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FILTERABLE VIRUS AND RICKETTSIA DISEASES IN THE TROPICS. I.

A GENERAL REVIEW[1]

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Tropical medicine includes not only those diseases which are peculiar to the tropics but a large number of diseases which are highly prevalent in temperate climates. It is true that there are diseases which are common in temperate climates and which are apparently absent or extremely rare in the tropics and the reverse of this is also true. We are concerned in this review with a group known as the "Filterable Virus and Rickettsia" diseases, and for the most part these affections are found both in temperate climates and in the tropics and are in no way peculiar to the former or the latter with the possible exceptions of one or two diseases which will be described later. It is interesting to note that most of the diseases of this group do not differ in this respect from definite bacterial diseases, many of which are common both to temperate and tropical climates.

It is the purpose of this review to make a survey of the filterable virus diseases of human beings which are present in the tropics with particular emphasis upon what is known concerning the *etiology* of these conditions. It must be remembered, however, that the human diseases which fall into this field represent only a fraction of the total number of diseases now classified as filterable virus in origin. Various plants, lower animals, insects, fowls and fish are affected by diseases of filterable virus origin. Indeed, according to d'Herelle [26], bacteria may also be affected by a filterable virus as demonstrated by the phenomenon of bacteriophagy. This question, however, is still open to debate. In all, the writer has recently collected data on nearly seventy diseases of man, animals, plants, insects, fowls

[1] This is the first of a series of eight articles on Filterable Virus and Rickettsia diseases. Other articles will appear in subsequent issues of the Review. This article and subsequent papers of this series are taken from a monograph on this subject now in press (Philippine Journal of Science).

and fish which fall into the category of filterable virus and rickettsia diseases. A detailed and comprehensive treatment of each of these diseases will appear shortly in a separate monograph [69]. For a critical analysis of the field the reader is referred to a recent work on this subject edited by Rivers [70] and to a recent paper by Mac Callum [4].

What is a filterable virus disease? What is a filterable virus? How do filterable virus diseases differ from well known diseases of bacterial origin? How do the filterable viruses differ from bacteria? Is immunity the same in the filterable virus diseases as in bacterial diseases? Are the virus diseases transmitted in the same manner as bacterial diseases? Are the epidemiological aspects of the filterable virus diseases the same as other diseases? How do the virus diseases differ from each other? These are only a few of the questions which modern investigations are trying to solve. Within the last few years the sujeet has become more or less specialized. Indeed one large University has established a chair in its medical school for the study of virus diseases. New impetus and interest has developed in this field as a result of recent discoveries and will continue to develop as other new discoveries are made. It is to be lamented, however, that many diseases of unknown etiology have been placed in the category of virus diseases, in many instances, upon meager scientific data. Indeed the field has offered a convenient waste basket in which to throw those diseases, the causes of which are unknown, and much time and labor will be necessary to extricate and reclassify some of these according to fundamental scientific facts.

HISTORICAL AND GENERAL

Definition:

Loeffler in 1898 defined a filterable virus as "the virus of an infections diseases which is so small that it will pass through the pores of a Berkefeld or Chamberland filter. An ultramicroscopic virus is a virus which is too small to be seen with a microscope. It is most difficult to formulate a definition of a virus which will fit even the meager facts known about viruses today and at the same time provide a concept for hypothetical viruses of which we know practically nothing. Undoubtedly we all have a mental concept or mind picture of what we consider a virus. We may adhere tenaciously to the belief that all viruses are living agents or particulate units or we may consider the vast majority of viruses in this light and recognize the further possibility that viruses may exist in an un-

organized state. We may even be willing to admit of the possibility that some viruses are non-living. The facts are that we do not know the exact nature of many so-called viruses and we do not possess enough accurate information to enable us to make a decisive statement in the matter. We have impressions, ideas, and theories; we have personal convictions based on experience, experiment, logic and reason; but with regard to many filterable viruses, the great majority in fact, we lack both cultural and morphological data and our information is essentially limited to the relation of these viruses to external physical agents. What then should be our attitude in defining a virus? Future studies in the field of the filterable viruses or protobiology may lead to startling discoveries and the nature of these minute structures, when it is definitely known, may alter some of our most fundamental theories of life and evolution. Suffice it to say that in the light of our present knowledge we believe the statement is justified that at least one type of virus (perhaps all types) may be defined as a living particulate agent which may be capable of inducing disease. In this sense we may recognize living particulate agents which are both pathogenic and nonpathogenic and include in this definition bacteria, protozoa, the filterable viruses, etc. In addition to this group we are further willing to admit of the possibility of the existence of a group of unorganized agents which may or may not cause disease. In this group we should place poisons, both chemical and animal, toxins, enzymes, etc., and any other hypothetical disease-producing substance or substances which, at present, are part of the great unknown and do not form part of our knowledge.

