FILTERABLE VIRUSES

A CRITICAL REVIEW[1]

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In all fields of work, times come when one must stop and take thought. New facts, new ideas, and new suggestions alter lines of endeavor in every field of research. We are here today for the purpose of taking thought concerning the knowledge of the so-called filterable viruses and the diseases caused by them. I have been asked to give a critique of this knowledge. It is quite obvious that I shall be unable within an hour to analyze thoroughly and to criticize authoritatively all the work in this field. Therefore, I shall review quickly some facts and ideas concerning this group of diseases as a whole and then discuss a few reports concerning several of its individual members.

In table 1 are listed most of the diseases which are included by different observers in the group under discussion. The etiological agents concerned in these diseases, or groups of them, have been given a variety of names, e.g., filterable viruses, invisible microbes, ultra-microscopic viruses, inframicrobes, protista, microplasms, chlamydozoa, and strongyloplasms. A superficial examination alone is convincing that none of these names is applicable to all of the etiological agents. Names, however, facilitate the interchange of facts and ideas between individuals. For practical purposes, then, the term "filterable viruses," mainly because of its wide usage, is as satisfactory as any name suggested. Throughout this discussion the term "filterable viruses" will be employed in a noncommittal way to designate certain active

[1] Read before the Society of American Bacteriologists, December 29, 1926.

TABLE 1

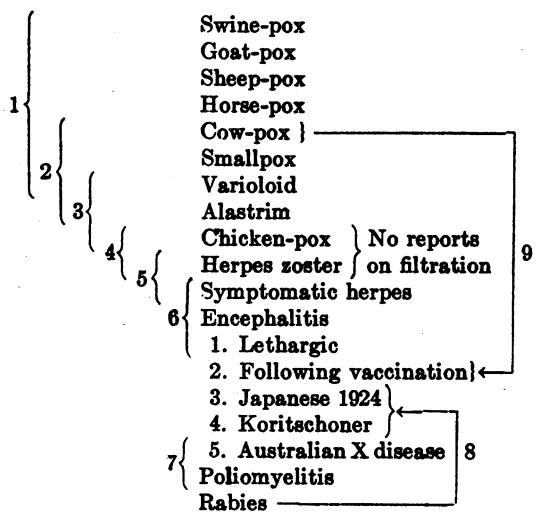
Majority of the diseases which have been placed in the filterable virus group by different workers

Bacteriophage

Mosaic diseases of plants (infectious chlorosis)

Sacbrood
Wilt of European nun moth
Wilt of gypsy moth caterpillar
Jaundice of silk worms

Epizoötic of guinea pigs
Hog cholera
Cattle plague (Rinderpest)
Pernicious anemia of horses
Virus III infection of rabbits
Foot-and-mouth disease
1. Type A
2. Type O
Vesicular stomatitis of horses
Paravaccinia (No report on filtration)



Borna's disease
Fowl plague and plague of blackbirds
Guinea-pig paralysis
Distemper of dogs

TABLE 1—*Continued*

Trachoma and inclusion blenorrhea		
Infectious papular stomatitis of cattle		
Molluscum contagiosum		
Warts		
Contagious epithelioma (fowl-pox)		
1. Chickens		
2. Pigeons		
Infectious myxomatosis of rabbits		
Rous sarcoma of chickens		
Leukemia of chickens		
Lymphocystic disease of fish	No reports on filtration	
Epithelioma of fish		
Carp-pox		
Mumps (According to Kermorgant, a spirochetal disease)		
Agalactia (According to Bridré, a bacterial disease)		
Salivary gland disease of guinea pigs		
Measles (rubeola)		
German measles (rubella) (No report on filtration)		
Grippe (influenza) (According to Olitsky and Gates a bacterial disease)		
Common colds		
A Insect-borne	A	Nairobi disease of sheep
		Catarrhal fever (blue tongue) of sheep
		African horse sickness
		Pappataci fever
		Dengue fever
		Yellow fever (According to Noguchi a spirochetal disease)
	B Rickettsia diseases	Typhus fever
		Trench fever
		Rocky Mountain spotted fever
		Heartwater disease
		Flood fever of Japan
B Bacterial diseases		Orroya fever and verruga peruviana
		Pleuropneumonia
		Avian diphtheria
		Scarlet fever

transmissible agents which are capable of producing pathological conditions in bacteria, plants, insects, fish, birds, and mammals, and which by general consent are more or less limited for the moment to the etiological agents of the diseases listed in the table.

The arrangement of the diseases in the table is for convenience of discussion and carries no taxonomic significance. In the first place, filterability of the etiological agents does not sharply delimit this group of diseases, as it is well known that the viruses share this characteristic with certain small bacteria and vibrios, and also with some spirochetes and protozoa. Furthermore, in regard to the etiological agents of some of the diseases wtihin the group, e.g., chicken-pox and paravaccinia, no filtration experiments have been recorded. The viruses of still other diseases within the group, e.g., typhus fever, and vaccinia, are either not filterable or filterable with the greatest difficulty. In the past all attempts to classify these diseases have been unsuccessful and there is every reason to believe that such attempts are still premature.

