FILTERABLE VIRUS AND RICKETTSIA DISEASES IN THE TROPICS. IV.*

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The present paper is the fourth of a series of eight articles dealing with the filterable virus and Rickettsia diseases. The three preceding papers have dealt with the general aspects of the problems in this field and specifically with some of the diseases which belong to the group of filterable virus diseases. As we have pointed out in our last article, most of these diseases occur in tropical countries as well as in colder climates and for this reason they should be considered as part of tropical medicine. So far we have touched only upon the so-called filterable virus diseases. The Rickettsia diseases will be discussed in our next article along with several other diseases, all of which are thought at present to be insect borne. In this paper we will consider some of the virus diseases which involve the central nervous system and the two very important conditions known as the "common cold" and "epidemic influenza."

HERPES SIMPLEX

Fever Blisters; Herpes (French); Blaschenflechte (German)

DEFINITION

Herpes simplex is an acute eruptive disease of the skin and mucous membranes and usually occurs upon the face and genitalia. It is characterized by a vesicular eruption, the vesicles appearing in groups upon a mild inflammatory base, accompanied by sensations of heat and burning. The disease is caused by a filterable virus, the manifestations of which are influenced by a number of factors such as local irritation, exposure to the sun's rays, drafts of cold air, traumatism, various constitutional and infectious diseases, etc. Herpes is designated, according to location and conditions under which it occurs, as herpes febrilis, herpes labialis, cold sores, herpes genitalis, herpes preputialis, and generalized herpes.

* This is the fourth 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).

OCCURRENCE OF HERPES

This disease has been known since ancient times. It occurs in connection with a number of infectious diseases. According to various dermatologists the disease is said to be present in about 40 per cent of cases suffering with cerebrospinal meningitis, lobar pneumonia, and malaria; in about 6 per cent of scarlet fever patients; 6 per cent of influenza cases; 5 per cent of typhus cases; and in a comparatively small number of patients having diphtheria, typhoid fever, relapsing fever, and smallpox. The affection is common in prostitutes and according to Unna it occurs, in Hamburg, in about 25 per cent of these women. The disease frequently manifests itself in women about the time of the menstrual period. It occurs in connection with the acute coryzas and various gastric and intestinal conditions. Focal infections in the mouth may also be accompanied by herpetic lesions. In other cases herpes has apparently been related to the ingestion of certain foods. In many individuals the affection tends to be recurrent and the lesions may appear in the same area over a long period of time. These recurrent lesions are particularly noted upon the face, about the buttocks, and upon the genitalia.

SYMPTOMS

Herpes may involve any part of the cutaneous surface but is more commonly found on the face and about the genitalia. The affection is self-limited and usually terminates within a week or ten days. More often the lesions are few and localized but occasional generalized distribution occurs. Mild constitutional symptoms may be present and the part affected is subject to sensations of heat and burning. There may be present some slight elevation in temperature and chilliness and on this account the disease is frequently referred to as "fever blisters". In a few cases the lesions appear upon the mucous membranes of the tongue, cheek, pharynx, and larynx. Occasionally the vesicular patches are quite large, and may coalesce, becoming cloudy and purulent. After a few days the vesicles dry and yellowish crusts are formed which drop off within a short time leaving a brownish red stain which soon disappears.

Epidemics of herpes have been reported by Savage (1) and by Seaton (2). Both epidemics occurred in schools for boys and were characterized by sudden onset, elevation of temperature, chills, headache, nausea and vomiting, and herpetic eruption chiefly on the lips and other parts of the face. The occurrence of the disease in

epidemic form is strong indication that the disease is caused by an infectious agent.

THE VIRUS

In 1913 Grueter ([3]) demonstrated that the inoculation of the rabbit cornea with scrapings from lesions of dendritic keratitis produces in rabbits an inflammatory process which is transmissible from animal to animal. This observation was confirmed later by both Loewenstein ([4]) and by Luger and Lauda ([5]) and these authors further demonstrated that precisely the same process can be induced in rabbits by inoculating the rabbit's cornea with the fluid from herpes vesicles. Lowenstein believed that the infectious agent existing in the fluid of the herpes vesicles is filterable and this belief was fully established in the later work Luger and Lauda, Blanc and Caminopetros ([6]), and Levaditi, Harvier, and Nicolau ([7]).

Lipschutz ([8]) in 1921 was the first to demonstrate cell inclusions in the lesions of herpes simplex, herpes genitalis, and herpes zoster. These inclusions are without doubt specific as indicated by the fact that they are also found in the epithelial cells of the inoculated rabbit's cornea. These bodies are found only in the actual seat of the lesion in herpes simplex (febrilis) and herpes genitalis. They have been found to appear in serial inoculations. Unlike most of the intracellular inclusions described in connection with other filterable virus diseases, the inclusions in herpes are found almost exclusively within the nucleus and not in the cytoplasm of the cell as in most of the other filterable virus conditions.

More will be said of the inclusion bodies later (last article of this series). For the present we may state that the exact nature of these bodies is unknown. However, it is well known that such bodies are frequently met with in connection with several of the diseases which are caused by agents of the filterable virus group and their presence is now considered as evidence of the activity of a filterable virus. Indeed in the case of the virus of herpes simplex and of herpes genitalis, the filtrability of the virus has been demonstrated.

As indicated before there are many other factors which apparently contribute to the development of herpes lesions. It is well known that in certain individuals herpes has never occurred during an entire life time. It is evident from the beginning, then, that there exist varying degrees of susceptibility and resistance toward this disease. Irritation, trauma, diet, emotional disturbances, and infectious diseases (meningitis, pneumonia, malaria, etc.) may all

contribute to the development of the disease. In certain men the simple act of coitus is sufficient to bring on an attack of the affection. Its occurrence in prostitutes and in women about the time of the menstrual period has already been mentioned. We have suggest- that all of these influences are only contributing in nature and none of them are related to the real cause of the disease. Herpes is an infectious disease, caused by a filterable virus. The virus of herpes is apparently very wide-spread in its distribution. Similar viruses have been isolated from the saliva and from the nasal secretions. Presumably there are untold numbers of healthy carriers of the virus. The extraneous factors mentioned above may contribute to the development of lesions by the herpes virus already present, latent in the individual by lowering the general resistance of the individual to the virus. We have suggested this concept in another publication (9).