The term "virus" is an old one and originally it was derived from the Latin, meaning poison. Time has modified our understanding of the original translation of this word. Several "virus terms", have been in common usage since the latter half of the nineteenth century such as "virus animatum", "dehumanized virus", "humanized virus", "virus fixé" and "street virus", with all of which the student is familiar. Some of these terms are little used today. Other words have been compounded with the term virus such, for example, as "viruliferous" (L. virus (poison) and ferre (to bear); hence the definition "conveying or producing a virus or infective germ"). Still another term more recently introduced into the literature is "virucidal" or "virucide" (virus (poison) and L. caedere (to kill) and is defined as "destructive to viruses."

History:

In 1659 and 1675 a Jesuit, Kircher, and a contemporary, van Leeuwenhoek, a Dutch linen-draper, invented the simple microscope. These two men were undoubtedly the first to see living cells too small to be seen with the naked eye. From all available records there remains little doubt that these men actually saw bacteria. Whether the imaginations of these two pioneers ever rested upon the possibility of living agents still smaller than those seen with their microscopes, or the compound and ultramicroscopes which were to come later, will always remain a matter of conjecture. We do know, following the invention of the microscope and the discovery of these minute living beings by Kircher and van Leeuwenhoek, the march of events in the science of bacteriology was very slow. It was not until 1762 that Plenciz wrote of the possible relation between bacteria and disease although the conception of "contagion" had been written of by philosophers for hundreds of years prior to that date. History records the fact that nearly two hundred years elapsed between the discovery of bacteria by Kircher and van Leeuwenhoek and the discovery by Pollender [6] in 1849 of the anthrax bacillus which was the first bacterium to be proved definitely to be the etiological agent in an infectious disease.

It is a matter of record, however, that in 1804, forty-five years before Pollender discovered the anthrax bacillus, Zinke had studied the filterable virus disease of Rabies in dogs and demonstrated the infectiousness of the saliva although this disease was not transmitted to rabbits by artificial inoculation until the experiments of Galtier in 1879. The method of immunization perfected by Pasteur during the next few years is one of the landmarks of medical history.

Before bacteriology then was established as a science investigators were concerned with the study of at least one disease which we now classify with the filterable virus diseases. While bacteriology in general has widened its frontiers to almost undreamed-of limits in many directions, comparatively small progress has been made in the study of the filterable viruses. The beginning of the study of filterable viruses is usually given in texts at a later date than that mentioned above. The foundation of this study is usually dated from 1886 when Loeffler and Pfeiffer [7] demonstrated minute bodies in the lesions of smallpox which they thought resembled protozoa. Shortly after in 1892, Iwanowski [8] when studying mosaic disease of tobacco, found that filtrates of this material remained active for several months and this work is usually considered the corner stone of the study

of filterable viruses. The work of Iwanowski was independently confirmed by Beijerinck [9] in 1899, who advanced the theory of the possible existence of a "contagium vivum fluidum". During the preceding year Frosch and Loeffler [10] demonstrated the filterable nature of the virus of Foot and Mouth disease in cattle. Since that time the study of the filterable viruses has developed in increasing importance and many discoveries have been made which will be described in this series of papers. Briefly some of the more important landmarks in the study of this group of viruses, since the work of Frosch and Loeffler in 1898 on Foot and Mouth disease, set down in chronological order are as follows: In 1903 Negri [11] described the bodies which now bear his name, in the central nervous system of animals dying from rabies; the same year Borrel [12] demonstrated minute granules, which stain with Loeffler's stain, in sheep pox (so-called sheep-pox bodies); in 1907 Prowazek [1] demonstrated the so-called trachoma bodies in the epithelial cells of the conjunctiva from cases of this disease and during that year published a review of filterable virus diseases up to that time; Heyman [13] in 1909, demonstrated "inclusion bodies" in a form of conjunctivitis present at birth known as conjunctivitis neonatorum; Linder [14] during the same year differentiated this disease from gonoblenorrhea showing that there might be two diseases, one due to a filterable virus—the other to the gonococcus. During 1908 Landsteiner and Popper [15] succeeded in transferring poliomyelitis to two monkeys from spinal cord emulsion taken from human cases which had died of the disease and demonstrated that the virus is filterable. This work was later confirmed by Flexner and Lewis [16].

In 1911–12, Rous [17 18] demonstrated the filterable nature of a sarcoma of chickens, a monumental piece of work which attracted attention again in the work of Gye and Barnard [19] in 1925. In 1913 there were several important contributions to the filterable virus field, Flexner and Noguchi [20] succeeded in cultivating the virus of poliomyelitis; Noguchi and Cohen [21] described the cultivation of minute bodies described by Prowazek as occurring in trachoma; Rocha Lima [22] demonstrated the filterable nature of the causative agent in Verruga peruviana, or peruvian warts, thought to represent a later phase of the disease known as Oroya fever. The interpretation of this work, however, may have to be modified in the light of more recent work by Noguchi [23] (1927) which appears to have established the true etiology of this disease. And finally during the same year Lipschütz [24] published a complete survey of the entire subject of