The diseases listed do not form a homogeneous group and some of them should be omitted. The evidence that epizoötic of guinea pigs is a virus disease is not convincing. The Rickettsia diseases do not belong here and there is considerable doubt as to how long the other insect-borne diseases will remain on the list. This is particularly true of yellow fever. Most observers no longer consider scarlet fever a virus disease. M'Fadyean, as early as 1908, suggested that pleuropneumonia be classified with bacterial diseases. Oroya fever and fowl diphtheria, in view of Noguchi's work and Bordet's experiments respectively, do not belong here. Enough has been said to convince one of the heterogeneity of the diseases listed in the table. In fact they exhibit so many differences that a discussion of the filterable viruses almost amounts to a separate discussion of each disease. Such a state of affairs is due to the fact that the filterable virus group has been used to a considerable extent for the indiscriminate segregation of infectious diseases of unknown etiology. Therefore, it is not unlikely that some of them will be shown to be caused by small bacteria or protozoa. When this occurs, such

diseases should be removed from the filterable virus group and given their correct position in the classification of diseases.

EPIDEMIOLOGY

From the epidemiological standpoint the group of filterable virus diseases is notable chiefly because of the remarkable differences exhibited by its members when compared one with another. Some are extremely contagious, e.g., smallpox; others, although inoculable, are not spread by ordinary contact, e.g., rabies; others are insect-borne, e.g., dengue fever and yellows of asters; and still others are transmitted only by grafting, e.g., certain infectious chloroses of plants (Baur). In general, however, the epidemiological problems presented by the virus diseases in regard to regional distribution, seasonal variation, host susceptibility, and virulence are similar to the problems found in connection with other infections.

IMMUNITY

Since immunity, either natural or acquired, plays such an important rôle in all epidemiological studies, a discussion of it at this point is not out of place. With a few exceptions, diseases produced by the filterable viruses, if recovered from, lead to a lasting immunity. In this respect virus diseases differ from those caused by ordinary bacteria. This is not universally true, however, since one attack of typhoid fever produces in the recovered individual a fairly lasting immunity. Many questions have arisen in regard to this kind of immunity, but so far they have not been satisfactorily answered. Nevertheless, a few of the possibilities will be discussed.

Adults, forty years of age, who had measles or chicken-pox when 1 year old are still refractory to reinfection. Some investigators state that the serum of these refractory individuals is slightly protective even after a period of 39 years, or contend that the cells are still supplied with sessile antibodies or an increased ability to make them. The majority of the cells in an adult, however, are not the same cells possessed by that individual when

1 year of age. If it is a question of sessile antibodies, then one must suppose that these characteristics are passed on to daughter cells. On the other hand, a child born of immune parents becomes susceptible to measles and chicken-pox within a few months after birth. Is it possible then that the lasting immunity is due to repeated infections so mild that they attract no attention except in the first instance? In regard to diseases as prevalent as measles and chicken-pox this might serve as an explanation. On the other hand, one can hardly explain the persistent protection against poliomyelitis and smallpox upon such grounds.

Another possible explanation for the lasting immunity is that it is due to a prolonged sojourn of the virus in the body or perhaps to its persistence in an individual once infected. Winkler, in his review of immunity to vaccine virus, suggests this possibility. When confronted with the idea one invariably says that it is impossible, because, if it were true, every one would spread measles and chicken-pox. This would not necessarily be the case, however. Typhoid bacilli have been found in the walls of gall-bladders many years after attacks of typhoid fever. Furthermore, when the mucous membranes lining the gall-bladders are normal, there is little danger of the disease being spread by these carriers. Most human beings carry tubercle bacilli, but only a few spread tuberculosis. Individuals harboring *Treponema pallidum* are not always infectious, particularly in the latent stages of syphilis. Furthermore, syphilis is an excellent example of a disease in which there is a persistent infection coincident with a refractory state in the host to reinfection. For information concerning discussions of this paradox one should read Chesney's review, "Immunity in Syphilis" (Medicine, 1926, **5**, 463).

Now, in regard to virus diseases, is there any evidence (1) of a prolonged or persistent infection, (2) of a coexistence of infection and refractory state in the host to reinfection from without, and (3) of a causal relation between the prolonged or persistent infection and the lasting immunity? There is considerable evidence that a prolonged infection occurs in some virus diseases and also that this infection can persist for a long time in a host refractory to reinfection. De Kock found a horse's blood infectious seven

years after an attack of pernicious anemia. Sir Arnold Theiler speaks of the persistent infectious nature of the blood of horses that have recovered from pernicious anemia. He also states that the blood of horses inoculated with African horse sickness may remain infective for periods up to three months after inoculation. In the majority of instances, a plant once infected with mosaic virus is never free from it. Vaccine virus has been recovered from the lymph nodes of an animal 28 days after inoculation and twenty-two days after the animal's skin was refractory to reinfection. A prolonged infection occurs in contagious epithelioma, and in regard to this disease Lipschütz says, "Der immune Organismus ist Parasitenträger." Furthermore, Cole and Kuttner have shown that the "salivary gland virus" of guinea pigs can be obtained at will from immune animals, and in this particular instance it appears that a pig once infected continues to carry the virus indefinitely in spite of a refractory state to reinfection from without. The question as to whether the lasting immunity is dependent *per se* upon a prolonged sojourn or persistence of viruses in the body cannot be answered at the present time. Nevertheless, such an idea, novel in regard to virus diseases, is worthy of serious consideration.

Another interesting feature concerning the immunity to virus diseases is the fact that only active virus protects against a second inoculation of the same virus. In other words it is doubtful, with a few exceptions, whether injection of a virus completely inactivated leads to a protection against the same virus in an active state. Furthermore, virucidal properties do not appear in the serum of naturally resistant animals which have received repeated injections of active virus. Therefore, it seems that an actively acquired immunity and evidences in the serum of such an immunity are dependent in some way upon an actual infection with the virus, even though it be so mild at times as to give rise to no symptoms.