Goodpasture and Teague (10) have shown that the virus of herpes passes up the axis cylinder of the nerve from its point of entrance to the spinal ganglia and the central nervous system in rabbits. It has, of course, been known for years through the work of Howard (11) and Mallory and Wright (12) that degenerative and inflammatory changes are present in the ganglionic centers supplying areas upon the face affected by herpes in cases occurring with pneumonia and cerebrospinal meningitis.

It appears then that the virus of herpes reaches the surface by way of the nerves. If the virus passes up the nerve trunk there is no reason to suppose that it cannot pass down the nerve to the cutaneous area supplied by that nerve. Does the virus remain latent then in the tissues of man, and more particularly in the nerve tissues such as the spinal ganglia? The fact that recurrent herpes is frequently brought on as a result of great emotional or nervous stress somewhat favors this idea.

The changes found in the ganglionic centers have been thought by some authorities to be of toxic origin. While no toxin has as yet been demonstrated for the herpes virus it is logical to suppose, from our concept of the mechanism of infection, that such degenerative and inflammatory changes are caused by a toxin elaborated by the virus. It must be left to future investigations to determine this question.

Within recent years the herpes virus has received a great deal of attention since several filterable viruses have been demonstrated in the brain substance and spinal fluids from cases of epidemic ence-

phalitis which are apparently identical, or at least closely related, to the herpes virus. Doerr and Vochting [13] have shown that the herpes virus is capable of inducing an encephalitis in rabbits when injected intraocularly. Since the work of Doerr and Vochting numerous investigators have shown that encephalitis in rabbits regularly follows the subdural injection of the herpes virus. Strains from herpes simplex (febrilis) and herpes genitalis are practically all found to be potent in this respect. So far no one has succeeded, in unquestioned experiments, in producing encephalitis in rabbits following the subdural inoculation of fluid from the vesicles of herpes zoster. Cole and Kuttner [14] failed in this respect with material taken from nine cases and McKinley and Holden [15] failed in three instances. However, there is strong evidence to suppose that herpes zoster is also a virus disease, but so far the hypothetical virus has remained undemonstrated.

To summarize we may conclude that herpes simplex and herpes genitalis are caused by a filterable virus. Cultivation experiments with this virus have so far resulted in only discouraging results. By several methods Le Févre and McKinley [16] failed entirely in the cultivation of this virus. Parker and Nye [17] have reported more encouraging results, but their work cannot be accepted at present as having demonstrated beyond doubt the artificial cultivation of this agent. Herpes is a common affection and as such it is indicated that the virus is wide-spread. We propose the theory that the herpes virus is present, latent in the tissues and secretions of man who serves as its reservoir. Under favorable conditions accompanied by a lowering of the individual resistance, brought about by a variety of influences, the affection takes root and manifests itself in cutaneous lesions.

The relation of this virus to epidemic encephalitis will be discussed in the following section.

EPIDEMIC ENCEPHALITIS
(Encephalitis Lethargica)

DEFINITION

Epidemic encephalitis is an infectious disease of protean manifestations. Encephalitis means brain inflammation. Epidemic encephalitis is an inflammation chiefly of the central nervous system and is characterized in most cases by lethargy, paralysis of the cranial nerves, and in some cases there are spinal and peripheral nerve involvement. Not all cases of epidemic encephalitis manifest

lethargy, for in many patients, depending upon the location and severity of the involvement, marked excitement may be a predominating symptom. This disease is also sometimes referred to as epidemic stupor, infective encephalitis, epidemic polio-encephalitis, and sleeping sickness (European).

HISTORY AND DISTRIBUTION

Little is known regarding the early history of epidemic encephalitis. Early after 1700 a disease broke out in parts of Germany which epidemiologists believe may have been related to epidemic encephalitis. Again in 1890 in parts of southern Europe there appeared a peculiar disease, which was designated "Nona" at the time, and which may have been related to encephalitis lethargica. From the records it is impossible to state definitely whether either of these diseases was related to epidemic encephalitis.

In 1917 Economo ([18]) described, under the name of encephalitis lethargica, a disease which he observed in eleven cases at Vienna. These cases had occurred during the Winter of 1916–17. During the Spring of 1918 the disease began to appear in various parts of England, and towards the end of 1918 the first indications of the disease were noted in the United States. The early cases of encephalitis lethargica were apparently regarded as brain inflammations due to botulism. The disease was characterized by drowsiness passing into lethargy, a progressive muscular weakness, and ophthalmoplegia. Often the first symptoms noted were a slight indisposition, mild indefinite muscular pain, and a feeling of drowsiness. Both males and females are affected and in about equal proportions. Most of the cases have appeared in individuals over twenty years of age. This is quite the opposite of poliomyelitis which occurs chiefly in children. While most cases of epidemic encephalitis occur in individuals in their twenties or thirties, the disease also occurs in later years after the age of fifty.

Since 1917 epidemic encephalitis has spread to all parts of the world. In England alone thousands of cases are now being reported each year. During 1924 England reported over 5,000 cases of this disease according to the Epidemiological Report of the Health Section of the League of Nations. This report states that in most countries epidemic encephalitis is decreasing at the present time. England, for example, has only reported 2,267 cases for the year 1926 with 1,325 deaths from this disease. In England the disease is more prevalent in urban than in rural districts. In New York City cases

of epidemic encephalitis are not at all uncommon, the same being true of other large cities in the United States. The disease is not limited to urban communities however and is frequently met with in the rural communities. The disease has a high mortality and shows a predilection for the winter months.

The only epidemics of a similar disease, which have been mentioned above, occurred in connection with, or following epidemics of influenza. In 1918 when epidemic encephalitis began its march over the world it was thought that the disease was related to influenza and perhaps resulted as a sequela, in certain cases, as a result of the same infection. Except for epidemiological data there is no evidence that epidemic encephalitis is related to epidemic influenza except as a concurrent infection. It is true that in England the incidence of epidemic encephalitis is highest in the north of England, decreasing through the south, and lowest in Wales. Also influenza is more prevalent in the north of England but the mortality of encephalitis is highest in urban communities while influenza has a greater mortality in rural districts. The disease is not limited to cold climates. The writer has seen cases of epidemic encephalitis in tropical countries such as the Philippine Islands and more recently two cases have come under my observation in Porto Rico, one of which has been proven at autopsy.