filterable viruses and presented a list of forty-one diseases affecting man and animals in which the filterable nature of the causative agent was established with more or less certainty. In 1915–1917 we find the work of Twort [25] and d'Herelle [26] on the subject of bacteriophage. Up until 1918, yellow fever was thought to be due to a filterable virus and temporarily at least this became quite doubtful when in that year Noguchi [27] described the leptospira icteroides as the cause of this disease. In view of the recent work of Sellards [28] on this subject we are again in doubt regarding the etiology of Yellow Fever and for the time being at least we have included it in this review. In 1919 Strauss and Loewe [29] claimed to have demonstrated and cultivated a filterable virus as the cause of epidemic encephalitis. This work, however, has not received confirmation. Levaditi, Harvier and Nicolau [30] have also described a filterable virus as the cause of this disease but researches of other investigators as well as our own [31 32] have shown this virus to be closely identified with the virus of herpes, if indeed it is not the same. During 1920, 1921 and 1922 appeared the work of Olitsky and Gates [33] describing *Bacterium pneumosintes* as the causative agent in epidemic influenza. More recent years have seen the development of the work on the Rickettsias, diverse studies on the various inclusion bodies in attempts to correlate the mass of work on this subject; and lastly the cultivation of the causative agent of trachoma, the transmissibility in series of the experimental conjunctival disease and the recovery of the microorganism from the experimental lesions by Noguchi [34] in 1927.

Ultrafiltration:

Filterable viruses, so we have seen by definition, are so designated because they are small enough to pass through the pores of a Berkefeld or Chamberland filter. The sole requisite, then, for an agent to be so classified, is for it to pass through one of these filters. It must be pointed out in the beginning that filtration is only a matter of gradation. There is no sharp dividing line and it has been said "like diffusibility, filtration is only a relative concept." There are several kinds of filters used in the study of filterable viruses but there are none free from objection. In the first place the technical habits of the investigator in the use of these filters is of great importance when results are to be analyzed and evaluated. Pressure, whether sunction or force pressure, time of filtration, the dilution of the material to be filtered, its viscosity, the amount of solid matter present, the reaction of the material, the possible variation in size of the virus at the time of filtration—all are important factors which

should be taken into consideration. Add to these factors the fact that each filter, whether made of porcelain, diatomaceous earth, collodion, asbestos, plaster of Paris or any other substance, differs from other filters, made of the same materials even though it is only slight in degree,—then the margin of safety is even much less, when the investigator attempts to interpret his results.

Aside from the mechanical objections already pointed out there are two factors which should be emphasized: (1) New filters vary each from the other, and (2) control filters are most essential in the interpretation of results. If these two points were always kept in mind the results of filtration experiments would be exceedingly more convincing. For example the spirochaetes which Wolbach [35] passed through a Berkefeld filter are not regarded as filterable viruses because it is believed that due to their flexibility this type of organism may be pulled or sucked through the tortuous pores of the filter. Wherry [36] has shown that an organism which causes a form of pneumonia in guinea pigs and which measures .5 to .7 of a micron may pass through a Berkefeld filter; von Esmarch [37] has passed spirilla through a Chamberland filter while Borrel [38] has succeeded in passsing water flagellates through artificial filters. It is possible, however, that cultures of organisms such as have been mentioned above may contain forms, some of which are extremely minute in size, either as a natural condition in the life cycle of the organism or as an abnormally dwarfed form existing as a result of heredity or environment. Recent work on filterable forms of *Bacillus tuberculosis* by Calmette and Valtis [39], Mellon and Jost [40], Potter [42] and others; recent investigations on filterable forms of *Bacillus pestis* by Burnet [43]; on filterable yeasts by Lewis [44] and the discovery by Noguchi [45] of a filter-passing virus obtained from Dermacentor andersoni, all lend support to this concept. Undoubtedly the gradations brought about by the filters now available are not fine enough and reports of filterable forms of bacteria which have never heretofore been classified with the filterable viruses give rise to many forms of speculation. Encouragement may be found, however, in the recent work of Kramer [46] on bacterial filters and of Zinsser and Fei-Fang Tang [47] in their studies in ultrafiltration. Kramer has shown that by preparing a filter of calcium carbonate and magnesium oxide of positive electrical charge, bacteria, viruses and colloids used in his test may be withheld though these agents readily pass through filters made of siliceous material carrying a negative charge. Zinsser and Fei-Fang Tang have attempted to arrive at the relative size of several different substances by filtration at a known pH through graded filters

prepared of collodion. The results of these experiments show an order of magnitude of the various substances tested as follows: Crystallized egg albumen; crystallized serum albumen; trypsin; collargol; casein; bacteriophage; Rous sarcoma, and herpes virus; and lastly arsenic trisulfide. These results, as pointed out by Zinsser and Fei-Fang Tang do not agree with the work of Levaditi and Nicolau [48] and Levaditi, Nicolau and Galloway [49] in that these investigators found that the virus of foot and mouth disease was filterable through membranes which held back trypsin. On the other hand the work of Zinsser and Fei-Fang Tang agrees favorably with the measurements made by Olitsky and Boez [50] for the virus of foot and mouth disease.