The degree of active immunity usually exhibited by individuals recovered from virus diseases seems disproportionate to the amount of passive protection afforded by their sera. This fact has led many observers to believe that the protection against

virus diseases is predominantly a tissue immunity rather than a humoral one. Be that as it may, protective substances do occur in the sera of individuals who have recovered from certain virus diseases. This is particularly true when animals have been hyperimmunized by means of repeated injections of the viruses, as is evidenced by Gordon's work concerning immunity to vaccinia.

Virucidal properties, precipitins, and complement-fixing antibodies have been demonstrated in the sera of individuals who have recovered from certain of the virus diseases. Gordon and others believe that agglutinins also exist in the sera of animals that have recovered from vaccinia, inasmuch as "vaccine granules" are agglutinated by such sera. Until these granules have been definitely shown to represent only vaccine virus, one must look upon the supposed agglutinins with a great deal of suspicion.

PREVENTION OF DISEASE CAUSED BY VIRUSES

The prevention of diseases caused by viruses depends upon the protection of susceptibles from exposure or upon their immunization. Quarantine measures are established for protection but frequently they are ineffectual. The eradication of insects or protection against them controls the spread of insect-borne diseases. Furthermore, susceptible species can be replaced by naturally insusceptible ones, and at times it is possible to breed refractory hybrids. This method has been used advantageously where animals and plants are concerned. Unfortunately, however, such methods cannot be employed in dealing with all animal diseases, nor can they ever be used in dealing with human diseases. Under these conditions attempts are made to decrease the number of susceptibles by means of vaccination with attenuated or modified viruses.

FILTERABILITY

Since the discovery of the first filterable virus in 1892, it has been determined by means of different kinds of filters that many diseases are caused by active agents smaller than ordinary

bacteria. Some are presumably much smaller and are most likely optically immeasurable. Others, however, do not seem to be so small and concerning the filterability of these there is much discussion. Methods of filtration are crude and inaccurate and the most one can say regarding the viruses is that under given experimental conditions they either pass or do not pass through certain filters. The failure to pass through a filter, however, is certainly not determined in every instance by the size of the virus. The electrical charge on the virus, the electrical charge on the filter, the adsorption of the virus by aggregates of protein or by cell detritus, the amount of protein or other substances in the virus emulsion, the temperature at which the filtration is conducted, the amount of negative or positive pressure employed, the duration of filtration, and other factors, not mentioned or not known, serve to influence the results of all filtration experiments. Furthermore, sufficient attention has not been given to the possibility that some filters may not only hold back certain viruses but may also inactivate them in some manner so that they can never become active again.

Filters, in spite of their faults, are useful in working with diseases of unknown etiology, and by means of them one is able at times to determine quickly whether a given disease is produced by an agent smaller than ordinary bacteria. Sometimes, however, small bacteria may still contaminate the filtrates or two viruses may be present in the filtered material. Therefore, filtrates from uncontrolled and even from well controlled sources may contain more than one active agent, some of which may be cultivated on simple or on special media. All investigators should be extremely careful in working with filtrates not to be misled by their findings and ascribe to an active agent an etiological rôle in a disease with which it has nothing more than accidental connection.

SIZE

Very little has been recorded in regard to the size of many of the viruses other than that they pass through certain kinds of filters. It is obvious that this method only indicates roughly

that the viruses which pass through tight Chamberland candles are very small. No virus has been obtained in an absoutely pure state. Not even the washed granules of vaccine virus can be accepted as representing only virus. Therefore it is impossible to say that virus alone is being filtered rather than virus attached to aggregates of protein or particles of degraded cells. Nevertheless, attempts have been made in various ways to determine the size of a few viruses. According to d'Herelle, the diameter of the phage is 20 to 30$\mu\mu$. Bechhold and Villa state that its diameter is $>35\mu\mu$ and $<200\mu\mu$. Duggar and Karrer believe that the virus of tobacco mosaic is approxmately the same size as the colloidal particles of fresh 1 per cent hemoglobin, 30$\mu\mu$.

The size and weight of molecules of crystalline egg albumen and crystalline hemoglobin are not agreed upon. Bechhold states that an aggregate of 50 molecules of egg albumen is >4 and $<10\mu\mu$ in diameter. According to Du Noüy, however, 1 molecule of egg albumen is 4.1$\mu\mu$ in diameter. If it is difficult to determine the size of molecules of relatively pure crystalline substances, what hope is there at present of ascertaining the size of the viruses which have not been obtained in a pure state? Furthermore, it is useless to pretend to know what is the lower limit in point of size for living things. In general, however, it can be said that many viruses are probably of sufficient size to exist in a living state, and that others are probably small enough to satisfy the demands of those who insist that they are not possessed of life.

CULTIVATION

Following the discovery of the first filterable virus, thirty-four years ago, numerous workers have claimed to have successfully cultivated *in vitro* by means of simple or complex media one or more of these active agents. Since all claims cannot be discussed, only the outstanding ones will be considered. The term *in vitro* will be avoided as there seems to be no agreement as to its exact meaning. I shall, therefore, discuss the cultivation of viruses in the presence or absence of living cells.

There is no reason to doubt that vaccine virus, herpes virus,

typhus fever virus, the virus of Rous' sarcoma, and the virus of Rocky Mountain spotted fever have been successfully cultivated in the presence of living cells in tissue cultures. Moreover, Levaditi has stated that the virus of poliomyelitis either survived or multiplied in fresh spinal ganglia (monkey) placed in plasma Harde was able to grow vaccine virus in the presence of living corneal cells, but, if the cells were killed by freezing or by hypertonic salt solution, the virus failed to multiply. The virus of fowl plague is cited as one that has been cultivated *in vitro*. One might ask, however, if it has been cultivated in the absence of living cells, inasmuch as a large amount of blood was added to the medium employed. Furthermore, Landsteiner and Berliner found that the virus would not multiply if laked or frozen blood was used, and stated in their report that one could not say that growth of the virus had taken place in a lifeless medium. The statement is frequently seen that Bordet cultivated the etiological agent of contagious epithelioma of chickens. Such statements are incorrect. Bordet claims to have cultivated a small bacterium which causes avian diphtheria. Furthermore, he specifically states that the bacterium does not cause contagious epithelioma and that avian diphtheria and contagious epithelioma are two distinct diseases in spite of the view held by some investigators.