SYMPTOMS

The usual picture of epidemic encephalitis is lethargy, associated with third-nerve and facial paralysis, and weakness in the lower extremities. There are many clinical forms of the disease which depend upon the location and degree of involvement of the central nervous system. Some of the different types of the disease have been described as follows: (1) Cases exhibiting general manifestations of the disease but no localizing signs; (2) cases with facial paralysis; (3) cases with third-nerve paralysis; (4) cases with spinal-cord manifestations; (5) cases with polyneuritic symptoms; (6) cases showing periods of great excitement; (7) mild cases of the abortive type having only transient manifestations. All degrees, variations, and combinations of the above types have been met with.

Prodromal symptoms may be present or absent. If present they may be noted from a few hours to a few weeks and are characterized chiefly by headache, diffuse pains, lethargy or drowsiness, stiffness of the back or of one or more limbs, conjunctivitis, and vertigo.

Lethargy, a prominent symptom of the disease, occurs in about

80 per cent of cases. It comes on as a rule very gradually but may occur suddenly. It may develop gradually from a slight drowsiness to a stupor from which the patient can be aroused and then pass on into a deeper stupor or coma. Ocular palsies, with double ptosis and diplopia occur early. The temperature ranges from 100° F. to 104° F. It usually lasts but a few days, may then disappear only to reoccur, in some cases, within a few days.

The disease is slowly progressive. The patient takes on an apathetic look, the pupils may be dilated, and unequal with complete third-nerve paralysis. The face becomes smooth and expressionless, the muscles being moved with great difficulty. Catalepsy is not uncommon. The patient may become delirious and develop a violent mania. The memory is lost gradually and the patient cannot remember one moment what he has been told a few moments before. Aroused he may answer simple questions intelligently. Tremors, and choreiform movements may occur in some cases and persist for some time.

Sensory disturbances such as hyperaesthesia, may occur but are rare. Paralysis of the arms and legs may occur. The reflexes may or may not be normal. Some cases exhibit paraplegia. Other cases may show bulbar features and signs of polyneuritis. Signs of meningeal involvement are rare. The cerebrospinal fluid is clear, may show 10 to 20 cells per c. mm. and in some cases a large increase. Both mononuclears and polynuclears are found. The duration of the disease is variable. It may last weeks, months, or years. As a rule its duration ranges from two to twelve weeks. Second attacks do occur and apparently, in many cases, are more severe than the first illness. These are probably not reinfections but a flaring up of the old process when conditions are favorable.

There are other forms of encephalitis from which epidemic encephalitis must be differentiated along with several other conditions which are similar in some respects. Acute encephalitis may result from a number of causes such as trauma, intoxications, (alcohol, food poisoning, and gas poisoning), following acute infections, and as a form of polio-myelo-encephalitis. The general symptoms are headache, somnolence, coma, delirium, nausea and vomiting, etc. Cases may occur following certain fevers, such as influenza and typhoid. A recent case observed by the writer in San Juan was of the very acute type. It occurred in a little girl of eight years. The first symptoms noticed by the parents was the inability of the child to swallow water or other fluids such as orange juice. The child had

complained of drowsiness some three days previous though she had attended school the following two days in apparent good health. The child died four days after the first symptoms were noticed. The post-morten examination of the brain presented typical lesions of epidemic encephalitis. It is interesting to note that this case stands alone in the above-mentioned community. No others have been reported though there exists at the time of writing a chronic case of this disease in one of the local hospitals, of over one year duration, in a child of about two years of age.

THE VIRUS OF EPIDEMIC ENCEPHALITIS

The virus of epidemic encephalitis is unknown. That the disease is infectious and communicable is agreed by most authorities. What the infectious agent is or how it is communicated from individual to individual is unknown at present. In 1919 Loewe and Strauss ([19]) described an organism as the cause of epidemic encephalitis which they obtained from the brain substance and nasopharyngeal washings from cases of this disease and claimed to have reproduced the disease in rabbits and monkeys with this material. Later they cultivated their organism and reproduced the disease with the cultivated micro-organism. These experiments have been open to grave doubt and have not been confirmed.

In 1922 Levaditi and Harvier ([7]) described a filterable virus which they believe to be the cause of epidemic encephalitis. In reality there were two strains of this virus obtained from cases of this disease. The first and most virulent virus was obtained from the brain substance of a case of encephalitis, while the second, and weaker virus, was obtained from nasal secretions. Flexner ([20]) has pointed out that "examination of Levaditi's reports indicates that from among inoculations made with thirty separate sets of specimens from cases of epidemic encephalitis, he succeeded in establishing in rabbits only one active virus" and that his conclusions are "based really on a single unequivocal experimental result". Further it is now well known that the case of encephalitis from which Levaditi obtained his first virus possessed a herpes infection over the entire right side of the face and subsequent experiments with the Levaditi virus indicates that this virus is identical with known herpes strains, or closely allied to them.

Other filterable viruses have been obtained from the brain substance and cerebrospinal fluid from cases of epidemic encephalitis. There are the so-called "Basel" viruses. The first of these was

obtained from the cerebrospinal fluid of a patient having encephalitis lethargica by Doerr and Schnabel ([21]). The second strain was obtained by Doerr and Berger ([22]) from the brain substance of a typical case of epidemic encephalitis. The third strain was derived from another case of epidemic encephalitis from the brain substance by Doerr and Berger. Zdansky ([23]) found that the brain lesions produced with the Basel strains II and III were identical with those produced in rabbits with the Levaditi so-called encephalitis virus and also with the herpes virus.

The "Berlin" virus was described by Schnabel ([24]) and was obtained from the cerebrospinal fluid of an acute case of epidemic encephalitis. Cross immunity experiments with this virus and a known herpes virus were found to be positive.

