, obtained from the Connaught Laboratory in Toronto, a laboratory which has played a vital part in research, such as in that on poliomyelitis vaccination.

Virology owes its greatest debt to the development of the electron microscope, the first such instrument having been completed in Germany in 1931, by Ruska and Knoll. The first photographs were taken in 1933, the first virus to be photographed being that of tobacco mosaic disease by G.A. Kausche, E. Pfankuch and Helmut Ruska. Robley Williams ,at the time in the University of Michigan, was an astrophysicist who had concerned himself with the task of preparing thin metal layers for use in telescope mirrors; he met Ralph Wyckoff, a biophysicist who, as a lecturer in the same university, interested himself in viruses, and they found the method of metal shadowing viruses by exposing them to a shower of gold particles from a gold laden tungsten filament in vacuum. Since this was placed sideways the gold was deposited laterally producing a shadow effect as if the particles had been hit

by snow driven by a strong wind. Subsequently palladium and uranium shadowing were used. In actual fact the heat produced destroys the virus but the metal produces a cast. Technique has now advanced to a point when investigators have in their hands methods for cutting tissue sections only 100 atoms thick and when electron microscopes can resolve detail only 10 atoms across.

Yet another and most important technical development consisted in progress in *in vitro* culture. Naturally no really fundamental advance of an academic character could be made until viruses could be grown away from an animal host. In 1907 Ross G. Harrison of Yale, working at Johns Hopkins, cultivated nerve cells in a plasma hanging drop preparation, and Edna Steinhards and her assistants first cultivated the smallpox virus in guinea pig or rabbit corneal cells, but although the virus survived there was no multiplication. One eminent worker in the tissue culture field was Alexis Carrel of the Rockefeller Institute who developed many of the methods still in use, but had to contend with the difficult business of preventing contamination at a time when antibiotics had not yet come into use. Frederick Parker Jr. and Robert Nye at Boston City Hospital in 1925 obtained reproduction of smallpox virus in rabbit testicle cells. A method which for a long time proved extremely useful was developed by Hugh and Mary Maitland of Manchester University, who devised a way of growing smallpox in a mixture of chicken kidney cells, serum and mineral salts. This was a real tissue culture system since cells definitely multiplied. The method was later also used for growing the 17 D yellow fever virus and it was the starting point for much of Ender's historical work. A great breakthrough in virus work came when the various parts of the developing chicken embryo could be made use of for growing viruses. Borrel apparently was the first person to use eggs for this purpose. In 1906 Constantin Levaditi first grew Spirilla in fertilised eggs, and Peyton Rous and James B. Murphy in 1910 used the membranes of the developing egg to grow fowl sarcoma virus. Still egg membranes as they are used to-day did not come into the virus laboratory until the classic work of Alice and Eugene Woodruffe, and Ernest Goodpasture of Vanderbilt University. They were all three working on avian pox and Alice Woodruffe, at Goodpasture's suggestion, used fertilised chicken egg membrane to grow the pox virus, her husband Eugene helping her to overcome the difficulties of contamination. The first evidence of success was a swollen leg in a chicken embryo. Then "colonies" were noticed on the membranes. The practicability of using eggs for this purpose was described in 1931 in the "American Journal of Pathology". Within a year egg membranes were being used for smallpox and herpes and since then, as is well known, their use has spread very widely indeed, especially for the purpose of producing vaccines, such as those for influenza, and rabies, the longer incubating duck eggs being used for the latter. Herald Cox used egg membranes very extensively during the last war for the large scale production of typhus vaccines.

It is possible that, in spite of the history of virology so far having been so varied and so fruitful, the most important contributions are yet to be made, for the last great outstanding problem in pathology is the origin of new growths and virology has already made important contributions towards the solution of this and may yet not only provide us with a complete answer to the conundrum but also supply us with a remedy for this sinister abnormality.

Peyton Rous of the Rockefeller Institute published in the "Journal of the American Medical Association" as far back as 1911 an article on "The transmission of malignant neoplasia by a cell-free filtrate". It dealt with a sarcoma in Plymouth Rock fowls. In 1919 U.J. Wile and L.B. Kingery of the University of Michigan proved that the common wart is attributable to a virus. Richard Shope proved the virus origin of fibromas in rabbits in 1930 and of rabbit warts in 1931. In 1936, John Bittner of the Jackson Laboratory in Maine, and later of the University of Minnesota discovered what for a long time was called a "principle" which was present in the milk of mice and transmitted to their offspring cancer of the breast. This was later on, at least partly proven to be a virus acting together with an inherited predisposition. In 1950 Ludwig Gross of the Bronx Veterans Administration Hospital of New York produced convincing evidence that leukaemia of mice was produced by a virus. Most pathologists agree that leukaemia is a neoplasia and when Gross's discovery was confirmed by Sarah Stewart, Bernice Eddy, and Charlotte Friend it was clear that an important contribution had been made in the etiology of a new growth type of illness which frequently occurs in man. Stephen O. Schwartz, primarily an internist but also the director of the Hektoen Institute for Medical Research of the Cook County Hospital in Chicago, has proved, mainly through the use of intracerebral inoculation in mice, that human leukaemia also appears to be of viral origin.

One interesting field of studies in virology which must not be left unmentioned simply for the reason that the historian who does so risks cutting a very poor figure in the future should any of its many possibilities come true is that of interference. G.M. Findlay and F.O. MacCallum as far back as 1937 established that an infection with Rift Valley Fever virus protected monkeys from infection with the immunologically unrelated yellow fever virus. This was the first definite example of viral interference. It was later found that the interfering virus can induce the same effect when it has been inactivated, and later still it was established that when certain cells are treated with different strains of myxovirus (the influenza group) a substance is produced which inhibits the growth of a wide variety of viruses. This has been largely the work of A. Isaacs and his associates of the National Institute for Medical Research at Mill Hill in London. The inhibiting substance has been named interferon. It must have been hoped that it could do in the virus field what penicillin did in the bacterial field, and, although progress has been relatively slow, this may eventually still be the case.

One of the most thrilling things in science is the cross-fertilisation which can often occur between the different branches of learning. In the last few years enormous progress has taken place in genetics and especially in the studies on the way in which genes transmit the instructions according to which inheritable features of an organism are determined. This has now centred on studies on deoxyribonucleic acid, the now famous DNA, and much of this work has really been a study in bacterial genetics. One of the most eminent workers in this field has been F.H.C. Crick of the Medical Research Council Unit for Molecular Biology at the Cavendish Laboratory, Cambridge and most of his work was done by the use of bacteriophage T4, which acts on *Escherichia coli*. The story is too involved to deal with in this essay, but it is clear that the story of genes is shedding an enormous amount of

light on the intimate structure of viruses and perhaps the chapter which is now being written will be the most important one of all. Who knows but that it may be not only a chapter in virology but also a most vital one in the history of the human race? Reverting to the problem of the origin of new growths, we can point out that Rubin, of the California Institute of Technology, suggests that virus entering a cell can unite with the cellular material, distort it, but go on dividing with it. By this theory, which receives support we believe by the work of Crick and others, the necessity is avoided of choosing between theories of neoplasia which depend on a change of a non-infectious character in the cells and those which attribute the change to viruses.

It is probable that the rate at which progress in virology has gone on will decrease, but certainly the end is not yet for the subject still has many growing points. So far it has been a chapter of history which many have found fascinating. Like so much else in the history of medicine in general, and unlike so much in general history, it is a chronicle the contemplation of which affords mankind nothing to be ashamed of and a great deal to spur it on to ever nobler achievement.