There are excellent reasons for stating that the etiological agents of foot-and-mouth disease, trachoma,[2] rabies, and poliomyelitis have not as yet been cultivated in the absence of living cells. The evidence is insufficient to convince one that "globoid bodies" are etiologically associated with poliomyelitis (Amoss). A consideration of the survival or the multiplication of the virus of poliomyelitis in the presence of pieces of fresh kidney is not germane to the discussion. Streptococci have been given an etiological rôle in many virus diseases. It is unlikely, however, that they cause all of the following diseases: poliomyelitis, lethargic encephalitis, influenza, measles, and German measles.

[2] Since this paper was submitted for publication Dr. Noguchi has reported his recent work concerning the cultivation of the etiological agent of trachoma.

Gye's reports concerning the cultivation of the virus of Rous' chicken sarcoma will be discussed further on.

Recently Olitsky reported that he was able to cultivate the virus of tobacco mosaic in a simple medium presumably free of cells. Mulvania and Purdy, working independently, were unable to confirm his work and suggested that his results are open to several interpretations. An observation of the kind reported by Olitsky, if correct, is one of a fundamental nature and significance. In fact, it is of almost as much significance as an observation upon the cultivation of bacteriophage in the absence of living bacteria. Unequivocal confirmation of Olitksy's work, therefore, would settle one of the most important problems in the whole field.

In general it can be said that no worker has proved that any of the etiological agents of the diseases in table 1 down to mumps is susceptible to cultivation in the absence of living cells. A satisfactory explanation of the difficulty experienced in cultivating the viruses on artificial media is not easily found. Their small size alone should not make them insusceptible to cultivation. Nor does it seem to be a question of delicacy or sensitiveness, because many of them are extremely resistant to chemical and physical agents. Therefore, the viruses appear to be obligate parasites in the sense that their reproduction is dependent upon living cells. Whether this reproduction occurs intra- or extracellularly is a debated question.

CELL TYPES IN RELATION TO VIRUS REPRODUCTION

In view of the fact that viruses apparently multiply only in the presence of living cells, it is advisable to ascertain what kinds of living cells promote their reproduction best, and what effect upon the cells is induced by this reproduction.

Species specificity. A remarkable species specificity is exhibited by many viruses. The Rous sarcoma grows only in chickens. Sanarelli's virus of infectious myxomatosis and Virus III are active only in rabbits. The "salivary gland virus" described by Cole and Kuttner apparently affects only guinea

pigs. A wilt virus that attacks one kind of caterpillar is innocuous for other caterpillars. The virus of poliomyelitis is active only in man and the monkey.

Importance of young cells. Frequently young cells seem essential for the activity of viruses. The bacteriophage multiplies only in the presence of young bacteria. Old or dead bacteria are not lysed except in the presence of young living forms. The activity of mosaic viruses is manifested only in young leaves. This applies also to the infectious chloroses transmitted by grafting only. Virus diseases usually attack insects in certain stages of development. In the higher forms of life virus activity is also best exhibited not in old, undernourished, sickly individuals, but in young healthy ones. Injury also plays an important rôle in the infectiousness of many virus diseases, not the rôle, however, of furnishing a *nidus* of dead tissue for the growth of the viruses, since dead tissues do not promote their growth, but the rôle of furnishing young cells or growth-promoting factors usually found in their vicinity. Injury necessitates repair. Restoration, as is well known, is accompanied by young cells. In a rabbit's cornea and skin the activity of vaccine virus, herpes virus, and Virus III is first seen along the lines of scarification. Furthermore, the evidence of this activity is first found in the young cells filling in the defects caused by the injury. Old cells may become involved later (see fig. 5). Rous and Murphy, working with chicken sarcomas, observed phenomena that seem to be related to injury. Injections of virus emulsion and kieselguhr give rise to more rapidly appearing and more diffusely growing tumors than does the inoculation of virus emulsion alone. More metastases are found in the ovaries during egg laying seasons than during quiescent periods. These phenomena are probably due to the presence of young cells participating in the repair of injured tissues.

Cytotropic phenomena. In some diseases produced by ordinary bacteria and in many caused by viruses, a certain amount of "selective tissue localization" is apparent. Variola, chickenpox, and contagious epithelioma usually attack the skin; rabies and poliomyelitis, the brain; Rous' sarcoma, mesodermal tissue.

Inasmuch as vaccine virus, herpes virus, and chickenpox virus attack both ectodermal and mesodermal cells, it seems that a position of exaggerated importance has frequently been accorded this phenomenon of "selective tissue localization." Nevertheless, some viruses, e.g., the virus of rabies and poliomyelitis, exhibit a remarkable affinity for cells of certain tissues and apparently can neither multiply nor produce signs of disease unless they come into a close relation with these cells.

Injury naturally plays an important part in the infectiousness of diseases that exhibit pronounced cytotropic phenomena. In this case it is not the function, however, of providing young cells, but the rôle of mechanically making it possible for the viruses to come in contact with susceptible types of cells.