The so-called "Wien" virus was isolated by Luger and Lauda ([5]) and was obtained from the cerebrospinal fluid and brain substance from a case of epidemic encephalitis. This strain first exhibited an incubation period of 18 days which gradually became shorter with animal passage. Symptomatically in rabbits the disease produced by this virus is typical of that induced in rabbits following inoculation with herpes virus. These authors also studied a virus which has been described by Koritschoner ([25]) which was derived from the brain substance of a patient who had been bitten by a supposedly rabid dog. The patient died and a post-mortem examination revealed a myelo-encephalitis. Inoculation of brain material from this case into two rabbits and two dogs resulted within a few days in paralysis and lethargy. Luger and Lauda believe that the Koritschoner virus is endowed with herpetiform properties but Doerr and Zdansky ([23]) identify it with the virus of pseudo-lyssa or infectious bulbar paralysis. These authors base their conclusions upon its transmisibility to dogs and the absence of Negri bodies in the brains of such infected animals.

Bessemans and Van Boeckel ([26]) experimented with material from five brains, twenty cerebrospinal fluids, and five nasopharyngeal washings from several cases of epidemic encephalitis. Sixty-one rabbits and thirty guinea pigs were inoculated with these materials. Of these only seven rabbits showed symptoms and lesions and only two guinea pigs showed lesions but no symptoms. Symptomatically these animals exhibited typical pictures of those due to herpetic infection. The lesions consisted of diffuse infiltration of the brain substance with mononuclear cells and in one case perivascular infiltration. This virus possessed only a moderate virulence and was soon lost

entirely. In regard to this virus Da Fano ([27]) states "these experiments seem to indicate the possible occurrence of weak encephalitis strains endowed with properties similar to those of likewise weak or somewhat anomalous herpetic viruses. This supposition is supported by the report of Netter, Cesari and Durand, who claimed to have recovered an apparently weak strain from the brain of a case of lethargic encephalitis 15 months after onset. This virus was regularly active when prepared with the brain substance of successfully inoculated animals, while the salivary secretion of the infected animals was uniformly virulent. Also Sicard, Paraf, and Laplane claim to have isolated an apparently weak encephalitis strain from a case of post-encephalitic Parkinsonism".

In addition to the above viruses which have been obtained Perdrau ([28]) in England has apparently had unusual success in isolating viruses from the brain substances from cases of epidemic encephalitis which he believes possess herpetiform properties.

As will be noted, the various viruses described above have all (with the exception of the virus of Loewe and Strauss, which is no longer taken seriously) been obtained from cases of epidemic encephalitis in Europe. Flexner and Amoss ([29]) and others in the United States have been uniformly unsuccessful in isolating a single virus from cases of this disease. Flexner ([30]) in 1923 reported transmitting a disease to rabbits with the cerebrospinal fluid from a patient with neuro-syphilis and from these rabbits he obtained a strain of herpes now known as the "Beckley" strain. In this case there was no question of encephalitis but it serves to illustrate that the herpes virus may occur in the spinal fluid of patients affected with some other disease process.

General opinion is that the various viruses described by European investigators as obtained from cases of epidemic encephalitis are identical with the herpes virus or they are very closely related. Doerr and Schnabel and later Levaditi, Harvier and Nicolau all found that cross immunity experiments with Levaditi's encephalitis virus and the herpes virus are positive. The latter also demonstrated that the Levaditi encephalitis virus produces an herpetiform eruption when inoculated on the skin of a rabbit. Levaditi and his associates then consider that the virus of encephalitis and herpes are identical varying only in degree of virulence. Doerr ([30]) also leans towards this concept and believes that the herpes virus is related etiologically to epidemic encephalitis.

In 1924 in discussing this question Parker ([31]) stated "There is

one fact that would seem to establish definitely the lack of identity between the virus of herpes and that of encephalitis lethargica; namely, the occurrence of the intranuclear bodies characteristic of herpes in the former and the absence of such bodies in the latter. Lipschutz described certain intranuclear, acidophilic bodies that occur, especially in the epithelial cells, in herpes in human beings and in experimental herpes of the rabbit's cornea. These bodies are perfectly definite and their demonstration renders the diagnosis of herpes positive in animals and also in human beings, provided that in the latter varicella can be excluded. Whether they represent the virus or a reaction or degenerative product of the cell is undetermined, but this does not detract from their diagnostic importance. Since the work of Lipschutz they have been described by Goodpasture and Teague in the brains of rabbits dying of herpetic infection". Parker goes on to state that "now if the virus of herpes and that of encephalitis lethargica are identical, these bodies should occur in the brains of human beings, dying of encephalitis lethargica. However, to date, no such bodies have been described".

The entire question of the relation of the herpes virus to epidemic encephalitis has become a very important one. Indeed the question has become one of controversy. Investigators are, for the most part, agreed that the cause of encephalitis lethargica is probably a filterable virus. Flexner and his associates have consistently held that the hypothetical virus of epidemic encephalitis remains to date undiscovered. European investigators have attached more and more etiological significance to the herpes virus as a cause of the disease. Zinsser and Tang ([32]) have brought further evidence against the herpes virus in its possible relation to epidemic encephalitis. These authors have shown that the serum from encephalitis patients possesses no virucidal effect for the herpes virus in vitro though this property is present in the serum of rabbits immunized with herpes virus.

In a recent publication McKinley and Holden ([9]) suggest that in the absence of a definite etiologic agent for encephalitis lethargica, and since herpes strains are occasionally met with in the nerve tissue of cases of this disease, it is advisable to retain an open mind on the entire question and attempt in every way possible to prove or disprove any relation which may exist between the herpes virus and encephalitis. The idea of encephalitis being due to a toxin, as previously suggested by Parker, was again emphasized. The occasional presence of the herpes virus in the central nervous system of

patients might be explained on the basis of the central nervous system barriers becoming permeable to the virus as a result of some other constitutional disorder or infectious process which lowers the resistance of the patient, and consequently alters those barriers which normally do not permit the herpes virus, or any other virus, to gain entrance into the central nervous system. Such an hypothesis might explain the occurrence of encephalitis lethargica following in the wake of influenza for example. If such were true it might explain the occurrence of these cases in which the herpes virus has been found in the brain substance. Also, as Perdrau has pointed out, the virus may be more easily obtained during the first few days of illness when the symptoms are acute. Parker suggests that the actual virus of encephalitis may be growing in some other region, such as the gastro-intestinal tract or nasopharynx, without causing local symptoms, but producing a poison which has a marked affinity for the central nervous system. Analogies of this are of course found in tetanus and botulism. Such a virus might also be present, latent in the spinal ganglia and produce its toxin from this focus.