Our own observations [51] have been that well controlled experiments with collodion membrance filters are very difficult. For example, particles of bacteriophage are for the most part absorbed on to the membrane though it is possible to recover the active principle by successive feedings of the filtrate with the susceptible organism, thus showing that some of the bacteriophage passed the filter although a substance like hemoglobin was withheld.

The size of these minute viruses is important without doubt and at present there is no way in which to arrive at their approximate size except through comparison with other known substances. Far more important, however, is their nature, their life cycle, the methods of cultivating them and the study of their functional activities. These are all problems for the future since for most of the filterable viruses none of these things are known. Rawlins [52] in writing recently of research on viruses causing plant diseases calls attention to the work of Mines [53] who has shown that the addition of certain protective proteins to colloidal gold may cause the latter to exhibit properties characteristic of proteins. In this respect Rawlins suggests that it is possible that protective colloids and other factors in the complex plant extract may so modify the properties of a virus as to give an erroneous impression of its real nature. Zinsser and Fei-Fang Tang clearly recognize this possibility in their experiments. Rawlins in his view of the field of virus diseases of plans suggests several lines of study such as selective adsorption, treatment with microorganisms, precipitation, cataphoresis, centrifugation, sedimentation and dialysis such as have been employed by Sherman, Caldwell and Adams [54] in their attempt to isolate enzymes. Some of these methods have already been used in the study of filterable viruses causing human diseases though the possibilities have by no

means been exhausted. Inactivation by methods similar to that used by Johnson-Blohm [55] in reactivating rennet is also suggested by Rawlins.

In the end we inevitably return to our conception of filtration which is practically our sole criterion in the classification of these agents. Contrary to general thought Bronfenbrenner and Muckenfuss [56] have recently shown that filters become more permeable the longer they are employed in a given operation. Filtering a strain of bacteriophage and its susceptible organism over long periods of time these authors demonstrated that while in the beginning the active principle passed the filter in a certain concentration, free from bacteria, after prolonged filtration the susceptible microbe itself passed the barrier. More recently there have been several attempts to employ animal membranes in vivo in filtration experiments. In our laboratory we have attempted filtration experiments with a strain of bacteriophage through the normal barriers of the central nervous system [57]. The bacteriophage was injected into rabbits intraspinously and recovered from the blood stream of the animal at a later period. Bacteriophage introduced into the animal intravenously could not be demonstrated in the spinal fluid. Le Fevre de Arric [58] has shown that certain dyes, such as methylene blue, trypan blue, neutral red, and certain drugs such as potassium iodide, urotropin, etc., exert a favorable influence upon the fixation by the central nervous system of certain neurotropic viruses such as the virus of herpes and of rabies, presumably acting upon the vascular endothelium of the meninges. Grasset [59] injected gravid rabbits and guinea pigs with a filtrate of colon bacillus bacteriophage and demonstrated the presence of the bacteriophage in the maternal blood though it was absent in the fetal blood. Evidently bacteriophage does not traverse the placenta and differs from antitoxin in this respect though toxins and anatoxins are also withheld.

Theories concerning the nature of filterable viruses:

When considering the theories concerning the nature of the filterable viruses one of the first questions which arises is whether these agents are animate or inanimate or whether some of them are living substance and others non-living. At present it is impossible to make a preëmptory statement concerning this question which will apply to the entire group of viruses. Doubtless there are few who would question the living nature of the virus of rabies, of poliomyelitis, of herpes, of hog cholera, of rinderpest, of smallpox and a host of

others, but there are many, for example, who have questioned the living nature of the bacteriophage.

Life (L.vita) is loosely defined as an aggregate of vital phenomena; a certain peculiar stimulated condition of organized matter; that obscure principle whereby organized beings are peculiarly endowed with certain powers and functions not associated with inorganic matter. One of these functions, and perhaps the most fundamental of all, is reproduction. For if there were no reproduction life would cease to exist after a time. Closely following in importance the power of reproduction which is possessed by living things comes adaptation. Living things have the power in general of adapting themselves to their environment. If they did not possess this power they would die. Still another function of living beings is respiration. Even bacteria respire and their respiration can be measured quantitatively by the methods described by Novy, Rhoem and Soule [60], by Bronfenbrenner [61] and McKinley and Coulter [62]. These then are all fundamental considerations and while there are many others, such as the assimilation of food, the power of locomotion, sensitiveness to external agents such as light, heat, chemicals and cold, etc.—these are the most important. There can be no question that most of the filterable viruses possess the power of multiplication and no further comment is necessary in this regard. Upon this point has hinged our conception of the bacteriophage for the past ten years. There are still many who will admit that increase in number of bacteriophage particles takes place under certain conditions but who do not recognize its living nature.[63] Both bacteriophage and herpes virus are susceptible to the destructive action of ultra violet rays yet this criterion is not sufficient to determine the living nature of these agents since enzymes are also destroyed by this form of energy.[64]

Filterable viruses possess the ability to adapt themselves to their environment, otherwise they would cease to exist. To be sure, like all living things, they are frequently modified in the process of undergoing adaptation as, for example, the modification of rabies street virus when passed through rabbits. That the filterable viruses assimilate various elements for the purpose of surviving and reproducing their kind is indicated in the few successful experiments on cultivation in artificial media, as for example the virus of vaccinia and possibly that of poliomyelitis. Furthermore it is well known that this group of agents is susceptible to external changes brought about by chemicals and changes in temperature, although in general

they appear to be more resistant than ordinary bacteria in this regard.