EFFECTS OF VIRUSES UPON CELLS

It has been shown that some viruses multiply only in a restricted number of hosts, that frequently this multiplication occurs only when the virus is in close relation with certain types of cells, and that young, actively growing cells play an important rôle in the infectiousness of many virus diseases. Now a word will be said in regard to the effects produced in cells by viruses. At first the involved cells show a remarkable increase in size, often with amitotic division of the nuclei. The increase in size gives one the impression that it is due to growth phenomena and to imbibition of fluid. This process is spoken of as ballooning degeneration. Eventually the cells die and go to pieces. This process is spoken of as colliquation (see figs. 1, 2, 3 and 4). Two forces seem to operate: one stimulating the cell, the other destroying it. Consequently the picture produced by a virus disease is more or less dependent upon which of these forces predominates. Chicken-pox, foot-and-mouth disease, zoster, variola, and lysis of bacteria by phage are diseases in which destructive agencies predominate. Rous' sarcoma, contagious epithelioma, fowl leukemia, and warts are diseases in which stimulating forces are dominant. A few observers have attempted to classify the cytotropic viruses under cytolytic and cytokinetic

headings with subdivisions under each according to the type of cells involved. Such a classification is premature. In table 1, however, a suggestion of the possibility is seen in the arrangement of the diseases.

It is not known whether the viruses multiply intra- or extracellularly. Nevertheless, they have a profound influence upon cells and cause remarkable changes within them. This influence most likely accounts for the fact that in lesions caused by many viruses intracellular changes assume appearances characteristic enough to be spoken of as inclusion bodies. In this respect many virus diseases differ from those caused by ordinary bacteria.

INCLUSION BODIES

Viruses usually produce characteristic macroscopic lesions in plants, insects, birds, and animals, or cause marked changes in their condition. Such alterations and lesions serve as indications of virus activity. In addition to the characteristic macroscopic lesions already mentioned, many viruses also produce equally characteristic microscopic changes as evidenced by the presence of inclusion bodies in the nuclei and cytoplasm of affected cells. There is no obvious reason why these microscopic changes, inclusion bodies, should not be used as guides or indicators with the same degree of readiness as that with which the macroscopic lesions are employed. Diagnoses based upon the pictures presented by aggregates of cells, as in tuberculosis and cancer, are familiar to all and no one is astonished any more at the correct diagnoses made by competent pathologists. Why not, then, use pathological pictures found within cells as aids in diagnostic and experimental work? Intracellular pathology can be used in this manner. As a matter of fact, it has been used for a long time in the diagnosis of rabies and smallpox.

Inclusions have been seen in the cells of plants, insects, fish, birds and mammals affected by virus diseases. Many of the inclusions described, however, cannot be accepted as specific or characteristic and it is these that detract from the significance of those which are well established and accepted by numerous

critical investigators. No worker familiar with the microscopic pathology of the virus diseases doubts the importance and significance of Guarnieri bodies, Negri bodies, Bollinger bodies, and the nuclear inclusions seen in varicella, herpes, and several other diseases.

Various ideas are held concerning inclusions. Some investigators consider them merely as products of degeneration, but others believe that they are the virus itself, while yet others think of them as virus surrounded by a mantle of altered cellular material. As yet their nature has not been definitely determined. Nevertheless, in spite of the ignorance concerning their nature, inclusion bodies have held and will continue to hold an important position in the study of this group of diseases. Many attempts to produce significant inclusions by artificial means have been unsuccessful. Therefore, under properly controlled conditions the presence of inclusions, accepted as significant, will undoubtedly in the majority of instances be indicative of the presence of a virus in the immediate vicinity.

Inclusion bodies have not been found in all virus diseases. In some they may have been overlooked, while in others they may not occur. A restudy of the diseases of unknown etiology may reveal many interesting changes within the cells. These studies, however, must be made or guided by well trained men with a wide knowledge concerning normal and pathological tissues in order to prevent the literature from being flooded with reports dealing with inclusions not of a characteristic or specific nature.

RESISTANCE TO PHYSICAL AND CHEMICAL AGENTS

It is generally believed that viruses are more resistant to glycerol than are ordinary bacteria. This is not universally true, however. Virus III, the "salivary gland virus" of guinea pigs, and others are not active after remaining in 50 per cent glycerol for six weeks. On the other hand, many bacteria, particularly if in tissues, remain viable in glycerol much longer than 6 weeks. The extensive use of glycerol for the preservation of viruses is

probably largely dependent upon the fact that viruses are usually very susceptible to conditions in autolysing tissues and that glycerol acts as a desiccant and retards autolysis of the tissues containing the viruses.

All viruses are inactivated by high temperatures. The degree of heat necessary to accomplish this varies from 45° to 80°C. depending on the virus. The majority of them resist low temperatures. Repeated freezing and thawing with liquid air (−185°C.), however, does not sharply separate them from ordinary bacteria on the one hand and from enzymes on the other. Under ordinary conditions some retain their activity *in vitro* for periods of 5 years, others become inactive within 48 hours. Some resist putrefaction and drying. Extraction with chloroform, acetone, alcohol, and toluol for periods of 2–8 days does not inactivate some dried viruses (vaccine virus). A few even in a wet state are not inactivated in this manner (virus of tobacco mosaic). Dry spores of certain bacteria (*B. subtilis*) also resist extraction by means of these agents. The virus of contagious epithelioma is active after exposure for twenty-four hours to 1 per cent sodium hydroxide.[3] Three per cent phenol does not inactivate the virus of African horse sickness. Plant cells are supposed to be more tolerant of the injurious action of bile and saponin than are animal cells. In view of the general susceptibility of the viruses to the action of these agents, some workers are inclined to believe that they are more closely related to protozoa than to bacteria. There are a number of striking exceptions to the rule, however. More evidence is not needed to convince one that a wide range in the degree of resistance to physical and chemical agents is exhibited by the viruses, and that a classification based upon resistance to such agents is as impossible of accomplishment as is an adequate classification of ordinary bacteria by means of thermal-death-point determinations.