In one of his most recent papers Flexner ([33]) states in commenting upon the ease with which herpes viruses may be implanted in rabbits: "On the other hand, it has proven extremely difficult to implant such a virus in rabbits with material taken from cases of epidemic encephalitis in man. The several hundred or more transfers of these materials from man to rabbit have yielded, as Flexner pointed out and Doerr concedes, six successful inoculations at most. The percentage of successes is almost minimal. The matter at issue is the explanation of the disparity, the burden of proof of course being placed upon those investigators who would identify the herpes virus with the supposedly microbic incitant of epidemic encephalitis". This may be taken as this author's attitude in the matter, as far as the herpes virus is concerned.

Up to this point we have omitted entirely from consideration the possibility of the streptococcus as the microbic incitant in encephalitis lethargica. In 1924 Rosenow ([34]) reported the isolation of a streptococcus from the tonsils, teeth and nasopharynx of cases of encephalitis and from the brain substance of such cases after death. Evans and Freeman ([35]) have also described a streptococcus isolated by them from nasal washings, heart blood, and mesencephalon of a patient with epidemic encephalitis. The streptococcus obtained by these authors is similar according to comparative test, with the streptococci described by Von Wiesner and by Rosenow. This organism,

so it is claimed, shows a tendency to elective localization in the brain and is said to produce nervous symptoms in rabbits and monkeys which, in some instances, simulate the disease in man. In another publication Evans ([36]) reports the isolation of six strains of streptococci from vesicles in cases of herpes, one from the cerebrospinal fluid from a case of syphilis, and one from the brain substance from a case of epidemic encephalitis. Freeman ([37]) has described the use of an antiserum prepared in horses with the streptococcus which was described earlier by Evans and himself. Administration of specific anti-streptococcus serum to cases of encephalitis was controlled by the administration of normal horse serum, antipneumococcus serum, and streptococcus bacterin. Freeman states "The injection of normal horse serum during one relapse, of antipneumococcus serum during another, and of streptococcus bacterin during a third thus had the same beneficial effect that the encephalitis serum had in the first place". Russell ([38]) has also described a number of recoveries of cases of encephalitis following administration of antidiphtheritic serum. As pointed out by Freeman such results indicate the need for proper controls in attempting to evaluate the efficacy of specific serum therapy. Certainly these results as reported by him lend little evidence in favor of the streptococcus etiology of this disease. They indicate, however, that non-specific protein therapy may have some beneficial effects.

In a recent review of the filterable virus diseases Mac Callum ([39]) in speaking of epidemic encephalitis and the experimental work with the various viruses which we have described above states: ". . . . . differences between the curves showing the effect of inoculation of encephalitis material on the one hand and of herpes material on the other, into rabbits (Ford and Amoss), make one suspect very strongly that all of the so-called viruses of encephalitis are really accidentally recovered herpes viruses. This seems a far safer conclusion than that ventured by some that the viruses of encephalitis and herpes are identical, and it is preferable to concede that as yet we know nothing of the cause of encephalitis. All of this has been clearly brought out by Flexner".

This is further indicated by the fact that Bastai and Busacca have found the herpes virus in the blood and cerebrospinal fluid of persons subject to herpes but at the time possessing no lesions. In such people slight indisposition frequently brings on an attack of herpes.

This summary may be taken as representing the thought of the

American school on the subject of the etiology of epidemic encephalitis. With regard to the streptococcus as a possible etiologic incitant, there are few who consider this organism seriously.

PATHOLOGY

The chief changes found in epidemic encephalitis are located in the upper part of the pons and in the basal nuclei and consist of a perivascular infiltration (large and small mononuclear lymphocytes), in some cases the areas of extravascular infiltration forming foci which may be seen with the naked eye. The destruction of the ganglion cells as found in poliomyelitis is not common. The spinal cord lesions are very mild. Changes in the Purkinje cells are noted but cortical lesions and extensive lesions of the gray matter are not common.

According to McCrae ([41]) hemorrhages in the meninges and in the region of the basal ganglia may be found. Lesions also occur in the cerebellum. Lesions are both nodular and diffuse. The nerve cells show degeneration, either localized or general. Thrombosis and necrosis have been noted but are rare. The gray matter at the base of the brain is particularly involved. Altogether, according to this author "the anatomical lesions are like those found in rabies and sleeping sickness". He states further "the lethargy may be toxic but is possibly mechanical due to interruption of stimuli in the thalamus, which is frequently involved. The latter changes involve (1) the vessels with hyaline and calcareous degeneration of the media and adventitia especially and particularly in certain areas, such as the basal ganglia, (2) hydrocephalus, chronic or intermittent, from imperfect drainage of the ventricles, and (3) meningeal thickening".

PREVENTION

Very little can be said regarding the prevention and control of epidemic encephalitis. That the disease is communicable is agreed by most authorities. However, it is only mildly so. Its relation to other infectious diseases is little understood. While the disease is apparently decreasing in certain parts of the world (England) it still remains in other countries as a serious and increasing menace. Until its cause is definitely known it is impossible to formulate rules for its prevention. At present it is only possible to employ ordinary hygiene measures which are indicated for any infectious and communicable disease. No vaccine or serum is as yet available for its prevention or treatment.

ACUTE ENCEPHALITIS
(Australian X Disease)

In 1926 Kneebone and Cleland ([42]) reported an acute encephalitis condition which appeared again in Australia during January and February of the year 1925. In previous reports Cleland and Campbell ([43]) had reported an epidemic of acute encephalo-myelitis in Australia which appeared in 1917–19. According to these authors the Australian disease (X disease) does not correspond with that of encephalitis lethargica reported in other parts of the world. Australian X disease is characterized by its high mortality, very high temperature, coma, convulsions, relative absence of eye symptoms, rapid approach to death in fatal cases, its general resemblance to cerebrospinal fever, and leucocytosis. Furthermore these investigators have offered evidence that the virus of X disease may be transmitted to sheep.

