basic histone amino-acid for every DNA phosphorus[45]. In order to achieve linkages with all the DNA phosphorus, histones would have to be in relatively extended configurations, that is, one molecule of mol. wt. 14,000–18,000 would be spread over 68 Å of the Watson–Crick double helix[45]. If this is indeed the state of histone, it could scarcely constitute more than an inner layer of the sheath, possibly functioning to bond the acidic sheath proteins to the nucleic acid. That the main bulk of the sheath protein is actually acidic is supported by the fact that isolated metaphase chromosomes are stabilized in acid solution[42].

The folded fibre model of chromosome structure is essentially a variant of the well-known 'differential coiling' model. Nevertheless, in the folded fibre hypothesis, differential DNA coiling, as such, is thought to be rare in occurrence (for example, in lampbrush and giant chromosomes) and relatively unspecific (by presence or absence of a regular secondary helix). Superimposed on the secondarily coiled DNA molecule is a non-differential and highly irregular folding, which is mediated by a contractile protein sheath around the DNA, and which accounts for condensation of metaphase chromosomes and of heterochromatin. The gross coiling sometimes observed in light microscopy of large metaphase chromosomes is regarded as quaternary structure which is absent in smaller chromosomes.

It is recognized that various apparently reliable observations in the literature cannot yet be accounted for by the model described here. Nevertheless, it has the merit of conforming with the facts of chromosomal and nuclear fine structure, and it is also compatible with most of the experimental observations concerning nuclei and chromosomes. It should perhaps be re-emphasized that whole chromosomes in higher organisms exhibit several of the most fundamental properties of single DNA molecules, including semi-conservative replication[46], linear frequencies of genetic recombination[47], focalized DNA synthesis[28], and the rule that DNA synthesis, once begun, does not normally end short of a complete doubling[48]. In view of the recent demonstration that nuclei and chromosomes are also composed primarily of long, irregularly folded fibres, each of which has a DNase-sensitive, trypsin-resistant core surrounded by a trypsin-sensitive sheath, it now seems likely that single, long DNA molecules are indeed the fundamental units of eukaryote chromosomes.

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GENETIC INFORMATION USED DURING SYNTHESIS OF VIRUS COMPONENTS AND ANTIVIRUS IMMUNITY

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THE first effect of a virus on an organism is determined by the structural properties of the virus surface. These structures are responsible for two major processes, the immunological reaction of the organism on virus inoculation, and the penetration of the virus into the cell.

Effective protection against virus infection has until now been immunological. But not all virus infections are subject to immune reactions. In this connexion the question arises as to what determines the nature of the organism's immunological reaction on virus inoculation. Why do we observe stable immunity after such virus infections as measles, smallpox, mumps and others, and not after influenza? The solution of this problem will involve the investigation of: (*a*) the chemical composition and properties of the surface structures and, primarily, of the antigenic determinants of the virus's immunological specificity; (*b*) the sources of genetic information employed during the synthesis of virus membrane components; (*c*) the sub-cellular structures which implement the synthesis of virus membrane components.

The importance of the study of the chemical structure of the antigenic determinants arises from their possible identity with blood antigenic determinants. But the organism does not form antibodies against its own blood

antigens, and hence if the virus and blood antigenic determinants are identical the organism will tolerate the virus. Incomplete or unstable immunity may similarly result from the identity of several or at least one virus antigen with blood antigens.

In principle such antigenic identity may be determined in either of two ways. First, the genetic information coded in the nucleic acids of the cell and of the virus may be identical. Such a situation might arise by virus mutation. Secondly, the genetic information of the host may be used in the synthesis of the virus surface components.

Generally speaking, the expression of the genetic information of the virus-cell system may take one of several courses: (*a*) Information coded in virus and cell nucleic acids may be used independently by the virus and the cell. In this case either the information introduced by the virus is realized, the virus is synthesized and the cell perishes, or the virus does not multiply. Processes of this kind frequently take place during infections caused by simple RNA-viruses of the poliovirus type. (*b*) Virus information is employed in the construction of cell components, its membrane in particular. The cell may in this case either perish or survive (avian myeloblastosis virus, Rous sarcoma virus, 12 and 18 type adenoviruses and Newcastle-disease virus). If the virus does not evoke a cytopathic effect it leads to malignity (12- and 18-type adenoviruses, avian myeloblastosis virus, possible Rous sarcoma virus). (*c*) Cell genetic information is employed during the construction of virus membrane components (perhaps fowl-plague virus). (*d*) Cell genetic information is employed during the virus's replication in constructing its membrane, and the cell membrane at the same time is reconstructed with the participation of the genetic information introduced by the virus (influenza virus).