[3] According to Friedberger, this statement is incorrect.

QUESTION OF THE CORPUSCULAR NATURE OF VIRUSES

The question of the organized or corpuscular nature of the viruses has not been satisfactorily settled. This is due to the fact that most workers realize that the granules which are seen, which are frequently held back by filters, and which are thrown down by prolonged centrifugation may not represent virus alone. This is particularly true since viruses exhibit a remarkable tendency to be adsorbed by many things with which they come in contact.

DO VIRUSES RESPIRE?

Very little information concerning the respiration of viruses is available. Recently, however, Bronfenbrenner reported that he was unable to detect any respiration on the part of phage, herpes virus, and rabies virus in the absence of living host cells. He also found, taking the rate of multiplication into consideration, that growing bacteria plus phage show no more respiratory activity than do growing bacteria alone.

MUTATION (?) OF VIRUSES OR THE RESULTS OF THEIR ADAPTATION TO NEW HOSTS

Mutations of bacteria with concomitant changes in their characteristics are at present of particular interest to bacteriologists. Naturally the question arises then as to whether viruses can mutate. In the field of filterable viruses, however, this is not a new question, inasmuch as it has been under discussion in regard to the relation between vaccine virus and the virus of smallpox since Jenner's time. In spite of all contradictions, it seems that smallpox virus passed through several calves becomes vaccine virus. Furthermore, if a sufficient number of passages is made in calves, it is impossible for this altered virus to regain the characteristics of smallpox virus even after repeated passages in men. Observations of a similar nature have been made in regard to other virus diseases, e.g., contagious epithelioma of chickens and pigeons, and mosaic disease of tobacco and cucumbers. Whether it is correct to speak of these phenomena as

examples of mutation is not known. In any event, when viruses are adapted to alien hosts, their characteristics are frequently altered as well as are those of the diseases produced by them.

DO THE VIRUSES EXIST IN A LIVING STATE?

The question as to whether the viruses are animate or inanimate is also an old one, inasmuch as it was propounded simultaneously with the discovery of the filterable nature of the viruses. Beijerinck's idea of a living contagious fluid called forth many protests. Sanfelice working with fowl-pox in 1914 found that the virus was not inactivated by 1 per cent sodium hydroxide, and, because of this fact, he was led to think of it as an inanimate poison capable of attacking normal cells and producing within them a poison of a similar nature which in turn could attack other normal cells. Thus he described his idea of how a lifeless agent might be passed in series reproducing itself indefinitely. The work of Twort, d'Herelle, Bordet, and others concerning the bacteriophage is familiar to all. The numerous discussions concerning the nature of this active agent have led investigators to question more closely the living nature of other filterable viruses. Many tests have been devised to act as criteria for the presence of life, but so far no one of them has been found satisfactory. Therefore, it is impossible at present to say whether the viruses are animate or inanimate. Furthermore, it is wise to leave the subject at this point as further pursuit of it leads one into the sterile discussion of what life is, a problem still in the realm of metaphysics.

IDENTITY OF THE EPITHELIOTROPIC AND NEUROTROPIC VIRUSES

In table 1 the diseases from swine-pox through rabies have been arranged and bracketed in a way that quickly shows the relation claimed by different workers to exist between members of the group. There is undoubtedly a close relation between the diseases in the upper part of the group-swine-pox through alastrim. It is now generally believed that chicken-pox and smallpox are distinct and different diseases. This has not always

been the case, however, and as late as the middle of the 19th century Hebra taught that they were identical. Even at the present time there is a difference of opinion in regard to the relation of smallpox and varioloid to alastrim on the one hand, and of chicken-pox to alastrim on the other. Gildemeister and Herzberg recently offered experimental evidence to support the idea of a close relation between herpes virus and vaccine virus and suggested that one might be a mutant of the other. Bokay's paper on the relation of chicken-pox to herpes zoster appeared in 1909, and since then a number of other papers have appeared in which the idea that the two diseases are identical has been supported or opposed. For many years there has been much discussion concerning the interrelationship existing between the various kinds of herpes, and this interest has been stimulated by the work of Doerr, Levaditi, Flexner and Amoss, and others on herpes and lethargic encephalitis. There is great confusion of ideas and facts in regard to encephalitis. Several kinds of viruses have been obtained from the brains of individuals who have died after showing signs of encephalitis, and to each of these viruses has been ascribed an etiological rôle. I am not convinced that this rôle, in many instances, is more than an accidental one. Furthermore, since encephalitis follows a number of infectious diseases, I am not convinced that the brain is the proper place to look for the etiological agent, inasmuch as other agents besides viruses and bacteria attack nervous tissue, toxins for instance.

Many of the viruses may be closely related or some may have evolved from a common ancestor. Nevertheless, it will be hard to convince observant workers that chicken-pox, symptomatic herpes, and smallpox now possess much in common. Since a great deal of the evidence in favor of the identity of these viruses has been obtained by means of cross immunity experiments conducted in the skin of human beings and animals, it is possible that a factor generally overlooked or underestimated is responsible for some of the confusion. Jenner and others of his time recognized the fact that skin diseases, exanthems, and extensive mechanical injury might induce a temporary refractory state to vaccine virus. This phenomenon was thought to be dependent

upon some non-specific factor. Ledingham recently reported that India ink injected into the skin of a rabbit rendered it resistant locally to vaccine virus for forty-nine days. Carnot has shown that skin treated several times with ultra-violet light is temporarily refractory to vaccine virus. Experienced workers invariably tell inexperienced ones not to use areas of skin previously handled when conducting cross immunity experiments. Busson has reported that guinea pigs immunized a short time previously to vaccine virus resisted a known lethal dose of rabies virus. He thought that the protection was probably non-specific. Enough has been said to show how easily one may be misled in regard to the identity of the viruses if one is not cognizant of the difficulties usually encountered in this field of work.