During 1917–18 the virus X disease was transmitted successfully to monkeys and at the same time was apparently transmitted to a series of sheep. Successful "takes" were obtained into the third series of sheep, by sheep to sheep inoculation, but failed in the fourth. In 1926 Kneebone and Cleland again attempted to transmit the virus to these animals. Five sheep were inoculated. The first animal inoculated directly into the brain substance with 1½ cc. of nerve tissue emulsion from a fatal human case of the disease, died eight days later with general convulsions. The second animal died with similar symptoms nine days following inoculation. The third sheep died with general convulsions seven days following inoculation. Sheep 4 was inoculated with brain emulsion from sheep 3 and died with general convulsions nine days after inoculation. The fifth sheep was inoculated with brain substance from sheep 4 and suffered no ill effects following the inoculation. Brains from sheep 1, 2, 3 and 4 all showed intense pial congestion but no evidence of suppuration. Bacteriologic cultures were uniformly negative.

The case described from which brain substance was obtained for the sheep inoculations is perhaps typical of the fatal cases of this disease. The authors described it as follows: "Case 3. (From this case the sheep inoculations were made). Lucy S., aged two years and ten months was admitted on March 1, 1925. She had whooping cough ten months before, but since then had been quite well up to two days ago. For the last two days she has had "turns" each day, lasting up to six minutes at a time, and three convulsions, followed by general twitchings during the day before admission. The bowels

had been opened once daily. She had refused food since she became ill. Examination showed that she was in a semi-comatose condition with generalized twitchings. Head retraction and Kernig's sign were present. Nothing abnormal was detected in the chest or abdomen. The urine showed no abnormality. The temperature was 101.6° F., the pulse, 140, and respiration 48. Next day her condition was worse, although the twitchings were not so severe. There was left abducent paralysis. Lumbar puncture yielded 60 cc. of clear fluid under slightly increased pressure. This fluid contained no increase of globulin, no pus cells, and no organisms either in smears or on culture. The temperature, on admission rose in 12 hours to 105° F. and maintained a high level, rising to 106° F. a few hours before death, which occurred 36 hours after admission. At the post-morten examination, 12 hours after death, the brain was removed with strict aseptic precautions. Very marked congestion of the vessels of the pia mater was present, both at the vertex and at the base. There was no evidence of tuberculosis or suppurative meningitis, and the other organs were healthy. Microscopic examination of sections from the brain and spinal-cord failed to reveal the presence of perivenous sheaths of cells or of cellular islands. These sections included the basal nuclei. There was marked capillary congestion in the frontal and occipital areas."

From the description of this case there can be no doubt that it is in many ways dissimilar to epidemic encephalitis both in its symptomatology and in its morbid anatomy. While the transmission of the virus to sheep is not conclusive, these experiments may be considered as strong evidence that such transmission is possible. If this point is accepted, this is also important evidence that the disease is at variance with encephalitis lethargica for no virus has ever been transmitted to sheep from cases of epidemic encephalitis or from cases of poliomyelitis. Indeed in our experience it has been impossible to infect sheep with herpes virus or for that matter to satisfactorily demonstrate antibodies in the blood stream of sheep which have received more than a dozen injections of herpes virus emulsion in an attempt to immunize them.

What the exact nature of Australian X disease is and its microbic incitant must be left for future experimental work to decide. For the present we must regard it as still another form of encephalitis and most probably it is unrelated to encephalitis lethargica.

JAPANESE ENCEPHALITIS
(Takaki virus)

In 1924 there was an epidemic of encephalitis in Japan. This epidemic occurred in the summer and involved about 6,000 cases. Various investigators attempted to transmit the disease to animals. Takaki ([44]) has reported that he succeeded in six transmissions of the virus of the disease to rabbits with material from six fatal cases. According to this investigator the virus in inoculable by both cornea and brain as well as other organs. It could not be cultivated artificially. Takaki states that the symptoms produced in rabbits by this virus are not similar to those induced in rabbits with the herpes virus. Furthermore cross immunity tests with the Takaki virus and herpes virus show that there is no relation between the two viruses.

Commenting upon the Japanese disease in a recent paper Flexner ([45]) states: "In view of this discordant finding, the question arises whether the Japanese and the European epidemic diseases are pathologically the same. Fortunately this question can be answered, and apparently in the affirmative. The clinical and pathological descriptions which have been published show close similarity. Through the kindness of Professor Kimura, of the Imperial University in Sendai, I have been enabled to examine specimens taken from the brain of fatal cases. These specimens show pathological changes closely resembling those found in the brain of Europeans and Americans who have succumbed to epidemic encephalitis. The changes or lesions are of two sorts: mononuclear (lymphoid) infiltrations of the blood vascular sheaths and brain tissue, and degeneration of ganglion and glia cells. The distribution of the lesions is also typical. Especial attention may be drawn to the lesions in the substantia nigra which are prominently present in the Japanese, as well as in the European cases of the disease."

This author calls attention to the virus reported by Kling and Liljenquist ([46]) in Sweden in 1921 which these investigators obtained from a case of epidemic encephalitis. The experimental disease produced by this virus shows a chronic pathological process rather than an acute process and in this respect differs from all the other viruses which have been reported. Some investigators take the stand that Kling and Liljenquist were dealing with the virus of spontaneous encephalitis in rabbits but Flexner states "There is no doubt that the Swedish cases of epidemic encephalitis are identical with the other European and the American cases. . . . . there is strong reason to believe that the Japanese epidemic disease is of the nature of the

European and American disease. The essential differences relate to the microbic incitant described by Kling and by Takaki. As tested by these discrepancies, the epidemics would have to be regarded as distinct. The fundamental question raised by the discrepancies is therefore, whether the experimental findings are not open to the suspicion of not revealing the real incitant of the epidemic disease."

For the present the Japanese epidemic of encephalitis must be regarded as related to epidemic encephalitis as it occurs in other parts of the world. Its virus is one of the few which has been isolated from the brain tissue of human cases of the disease and is unique in its unlikeness to the herpes virus.