The state of being of the filterable viruses meets fully our definition of life. They are, beyond peradventure, endowed with certain powers and functions not associated with inorganic matter. Having the power of reproduction or multiplication, the function of adaptation, susceptibility to physical and chemical agents, ability to assimilate food in artificial culture media, can there be doubt that they are living beings? To be sure it has not been demonstrated that filterable viruses respire though this may be due to the lack of a suitable method fine enough in its technique to permit demonstration of what may be an extremely small interchange of oxygen and carbon dioxide.

It was first suggested by Beijerinck [9] in his study of the mosaic disease of tobacco that a possible "contagium fluidum vivum" might exist. Simon [3] has suggested another term in his "contagium inanimatum". These two concepts are diametrically opposed to each other as regards the living nature of the "contagium" but both suggest in their meaning that the filterable virus may exist in a chemical form. There is no direct evidence to support this concept though the theory is of great interest.

A concept which is quite wide-spread is that the filterable viruses exist as filterable or ultramicroscopic forms of bacteria and perhaps in some cases as protozoa. The physicist regards them as particulate beings which have up to the present been undemonstrable because of the lack of suitable optical instruments with which to see or photograph them. The particulate nature of a few viruses has been demonstrated, especially those which have undergone artificial cultivation. The susceptibility of herpes virus to ultraviolet light is also suggestive of this while in the case of the bacteriophage actual partition has actually been accomplished by d'Herelle [26] by Bronfenbrenner and Korb [65] and in our own experiment.[63] It has been suggested by many investigators that the filterable viruses are more resistant to external agents than bacteria because of adsorption of the filterable agent upon protein aggregates or vice versa thus introducing the concept of protective colloids.

Opinion is divided regarding the significance of the so-called cell-inclusion bodies such as trachoma bodies, sheep-pox bodies, the inclusions of herpes, Negri bodies of rabies, vaccine bodies, intranuclear inclusions in visceral disease described by von Glahn and Pappenheimer [66], the cellular inclusion in the salivary glands of guinea

pigs, Kurloff bodies in guinea pigs, and others. It is quite evident that these bodies for the most part are uniformly present and associated with many virus diseases. Prowazek [1] in 1907 suggested the name "chlamydozoa" for this group of "cell-inclusion bodies", a term derived from the Greek meaning "cloak" and "animal" and defined as protozoa consisting of a cell surrounded by material secreted by the invaded cell. Reference has already been made to the theory that Negri bodies are in reality protozoan in nature. Lipschütz [2] has suggested another term "strongyloplasma" for this group of bodies, a term also derived from the greek, meaning 'round' and 'to mold' hence the definition "to mold round". One school of thought considers these bodies as representing the virus proper, either singly or in groups, while another believes them to be simply the reaction products of the cell massed together and capable of taking stains by which they are demonstrated. The inclusion bodies will be considered in detail in a paper devoted to this subject.

Classification of filterable virus diseases:

The filterable virus diseases represent one of the most difficult groups of diseases to classify. This is partly due to the fact that new developments in their study necessitate frequent modification but chiefly difficult because of our lack of exact knowledge concerning many of them. They cannot be classified according to the pathologic changes they produce because in many instances the pathology is unknown, as for example in Dengue fever. They cannot be classified according to bacteriologic or protozoan criteria for so little is known of their nature. They cannot be grouped according to transmission because the method of transmission in many instances is doubtful or unknown. They cannot be classified from the cytological point of view for as Cowdry [67] has stated "The inclusions themselves, occurring as they do not only in man and many vertebrates, but also in certain insects and plants, are characterized by great diversity. For this reason generalizations are difficult to make, and are often stultified by the number of qualifications and exceptions which must be noted." Further, Rivers [5] in an abstract of his review on filterable viruses states: "it can be said that they exhibit, when compared one with another, a diversity of characteristics equal to, if not greater than, that exhibited by ordinary bacteria and other known forms of life".

In 1912 Wolbach [68] published a chart of the diseases presumably caused by filterable viruses. In his tabulation Wolbach attempted to set down the transmission as well as the occurrence of the disease

but in many instances the transmission was not known to be either direct or indirect. While Rivers [5] does not offer his table of filterable viruses as a classification, he has attempted to correlate the known facts in the grouping of filterable virus diseases and his table is exceedingly interesting.