Research conducted in recent years with the antibiotic actinomycin *D* (a compound reacting specifically with DNA[1-8]) has shown that this antibiotic can halt the synthesis of structures the information of which is contained in DNA[1-9,12]. It thus appeared possible to differentiate between the sources of information employed by the RNA-virus synthesis. It turned out that simple RNA-viruses (polioviruses[10,11], Coxsackie virus[1], Mengo virus[1,10,11], some arboviruses of the *A* group[1,13,57]) are insensitive to actinomycin *D* action. This indicates that their synthesis does not require the information contained in the host-cell DNA. Of even greater interest is the existence of complex RNA-viruses as, for example, Newcastle-disease virus[1,14-16], or para-influenza Sendai virus[17,18], which are also insensitive to actinomycin *D*. The influenza virus[19,63,65,66,69] and the fowl-plague virus[1,17,18] are, on the other hand, sensitive to the action of actinomycin *D* and thus employ the genetic information contained in the host-cell DNA during their synthesis.

The results of experiments with actinomycin thus permit evaluation of the role of host genetic information during virus component synthesis and illustrated the reality of the processes indicated here (*c*).

Information concerning the processes indicated under (*b*) cannot be obtained by this method. Immunological experiments, however, in which virus-infected cells were exposed to the action of specific sera, have shown that in the infected cells the antigens of the Newcastle-disease virus[70-72], respiratory syncytial virus[58], influenza virus[22,23], avian myeloblastosis virus[24], Rous sarcoma virus[25], perhaps the mouse leucosis virus[26], and the 12- and 18-type adenoviruses[27-29,67].

The haemadsorption phenomenon also demonstrates the alteration of the cell antigenic structure under the influence of viral infection. It is, however, possible that the action of the virus in this case can be manifested not only in the transmission of its own information for the construction of the cell membrane, but also in the release of the cell DNA information blockaded in an intact condition.

In considering the data concerning the various types of virus and cell interaction one can draw certain parallels and deduce some interesting consequences. There is a parallel between the ability of the virus to evoke stable immunity, and independence of its synthesis from host-cell genetic information (judging by the independence of virus propagation with respect to the action of actinomycin *D*). Poliovirus, Coxsackie virus, arboviruses, and Newcastle-disease virus demonstrate this. The opposite relation is observed in the case of influenza virus, which utilizes the host-cell genetic information (suppression of influenza virus propagation by means of actinomycin *D*[19,20,63,65,66], and the presence of host-cell components in the virus membrane[30-32]) and does not produce stable immunity[33]. Of no less interest is the fact that good vaccines have been obtained for the first group of viruses, while it has been impossible to obtain one for the influenza virus.

In attempting to explain the correlations described let us consider how the virus using the host-cell genetic information can affect the character of the organism's immunological reaction. Referring to the first group of viruses one may assume that they are immunologically alien to the organism and therefore produce a stable immunity after infection. A different situation exists in the case of the second group of viruses, influenza virus in particular, which utilizes the host-cell genetic information for the construction of its membrane and may obtain antigenic determinants which the organism tolerates, as, for example, antigenic factors that determine the specificity of the red blood cells, or tissue determinants in which antibodies may form in certain circumstances. The formation of antibodies to the antigenic determinants is in the first case excluded, and if these sections of the virus membrane determined the ability of the virus to penetrate into the cell, then the organism may turn out to be defenceless against such a virus. In the second case, infection may cause autoimmunity diseases since the virus makes its way into the blood stream and causes the synthesis of antibodies to the virus antigens which are identical with the host-cell antigens.

Such diseases as rheumatism, therefore, the whole group of collagenosis diseases, such brain diseases as diffuse cerebral sclerosis and even schizophrenia (one should keep in mind the degenerative nature of the changes of the brain cortex cell during this disease[34,59-61] and the appearance of antibodies with respect to the brain tissue[62]) may actually have the viral aetiology and pathogenesis described.