VACCINATION ENCEPHALITIS

Within the last two or three years there have appeared cases of encephalitis which have apparently been related to vaccination. Turnbull and McIntosh ([47]), Heymann ([48]), Aldershoff ([49]) and others have written reports upon this subject. Heymann quotes Jenner's observation on the inhibition of the development of the smallpox vaccine pustule in patients with herpes. Turnbull and McIntosh have reviewed seven cases of encephalomyelitis which were definitely connected with vaccination. The only virus demonstrated experimentally in the brain and cord was a vaccinal virus. The post-vaccinal encephalitis develops from nine to fifteen days after the vaccination.

Levaditi, Nicolau and Bayarri ([50]) regard this form of encephalitis as the flaring up of a latent virus of epidemic encephalitis already present in the central nervous system. This theory is also concurred with by Netter ([51]). Bastiaanse, Bijl and Terburgh ([52]) support a similar idea. Fielder ([53]) states that 52 instances of disease of the central nervous system, after vaccination are recorded and he believes that vaccination activates viruses already present in the system.

Lucksch ([54]) on the other hand maintains that encephalitis following vaccination is caused by the vaccine virus. Wilson and Ford ([55]) point out that a diffuse nonsuppurative encephalomyelitis may occur as a rare but specific complication of variola, vaccinia and varicella. These authors further state that the vaccine virus has been demonstrated in the cases ef encephalitis following vaccinia but not in connection with variola and varicella. These authors believe that the condition is in reality uncommon and that many such cases have been mistaken for tetanus.

Lucksch has suggested the use of the Paul test with spinal fluid from these cases. He believes that corneal lesions may be obtained in rabbits with spinal fluid from these cases which may be regarded as characteristic of smallpox virus.

This question is of special interest from the medico-legal point of view particularly if the possibility of tetanus infection is involved.

SPONTANEOUS ENCEPHALITIS IN RABBITS

The study of experimental encephalitis in rabbits has been complicated by the presence in these animals of spontaneous encephalitis. Spontaneous encephalitis in rabbits was first noted by Bull ([56]) in 1917. Bull was studying the brains of rabbits inoculated with streptococci and found focal areas of necrosis surrounded by lymphocytic cells. These areas were near the blood vessels showing a perivascular infiltration extending from the meninges. Subsequently Bull examined several hundred rabbits having snuffles and found one which had acute meningitis with perivascular infiltrations within the cerebrum. Reasoner ([57]) in 1916 had noted similar changes in animals which had received intravenous injections of syphilitic material. These observations indicated that the stock animals might be originally affected by this process and that it bore no relation to the experimental procedures being studied.

In 1922 Oliver ([58]) first spoke of a spontaneous chronic meningoencephalitis of the rabbit. This author found about 20 per cent of stock animals and animals bought on the market showing the changes noted above. The animals were in apparent healthy condition. During the same year Twort ([59]) described spontaneous encephalitis in a batch of rabbits which was characterized by definite symptoms. The onset was insidious, the temperature subnormal, the hair fell out, the animals lost weight and there was a discharge from the eyes. Later muscular weakness progressed, the animal developed convulsions and died in coma. Twort and Archer later transmitted the malady to four young rabbits and attempted to link up this virus with nephritis in animals.

McCartney ([60]) found that about half of 372 rabbits examined had such lesions and that in certain groups of animals as high as 76 per cent were affected. The lesions consisted of perivascular, meningeal, parenchymatous, and subependymal infiltrations with mononuclear cells. Here and there were focal areas consisting of aggregations of cells. These areas were distributed throughout the

brain. Necrotic foci were found in 15 per cent of the brains examined.

Later several investigators made a study of this condition in rabbits and among them Levaditi, Nicolau and Schoen ([61]). These authors noted a micro-organism in the lesions which they designated "Encephalitozoon cuniculi". The parasites were found next to the subcortical nodules of epithelioid and lymphocytoid cells and occasionally in the brain substance. They appeared to be in cysts and usually 20 to 40 microorganisms were found in each cyst. Similar organisms had already been described by Wright and Craighead in 1922 and by Doerr and Zdansky. Later in 1924 similar organisms were described by Cowdry and Nicholson ([62]) who termed them protozoan-like parasites.

That spontaneous encephalitis exists in apparently healthy rabbits is now an established fact. This knowledge should be carefully considered in connection with experimental studies with encephalitis material.

POLIOMYELITIS
(Infantile Paralysis; Acute Anterior Poliomyelitis)

DEFINITION

Infantile paralysis is an acute, systemic, infectious disease, occurring both epidemically and sporadically, and is caused by a specific filterable virus. The virus of poliomyelitis attacks the nervous system and may affect every part of the cord although it is prone to localize chiefly in the anterior horns of the gray matter. The posterior horns, however, may be seriously involved. In some instances the brain itself may be affected, the changes as a rule being more pronounced in the base of the brain. Symptoms of spastic paralysis indicates that the meninges are also involved in certain cases.

HISTORY

Poliomyelitis has undoubtedly existed since ancient times. To Underwood is generally given the credit for the first description of this disease. We have been unable to read a book by this author entitled "A Treatise on the Diseases of Children" published in 1784 but we are told by Vaughan who has studied his work that this author undoubtedly described infantile paralysis at that time under the title "Debility of the Lower Extremities". Until recent years poliomyelitis was not recognized as an infectious disease. The literature of the last century spoke of this disease as the Heine-Medin dis-

ease because Heine ([63]) in 1840 definitely established the disease as a clinical entity and Medin ([64]) in 1890 was the first to carefully study an epidemic of the disease and describe its various clinical manifestations.