MEASLES

Measles is usually placed with the filterable virus diseases. Recent reports, however, support the idea that it does not belong here. Results obtained in its prevention constitute much of the evidence used to substantiate different etiological claims. The conflicting reports concerning the cause and prevention of measles afford an excellent example of the difficulties frequently experienced when one attempts to evaluate work in the virus field. The importance of this disease and the special interest recently aroused concerning it make it advisable to examine in detail some of the reports in the hope of finding an explanation for the diversity of opinions.

Etiology. Blake and Trask, and others have reported that sterile filtrates obtained from measles patients produce lesions in monkeys similar to those seen in man. Tunnicliff, Donges, Ferry and Fisher, and Hibbard and Duval have cultivated a non-hemolytic streptococcus from the blood of measles patients. Tunnicliff recovered the streptococcus in 42 instances from the blood of 52 patients, but from 20 of the cases she was also able to cultivate other bacteria in addition to the streptococcus, e.g., 10 aërobic and 12 anaërobic diphtheroids, 6 filamentous organisms, 4 Gram-negative spirilla, 1 black-pigment-forming bacillus, 4

large spore-forming bacilli, and 3 staphylococci. Furthermore, she was able to obtain a different kind of streptococcus from the blood of patients with German measles. Ferry and Fisher, and Tunnicliff are now able to show that the "measles streptococcus" produces a toxin which may play an important etiological rôle. According to this view there is a striking analogy between measles and scarlet fever. From the blood of measles patients Salimbeni and Kermorgant have cultivated a delicate spirochete associated with a Gram-negative bacillus; Sellards and Bigelow, a small Gram-positive bacillus; Kusama, by means of passage through monkeys, a Gram-positive diphtheroid-like bacillus. Caronia believes that a Gram-negative, anaërobic, filter-passing organism, which he obtained from the blood and several other sources in measles patients, is the cause of the disease. Furthermore, filtrates from Caronia's cultures apparently give negative skin reactions in measles susceptibles and positive ones in individuals who have recovered from the disease.

In spite of the fact that measles is generally considered a virus disease, a great variety of bacteria have been recovered from the blood of measles patients. All of these bacteria cannot be the cause of the disease, however. It seems not unlikely that the blood of measles patients is easily invaded by many kinds of organisms. This fact does not seem very remarkable when one considers the leucopenia and the abnormal condition of all the mucous membranes that regularly accompany the disease.

Prevention. Cenci, in 1907, was probably the first to use convalescent serum in the prevention of measles, and this measure has since been shown to be fairly effective in preventing the disease provided the serum is administered within five or six days after exposure. This type of protection usually lasts only a few weeks. Salisbury, in 1862, reported that subcutaneous injections of wheat rust, a fungus, if made within a few days after exposure, usually prevented the development of measles. Galli, in 1922, reported that injections of normal horse serum protected exposed children. Caronia claims that his vaccine, given within five or six days after exposure, protects as well as convalescent serum. This claim has been confirmed by Nobel

and Schönberger in Pirquet's clinic. They state, however, that the protection is probably non-specific or that it is due to heterogenetic antibodies. De Gröer and Redlich made a Forssmann antigen from kidney extracts of certain animals. With this antigen they obtained as good, if not better, protection than that secured with convalescent serum. The protection lasted only two to eight weeks. Schilling reported that injection of Caseosan protected children exposed to measles. Tunnicliff immunized goats to the "measles streptococcus." The immune goat serum is said to protect against measles and to exhibit local rash prevention propensities. No reports have been seen in regard to the action of normal goat serum. In fact, there is no evidence that such controls were made. By means of virus cultivated in human blood cells and plasma, Degkwitz immunizes the sheep, an animal that has not been shown to be susceptible to measles. This immune sheep serum is reputed to prevent and possibly to cure measles. To act as a preventive it must be administered between the seventh and eleventh days after exposure. This seems odd, since convalescent serum and Caronia's vaccine must be given within five or six days after exposure. Many reports have appeared concerning the action of the immune sheep serum; some favorable, others unfavorable.

The facts presented concerning the work on measles make it obvious that all of the reports cannot be correct. Furthermore, it seems that the successful prevention of the diseases is not always dependent upon specific measures. When one is exposed to measles in the natural way, it is unlikely that one comes in contact with much more than a minimal infecting dose. Under these circumstances there is a possibility that many foreign substances if injected into patients at the proper time after exposure may in a non-specific manner protect them temporarily. This possibility, however, is inadequate excuse for the injection of all kinds of foreign substances into patients, and, if such tactics are continued, it will be difficult to establish the proper measure of prevention when it is found.

MALIGNANT GROWTHS

A discussion of malignant growths in connection with filterable virus diseases may seem out of place. Nevertheless, recent reports concerning the nature and origin of tumors make it necessary to say a word in regard to the subject.