Certain consequences can be conveniently considered with reference to the influenza virus. If the hypothesis is correct two phases will be observed in the clinic and epidemiology of influenza: (1) the first phase embraces the direct inculcation of the virus which has in some way acquired (for example by passage through a definite but as yet unknown host of another antigenic structure of sensitive tissue) an antigenic structure which is analogous or kindred to the tolerant host antigens, for example, to the red blood cell antigens. In this case the organism will not be able to maintain the complex of antibodies fully covering the virus surface. But after further passages on other hosts the antigenic structure of the influenza virus must change and acquire antigenic determinants identical to the host-cell antigenic determinants. The latter, however, are not tolerant for the organism, so that the virus now evokes the formation of antibodies with respect to all the antigenic determinants of its surface. One consequence will be the reaction between the antibodies towards the 'variable' virus antigens and the cells of the organism. This may perhaps be the cause of complications during the second phase of influenza. The work of Buron *et al.*[35] is of interest in this connexion. They showed that when the formation of antibodies was suppressed in mice infected with the influenza virus the mice recovered, while the mice of the control group all died.

At the same time the situation in the second phase should epidemiologically improve, and such is the case.

The central point of the concept that has been developed is the immunological tolerance of the organism to the virus, established as a result of the identity of certain blood antigens and those virus surface antigens which participate in the virus's penetration into the cell. It may be assumed that the simpler the chemical structure of the antigenic determinant the more rapidly identity is established. Carbohydrate antigenic determinants are chemically the simplest[36]. In this connexion it is of interest that carbohydrates have been shown to be components of the influenza virus[37–39]. Furthermore, we have shown that carbohydrate components of the influenza virus actually localize on its surface, which suggests that the antigenic determinants of the influenza virus may be of carbohydrate nature[40]. The human A-antigen, which consists of carbohydrates[42], was a component discovered in the influenza virus type *A*, strain *PR8*, obtained by passages through chicken embryo[41]. What is not clear, however, is the identity of this antigen with the carbohydrate prosthetic group of influenza virus haemagglutinin[40]. The discovery of such an identity would make it possible to connect two important points in the hypothesis that has been set up: the carbohydrate nature of the antigenic determinants and the participation of antigens, determined by the host-cell genetic apparatus during the process of the influenza virus's penetration into the cell.

The presence of antigenic determinants of a carbohydrate nature in the structure of the influenza virus can also be argued from certain other data. Thus, it was recently shown that the antibodies which accumulate in the hyperimmune serum after protein antigenic immunization belong to the 7S γ-globulins, and after immunization by means of antigens with determinants of a carbohydrate nature, to the 19S γ-globulins[43,44]. Proceeding from this one may expect the presence of antibodies with a 19*S* sedimentation constant in the hyperimmune anti-influenza sera. Preliminary experiments have in fact shown that the 19*S* fraction of horse hyperimmune anti-influenza serum contained a component which was active in the haemagglutination inhibition reaction and did not inactivate under conditions usual during the removal of inhibitors[45]. Similar data have been obtained by Czechoslovakian research workers[46]. And finally the presence of an antigen component in the influenza virus, identical to the A-antigen of human red blood cells, is indicated by the choice of O-group red blood cells for the haemagglutination inhibition reaction. They are known not to contain A-antigens and therefore exclude the possibility of 'spontaneous' agglutination observed with red blood cells in lightly diluted sera. Keeping in mind the discovery of an antigen identical with the human A-antigen in chicken embryo[41], it is to be noted that chicken red blood cells frequently, in the haemagglutinin inhibition reaction of influenza virus, demonstrate 'spontaneous' agglutination. In favour of the views outlined here is the research regarding the role of the blood group in epidemiology of human respiratory diseases[47]. An attractive aspect of the hypothesis is that it explains the unusually high variability of the influenza virus as compared with other myxoviruses, and the consequent failure to obtain a reliable anti-influenza vaccine.

Interference with the expression of genetic information during virus infection may not only alter the antigenic structure of the cell. Without referring to facts well known in the literature of metabolism, disturbance caused by the virus may induce the synthesis of new enzymes[21,48,49,68] and the formation of syncytia—giant multinuclear agglomerations surrounded by cytoplasm with practically no wall. The latter is characteristic of the measles virus[50,64], mumps virus[49,51], para-influenza viruses[52–54], respiratory syncytial virus[58] and the Newcastle-disease virus[75], and is not observed during influenza-virus propagation. Keeping in mind the sensitivity of the para-influenza Sendai virus and the Newcastle-disease virus to actinomycin *D*, one can explain the formation of syncytia effected by the virus through the complete suppression of the genetic information of the cell necessary for the synthesis of its membrane, since such information is not needed for the construction of the virus. Failure to form the membrane results in the formation of a syncytium. This explanation requires an insensitivity to actinomycin *D*, and this has yet to be verified. The association of insensitivity towards actinomycin among the Sendai, Newcastle disease, mumps (?), and measles (?) viruses, and syncytia formation by those viruses, contrasts with the sensitivity to actinomycin of the influenza virus, with absence of syncytia formation and unstable immunity.