Probably the most general classification of this group of diseases can best be made upon the basis of host susceptibility. This factor is quite generally known and in grouping the diseases according to their occurrence the finer known characteristics of the viruses may be taken into account and upon these points the place of each particular disease in the grouping may be determined. A classification of the human diseases follows:

CLASSIFICATION OF FILTERABLE VIRUS AND RICKETTSIA DISEASES ACCORDING TO HOST SUSCEPTIBILITY

I. Virus Diseases of Man

	Disease	Transmission	Incubation period	Chief distribution	Filtration of virus	Inclusion bodies	Lesions	Susceptible animals	Immunity	Mortality
A	Variola	Direct	9 to 15 days Average 12 days	General	Filterable	Present	Skin	Man, rabbits monkeys, cattle, rats, camels, guinea pigs	One attack confers immunity	Up to 25 percent
	Varioloid	Direct	4 to 13 days	General	Filterable	Present	Skin	Man, rabbits monkeys, cattle, rats, camels, guinea pigs	One attack confers immunity	Nil
	Vaccinia	Direct	3 days	General	Filterable	Present	Skin	Man, rabbits monkeys, cattle, rats, camels, guinea pigs	One attack confers immunity	Nil
	Paravaccinia	Direct	3 days	Austria	Filterable	Present	Skin	Man	One attack confers immunity	1 to 2 percent
	Alastrim	Direct	3 to 12 days	Africa, West Indies, South America	Filterable	Present	Skin	Man	One attack confers immunity	Nil
B	Varicella	Direct	14 to 21days	General	No report	Present	Skin	Man	One attack confers immunity	Nil. Fatalities due to complications
	Herpes zoster	Unknown	Unknown	General	No report	Present	Skin, Nerves, ganglia	Man	Of very short duration if any	Nil
C	Rubeola	Direct	11 to 14 days	General	Filterable	Absent	Skin	Man and monkeys (Exp.)	One attack confers immunity	Nil fatalities due to complications
	Rubella	Direct	14 to 21 days	General	No report	Absent	Skin	Man	One attack confers immunity	Nil
D	Verruca	Probably direct and indirect	4 week to 6 months (experimental)	General	Filterable	Present	Skin	Man, dogs	None	Nil
	Molluscum contagiosum	Probably direct and indirect	14 to 25 days (experimental)	General	Filterable	Present	Skin	Man	None	Nil
E	Trachoma †	Direct	2 to 4 weeks (experimental in monkeys	China, Japan, Egypt, Russia, U. S. A.	Filterable ??	Present	Conjunctivae	Man and monkeys (exp)	?	Nil
	Inclusion Blennorrhea	Direct	?	?	?	Present	Conjunctivae	Man	?	Nil

F	Herpes simplex	Unknown		General	Filterable	Present	Skin	Man, rabbits guinea-pigs. rats	Little if any	Nil
	Epidemic encephalitis	Probably direct	Few hours to few days	General	Probably filterable	Present ?	C. N. S.	Man (chiefly adults)	One attack confers immunity	30 to 70 percent
	Epidemic poliomyelitis	Probably direct	1 to 3 days up to 14 or 18 days	General	Filterable	Absent	C. N. S.	Man (chiefly children) Monkeys	One attack confers immunity	5 to 30 percent
	Rabies	Direct	2 to 8 weeks up to 1 or 2 years	General	Filterable	Present	C. N. S.	Man and various animals	Immunity conferred by vaccination	Very high unless treated
G	Common colds	Direct	Few hours to few days	General	Probably filterable	Absent	Respiratory tract	Man	Little if any	Nil
	Influenza +	Direct	Few hours to few days	General	Probably filterable	Absent	Respiratory tract	Man	Definite but probably temporary	Nil. Fatalities due to complications
H	Dengue fever. ± |	Indirect Direct (Exp.)	3-6 days variable	Southern U. S. A. Tropics	Filterable	Absent	Skin, throat	Man	Temporary immunity	Nil
	Yellow fever. ± |	Indirect Direct (Exp.)	4 to 13 days average 4 to 5 days	South America, Africa	Filterable	Absent	Skin, liver, kidneys	Man, monkeys (Exp.)	One attack conferred immunity	30 to 80 percent 7 to 10 percent in natives
	Pappataci fever. ± |	Indirect	3-5 days	India. Egypt. South America Southern U. S. A. Mediterranean.	Filterable	Absent	Nil	Man	One attack conferred immunity	Nil
I	Typhus fever. ± | R	Indirect	4 to 14 days average 12 days	Europe. Asia. Africa. America, Russia. Mexico	Not filterable	Absent	Blood vessels	Man, monkeys. guinea-pigs (Exp.)	One attack confers immunity	Very high
	Trench fever. ± | R	Indirect	5 to 30 days average 14 to 30 days	Prevalent during world war	Filterable ?	Absent	Blood vessels	Man	Temporary	Nil
	Rocky mountain spotted fever ± | R	Indirect	3 days (Exp.)	Western States U. S. A.	Not filterable	Absent	Blood vessels, spleen, liver, lungs	Man, monkeys, rabbits, guinea-pigs (Exp.)	One attack confers immunity	Ver high
	Tsutsugamushi ± | R	Indirect	4 to 12 days average 4 to 7 days	Japan, Formosa.	Filterable ?	Absent	Spleen, liver, pancreas, thyroid	Man, monkeys (Exp.)	One attack confers immunity	10 to 60 percent
J	Scarlet fever. + |	Direct and indirect	2 to 6 days	General	Doubtful	Present ? ?	Skin, throat	Man	One attack confers immunity	Under 5 years 20-30 percent
	Oroya fever, verruga Peruviana + |	Probably direct	About 3 weeks	Perú	Doubtful	Absent	Skin, blood liver, spleen, endothelium	Man, monkeys (Exp.), rabbits? Dogs?	One attack confers immunity	10-40 percent
K	Epidemic parotitis	Direct	3 to 25 days average 14 to 21 days	General	Filterable	Absent	Salivary glands	Man, cats (Exp.)	One attack confers immunity	Nil
	Foot and mouth disease	Direct	2 to 7 days	General	Filterable	No report in man	Counterpart of the disease in animals	Numerous different animals and man	Temporary immunity	Nil