Sanarelli, in 1898, described an infectious myxoma of rabbits. Later Moses was able to transmit the tumor by means of sterile filtrates. Rous and Murphy have shown that some spontaneous tumors in chickens are transmissible by means of tumor filtrates. These chicken tumors have led to a great deal of discussion in regard to their importance in the general study of malignant growths. Recently increased interest has been aroused in the Rous sarcoma and in the general cancer problem by Gye, who reported that two factors are essential for the production of malignant growths, one of which is a living organized virus capable of multiplication in certain complex media. The virus cultivated under these conditions, however, is innocuous and only becomes capable of producing tumors when mixed with a second specific factor found in tumor filtrates inactivated by means of chloroform, heat, and antiseptics. Murphy, Cori, and Harde are of the opinion that Gye did not properly control his experiments. Furthermore, the two former workers have been able to reactivate a chloroform treated filtrate by the addition of substances containing no virus. Since Gye has not conclusively demonstrated that all the virus in his treated filtrates was inactivated and since others have shown that 4 cc. of such filtrates produce tumors when 2 cc. fail, the proof that two factors are essential or that the virus has multiplied in cultures is unconvincing.

Gye's ideas and experimental results concerning the production of chicken sarcomas are diametrically opposed to those of Carrel, who has reported that he was able to produce sarcomas, transmissible by filtrates, by injecting into chickens embryonic tissue mixed with tar, arsenic, or indol. Carrel believes that the etiological agent of these tumors originates within cells of the host under certain conditions and is of a phage-like nature in the sense that it transforms normal cells into malignant ones

which die and liberate more of the active agent. In this manner the virus is supposed to reproduce itself indefinitely. On the other hand, Murphy and Landsteiner were unable to produce sarcomas, transmissible by filtrates, by injecting into chickens mixtures of embryonic tissue and tar. Carrel's conception of the origin of tumors is not a new one, inasmuch as Sanfelice in 1914, Twort, and Doerr more recently voiced exactly the same idea. Nevertheless, no one has offered as much evidence as Carrel that the conception is correct. In view of the fundamental significance of such a conception from a broad biological standpoint, reports concerning attempts to confirm this work will be eagerly awaited by workers in this field. At the present time no final conclusion can be drawn.

FUTURE STUDY OF VIRUS DISEASES

The etiological agents of some of the diseases in table 1 will probably be cultivated or otherwise definitely identified. Consequently attempts to cultivate them should not be abandoned entirely. On the other hand, the indications are that some viruses will not be cultivated in the absence of living cells until cells and their activities can be more accurately imitated. Therefore, cultivation experiments should not engage our entire attention. Kraus and others have suggested that filterable stages of bacteria, protozoa, and spirochetes may play a rôle in certain virus diseases. This is unlikely. The fact that it is impossible to cultivate in simple media the filterable forms of these etiologic agents does not explain why the non-filterable forms are invisible or insusceptible of cultivation.

How, then, is progress to be made in the study of virus diseases? It will be difficult for the best trained workers and doubly difficult for ones poorly trained to progress rapidly in this field. As long as viruses resist cultivation on simple media, just so long will it be necessary to study them in the host, in the tissues of the host, or in emulsions and filtrates of the tissues. At times it may be impracticable to study a disease adequately in its natural host, e.g., man. In such instances efforts are usually

made to establish the disease in a suitable experimental host. In order to recognize and identify the disease in the new host, the worker must be familiar with the clinical and pathological picture in the old one and at the same time capable of employing the necessary immunological tests. Furthermore, it must be remembered that the new host may decidedly alter both the disease picture and the virus, and that this host may be subject also to natural virus diseases of its own. Therefore, under such circumstances, one should be careful in explaining the unknown in the old host by means of facts obtained from studies conducted in the new.

Sufficient attention has not been paid to the effect that viruses have upon each other when acting simultaneously or alternately in the same animal or to the effect that other kinds of diseases have upon the localization and activity of viruses. In regard to herpes zoster, herpes simplex, cancer, and encephalitis following vaccination one frequently hears the statement that a latent virus has become active in the presence of injury or the activity of a new virus. I have already suggested that some viruses might persist in the body for a long time. There is definite proof of this persistence, however, in only a few instances. In how many more it occurs is not known. One should not assume the presence of a latent virus without at least attempting to prove the validity of the assumption.

Prevention of a virus disease does not necessarily depend upon the visibility of the etiological agent or upon a complete knowledge of its pedigree, as is evidenced by vaccination against smallpox and rabies. It appears that the use of active virus either in small amounts or in an attenuated state is the only means by which a lasting protection can be obtained. Money and time would be well spent, then, in attempting to remove the unnecessary and objectionable ingredients of virus emulsions used for vaccination purposes. Moreover, it might be wise to make further attempts to determine whether, in some instances, instead of vaccination with active viruses, the repeated subcutaneous injections of purified and inactivated viruses lead to a degree of immunity sufficient to warrant their use.

SUMMARY

In the majority of virus diseases a close relationship between the etiological agents and the cells of the hosts exists. This intimate type of parasitism is emphasized by the fact that some of the diseases exhibit a striking species specificity, that the viruses have resisted cultivation in the absence of living cells, that characteristic or specific pathological changes are frequently observed in cells affected by viruses, and, finally, that a host once recovered from a virus disease usually exhibits a lasting immunity.

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PLATE 1

FIGS. 1 AND 2. Hyperplasia and necrosis in mosaic tomato fruits. Compare with figures 3 and 4. (Reproduced from Jour. Agric. Research, 1925, **30**, 871, by the courtesy of M. W. Gardner.)

FIGS. 3 AND 4. Stimulation and destruction of epidermal cells by the virus of chicken-pox. Compare with figures 1 and 2.

FIG. 5. Section of rabbit's cornea removed forty-eight hours after inoculation with herpes virus. Intracellular changes, nuclear inclusions, are only in the young cells filling the defect caused by scarification.