It may be assumed that in their evolution the viruses have passed through a number of stages. The first stage perhaps was the suppression of the cell by the virus, organizing self-propagation without resorting to any host-cell genetic information. During the second stage it acquired the ability to suppress some, but not all, of the information contained in the host-cell DNA. An example of this is the Venezuelan encephalitis virus, the haemagglutinin synthesis of which can be suppressed by actinomycin *D* without affecting the synthesis of the infectious virus[55]. During the third stage the virus acquired the ability effectively to employ the haemagglutinins, including them in the structure of its own particle (influenza virus). During the fourth stage the viruses became capable of haemagglutinin synthesis at the expense of their own genetic information (Newcastle-disease virus). A parallel series can be postulated with respect to the use of carbohydrates for the construction of virus surface structures: proceeding from simple viruses (such as poliovirus) without carbohydrates, to reovirus[73], and influenza virus with carbohydrates of a mosaic pattern[40], to trachoma virus (RNA–DNA)[74] with carbohydrates of a net pattern. Analogous associations can probably be observed in the series of 'genuine' DNA-viruses (adenoviruses, herpes simplex and vaccine viruses).

It is hoped that this review will suggest a number of purposeful experiments which may elucidate a number of virological problems, irrespective of whether they confirm or confute the hypothesis that has been outlined. It has been said that "It is the main—strictly speaking, the only—virtue of a good generalization that it can provoke scientists to design experiments which can prove it wrong[56]".

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OBITUARIES

Sir Alwyn Crow, C.B.E.

THE announcement of the death of Sir Alwyn Crow, in Washington on February 5 at the age of seventy, will have been heard with deep regret by ballisticians and rocketeers in the United States as well as in Great Britain. He has been described as a pioneer of rocket design, and there is little doubt that his leadership of the early small teams of scientists, first on small solid-fuel rockets and later on guided weapons, laid the first foundations of a modern technology and industry which he could scarcely have foreseen.

Alwyn Douglas Crow was born in London on May 10, 1894, and was educated at Westminster School and Queens' College, Cambridge. The outbreak of the First World War prevented him from taking his degree and he was commissioned in the East Surrey Regiment in 1914. He served until the end of 1916, when he was invalided, having been gassed and later wounded. He was seconded in 1917 to the Proof and Experimental Department at Woolwich Arsenal. This gave him his introduction to ballistics and, after completing his degree, he was appointed the first director of ballistics research at Woolwich, at the early age of twenty-five.

For nearly the next twenty years gun ballistics was to be Crow's subject and much was to be done to absorb the artillery experiences of the War; anti-aircraft artillery particularly was in its infancy. His scientific interest was perhaps directed more to the problems of internal ballistics rather than external. The subject, largely empirical, had not received much attention before the early years of the century—the first scientific treatment was by Vielle in 1893—and modern writings were few. Crow wrote a few papers on this subject, the best known being those written in collaboration with a colleague, the late W. E. Grimshaw, and published in the *Philosophical Transactions of the Royal Society*: "On the Equation of State of Propellant Gases" (1931) and "The Combustion of Colloidal Propellants" (1932). During this time he had created a research team which, although not large was available to meet the challenge of the rocket when it came.

The history of rocket development for military use goes back to Congreve in 1800, but its popularity as a weapon of war had been spasmodic; no work was in progress after the First World War. However, in 1934 intelligence reports of German developments revived interest in rockets, and after much discussion and preliminary investigation Crow was appointed in 1936 to form a team to undertake initial examination and research into rockets to meet a variety of possible military requirements. Foremost among these was anti-aircraft defence. The early designs and initial experiments met with varying degrees of success, but he was not deterred by setbacks and sufficient work was done to justify the creation of a Projectile Development Establishment shortly before the beginning of the Second World War of which he was the first chief superintendent. Under the impetus of war a number of investigations were undertaken to meet various suggested applications, but it was some time before rockets went into service, due in part to various disappointments or partial failures. Crow, however, did not lose faith, and, once success was achieved in the first projects, applications became numerous. Based essentially on three rockets of 2-in., 3-in. and 5-in. calibres some 20 major weapons were produced. Many of these are now matters of history:—the '*Z*'-batteries deployed around London and elsewhere; 3-in. rockets fired from all types of fighter aircraft for the attack of ground and sea targets; 'Mattress' coast bombardment 5-in. rockets used in Sicily and Normandy.