\+ \| Bacterial?

± \| Insect-Borne,

± \| R Insect-Borne-Rickettsia.

BIBLIOGRAPHY

(1) *v Prowazek, S.:* (1907) Chlamydozoa., 2. Gelbsucht der Seidenraupen. Arch. f. Protistenk., **10**: 359.
(2) *Lipschutz, B.:* (1913) Filterierbare Infektionserreger. Kolle Wassermann's Handbuch der pathogen Mikroörganismen, **8**.
(3) *Simon, C. E.:* (1923) Physiological Reviews., **3**: 483.
(4) *Mac Callum, W. G.:* (1926) Medicine., **5**: 59.
(5) *Rivers, T. M.:* (1927) Jour. of Bacteriology., **13**: 16.
(6) *Pollender:* (1849) Quoted from Zinsser's Text Book of Bacteriology., **5th** Edition, 1922, p. 773.
(7) *Loeffler and Pfeiffer:* (1886) Zeit. f. Hyg., **23**.
(8) *Iwanowski. D.:* (1892) (abst.) In Beiheft Botan. Centbl., 3: 1893, p. 266. The original in Land—u. Forstwiss. Russian; see also Bull. acad. imper. d. sci. de St. Petersburg., **13**: 237.
(9) *Beijerinck,* M. W.: (1899) Centbl. f. Bakt., O. **5**: 27.
(10) *Frosch and Loeffler:* (1898) Centbl. f. Bakt., O. **5**.
(11) *Negri.:* (1903) Zeitschrift fur Hygiene und Infektionskrankheiten., **43**: 507.
(12) *Borrel:* (1903) Anal. de L'Inst. Pasteur.
(13) *Heymann, B.:* (1909) Deutsch. Med. Wochenschr., **35**: 1692.
(14) *Linder, K.:* (1909) Wien. Klin Wochenschr., 1555 and 1659. (1913) v. Graefe's Arch. f. Ophthal., **84**.
(15) *Landsteiner and Popper:* (1909) Zeit. f. Immunitatsforch., 2: 377.
(1911) Die Heine-Medinsche Krankheit, Berlin.
(16) *Flexner, S. and Lewis. P.:* (1909) Jour. Am. Med. Assn., **53**: 1639. (1909) Jour. Exp. Med., **12**.
(17) *Rous, P.:* (1910) Jour. Exp. Med., **12**: 696. (1911) Jour. Exp. Med., **13**: 397.
(18) *Rous, P.:* (1913) Jour. Exp. Med., 18: 416. *Rous, P.* and *Murphy, J. B.:* Jour, Exp. Med. **19**: 52.
(19) *Gye, W. E.:* (1925) Lancet., **209**: 109.
Barnard, J. E.: (1925) Lancet., **209**: 117.
(20) *Flexner, S. and Noguchi, H.:* (1913) Jour. Exp. Medicine., **18**.
(21) *Noguchi, H. and Cohen, M.:* (1913) Jour. Exp. Med., **18**: 572.
(22) *Da Rocha Lima:* (1913) Centbl. f. Allgem. Pathol. u. pathol. Anat. Verhandl. d. deutsch. path. Gessellsch. zu Marburg., **24**: 409.
(23) *Noguchi, H.:* (1927) Jour. Exp. Med., **45**: 175.
(24) *Lipschutz, B.:* (1913) See reference (2)
(25) *Twort:* (1915) Lancet., **2**: 1241.
(26) *d'Herelle, F.:* The Bacteriophage (Translation 1922); Immunity in Natural Infectious Diseases (1924); The Bacteriophage and its Behavior (1926). Williams and Wilkins Co., Baltimore, Md.
(27) *Noguchi, H.:* (1919) Jour. Exp. Med., **29**: 547. Jour. Exp Med. **30**: 87.

(28) *Sellards, A. W.:* (1927) Am. Jour. of Tropical Medicine., **7**: 71.
(29) *Straus and Loewe:* (1919) Jour. Am. Med. Assn., **73**: 1056.
(30) *Levaditi, Harvier et Nicolau:* (1921) C. R. Soc. de Biol., **85**: 161, 213, 287; (1923,) **89**: 984; (1924) **90**: 1372; Ann. Inst. Pasteur., (1922) **36**: 63; C. R. Acad. d. Sc., (1923) **177**: 985.
(31) *McKinley, E. B. and Holden, M.:* (1926) Jour. Infec. Diseases., **39**: 441.
(32) *McKinley, E. B. and Holden M.:* (1927) Archives of Pathology and Lab. Med., (1927) **4**: 155.
(33) *Olitsky, P. and Gates, F.:* (1921) Jour. Exp. Medicine., **33**: 125.
(34) *Noguchi, H.:* (1927) Jour. Am. Med. Assn., **89**: 740.
(35) *Wolbach:* Quoted from Park and Williams, Pathogenic Microorganisms., **7th** edition. (1920) p. 530.
(36) *Wherry:* Ibid., p. 530.
(37) *v. Esmarch:* Ibid., p. 530.
(38) *Borrel:* Ibid., p. 530.
(39) *Calmette, A. and Valtis, J.:* (1926) Ann. de med., **19**: 553.
(40) *Mellon, R. R. and Jost, E.:* (1927) Soc. Exp. Biol. and Med., **24**: 743.
(41) *Fabry, P.:* (1921) Bruxelles Medical., **7**: 596.
(42) *De Potter, F.:* (1927) C. R. de la Soc. de Biol., **96**: 138.
(43) *Burnet, E.:* (1926) Arch de L'Inst. Pasteur de Tunnis., **15**: 292.
(44) *Lewis, P. A.:* (1927) Jour. Exp. Med., **45**: 277.
(45) *Noguchi, H.:* 1926) Jour. Exp. Med. **44**: 1.
(46) *Kramer, S. P.:* (1927) Jour. Infect. Dis., **40**: 343.
(47) *Zinnser, Hans and Fei-Fang Tang:* (1927) Jour. Exp. Med., **46**: 357.
(48) *Levaditi, C. and Nicolau, S.:* (1923) C. R. Acad., **176**: 717.
(49) *Levaditi, C. and Nicolau, S. and Galloway, I:* (1926) C. R. Acad., **182**: 247.
(50) *Olitsky, P. K. and Boez, L.:* (1927) Jour. Exp. Med., **45**: 673.
(51) *Pierce, H. F. and McKinley, E. B.:* Unpublished data.
(52) *Rawlins, T. E.:* (1927) Science., **65**: 398.
(53) *Mines:* (1912) Koll. Chem. Beihefte., **3**: 191.
(54) *Sherman, Caldwell and Adams:* (1926) Jour. Amer. Chem., Soc., **48**: 2947.
(55) *Johnson-Blohm:* (1912) Zs. Physiol. Chem., **82**: 178.
(56) *Bronfenbrenner, J. J. and Muckenfuss, R.:* (1926) Proc. Soc. Exp. Biol. and Med., **24**: 372.
(57) *McKinley, E. B. and Holden, M.:* (1927) Proc. Soc. Exp. Biol. and Med., **24**: 595.
(58) *Le Fevre, M. de A.:* (1927) C. R. de la Soc. de Biol., **96**: 206.
(59) *Grasset, E.:* (1927) C. R. de la Soc. de Biol., **96**: 839.
(60) *Novy, F. G., Rhoem, H. and Soule, M. H.:* (1925) Jour. Infec. Dis., **36**: Nos. 2, 3, 4.
(61) *Bronfenbrenner, J. J.:* (1926) Science., **63**: 51.

(62) *McKinley, E. B. and Coulter, C. B.:* (1927) Proc. Soc. Exp. Biol. and Med., **24**: 685.
(63) *McKinley, E. B. and Holden, M.:* (1926) Jour. Infect. Dis., **39**: 451.
(64) *McKinley, E. B., Fisher, R. and Holden, M.:* (1926) Proc. Soc. Exp. Biol. and Med., **23**: 408.
Fisher, R. and McKinley, E. B.: (1927) Jour. Infect. Dis., **40**: 399.
(65) *Bronfenbrenner, J. J. and Korb.:* (1925) Jour. Exp. Med., **42**: 483.
(66) *Von Glahn, W. C. and Pappenheimer, A. M.:* (1925) Am. Jour. Path., **1**: 445.
(67) *Cowdry, E. V.:* (1927) Jour. Bact., **13**: 20.
(68) *Wolbach:* (1912) Jour. of Med. Res., **27**.
(69) *McKinley, E. B.:* (1929) Filterable Virus and Rickettsia Diseases. (In Press.) (Monograph). (Lit.) (Phil. Jour. Sci.).
(70) *Rivers, T. M.:* (1928) Filterable Viruses. Williams and Wilkins Co., Baltimore, Md.