The first outbreak of infantile paralysis in the United States in 1894 was described by Caverly ([65]). This epidemic occurred in the state of Vermont. The first reported epidemic of this disease had occurred in Sweden in 1881, the disease appearing the next year in Italy and in 1886 small outbreaks were noted in Germany, France and Norway. During the decade 1890 to 1900 there were minor outbreaks of the disease in Italy, France, Australia, England, and in the United States. The epidemic at Rutland, Vermont, in 1894, consisted of 132 cases. Between 1900 and 1910 epidemics of the disease increased in proportion and severity. The disease was practically pandemic in Norway and Sweden from 1903 to 1907. From 1907 to 1910 large epidemics occurred in several of the Eastern and Midwestern states including New York, Massachusetts, Iowa and Minnesota. At the same time the disease was endemic in various parts of Europe. Up to 1910 the United States had contributed over five thousand of about eight thousand cases which had been reported in various parts of the world ([66]). Rosenau states that from 1910 to 1914 there were over 18,000 cases of this disease reported in the United States and during 1915–16 there were 31,500 more. In 1916 alone this author states there were 29,000 cases, and 6,000 deaths resulted from this disease. New York City reported in this epidemic nearly 9,000 cases with over 2,400 deaths.

DISTRIBUTION

Poliomyelitis is essentially a warm-weather disease yet cases are exceedingly rare in tropical countries. It does occur in the tropics, however, but never in large epidemic proportions. The disease also occurs in cold countries as evidenced by the epidemic in Iceland in 1924. The greatest number of cases are reported during the summer months. As a rule the disease is manifested only by sporadic cases during the winter months although cold-weather epidemics have been reported. (Sweden 1911.)

Epidemiologists state that infantile paralysis is usually more prevalent in sparsely settled communities than in the large cities. Its incidence was extremely high in New York City during 1916 but as a rule it is highest in rural communities. From available statistics males are slightly more susceptible than females and 95 per cent of

cases are found in children under ten years of age. In the New York City epidemic in 1916 the case mortality rate was 26.96 per cent.

THE VIRUS OF POLIOMYELITIS

In 1905 Geirsvold ([67]) isolated certain bacteria and especially cocci from spinal fluids and tissue specimens from cases of infantile paralysis. In 1909 Landsteiner and Popper ([68]) attempted to infect two monkeys with emulsified spinal cord obtained from a child who died on the fourth day of an attack of infantile paralysis. Both monkeys were injected intraperitoneally and one monkey died on the eighth day following the inoculation. The second monkey developed paralysis on the seventeenth day and was sacrificed for study on the nineteenth day. Two monkeys were inoculated with cord emulsion from the second monkey but neither were apparently affected by the injections.

While Landsteiner and Popper were unable to transmit the disease from monkey to monkey they were able to study carefully the anatomical changes produced in the first two monkeys. The examination of the cords of these two animals showed the pia to be infiltrated with small, round, deeply-staining cells chiefly along the anterior median fissure. The substance of the cord exhibited areas of inflammation chiefly in the cervical area. These areas consisted of perivascular infiltration and diffuse infiltration into the substance of the cord. Hemorrhages were also noted in the gray matter. These lesions were also found in the medulla, pons and brain stem though they were not so intense. The ganglion cells of the anterior horns also showed evidences of invasion and degeneration. The lesions in the second monkey were similar but more pronounced in the lumbar regions. Hemorrhages were absent and there were fewer infiltrating polymorphonuclear leucocytes in the cord substance.

About the same time Knoepfelmacher ([69]) reported the successful transmission of this disease to a monkey in Vienna. This animal was also injected intraperitoneally and developed symptoms of paralysis on the twelfth day. A second monkey injected with material from the first monkey remained unaffected although the histological findings in the first animal agreed with the description given by Landsteiner and Popper. During the same year Landsteiner and Levaditi ([70]), Leiner and Wiesner ([71]), and Romer ([72]) succeeded in transmitting the virus of poliomyelitis by the intracerebral route to monkeys. Landsteiner and Levaditi also demonstrated that the virus is filterable, a fact which, unknown to them at the time, had

been learned by Flexner and Lewis in the United States. Lainer and Weisner also found that paralysis resulted following the injection of the virus into the intestine or stomach.

In 1909–10 Flexner and Lewis ([73]) demonstrated independently that the infections agent in poliomyelitis is a filterable virus. These authors were able to infect monkeys at will with bacteria free filtrates by both subcutaneous and intracerebral inoculations. They were also able to pass this virus from monkey to monkey by means of filtrates and in this way study the incubation period of the disease in this animal, the clinical forms of disease, and the anatomical changes produced by the virus. Under the dark field microscope Flexner and Lewis observed innumerable bright, dancing points and when stained with Loeffler's flagella stain they found minute roundish or oval particles which were absent in filtrates prepared with normal rabbit spinal cord emulsions.

Flexner and Lewis used for material the spinal cords from two cases of infantile paralysis in human beings. One patient had died on the fifth or sixth day of the disease while the second succumbed on the fourth day. The spinal cord obtained from the latter case contained wide-spread lesions affecting both the gray matter and white. Sixteen hours after death the cord was emulsified and injected intracerebrally into monkeys. Symptoms of the disease began to appear in from six to forty-eight hours before paralysis developed. Symptoms of paralysis were found to develop in from four to thirty-three days with an average period of about nine days. Altogether these authors infected 83 monkeys in their first study. In regard to the virus, Flexner and Lewis found that in common with many other filterable viruses, the virus of poliomyelitis resists the action of glycerine for at least seven days and also resists drying over caustic potash for the same period. They also demonstrated that the virus of poliomyelitis retains its virulence when kept constantly frozen at 2° to 4° C. for at least forty days. The virus is destroyed in the filtrate when heated for one half hour at 45° to 50° C.

Out of 83 monkeys (of several species) infected with the virus of poliomyelitis by Flexner and Lewis only 6 failed to develop paralysis. These authors believe that they have detected some evidence of immunity in monkeys which had been previously infected and at least partially recovered, and were then reinoculated. They state "in no instance did the second inoculation produce a frank renewal of the disease or appear to retard the progress toward recovery". In other experiments a heated vaccine prepared of infected spinal

cord was tried for preventive purposes but in each case failed to protect the animal when given simultaneously with the test dose of virus.

The cultivation of the virus of infantile paralysis yet remained. Flexner and Lewis noted the clouding of serum bouillon when a Berkefeld filtrate of the central nervous system tissues of poliomyelitic monkeys was added to it, an observation which was also confirmed by Levaditi ([74]) but which proved to be due to protein precipitate and not to virus. In 1913 Proescher ([75]) found in stained smears from the nerve tissue of poliomyelitis-infected monkeys certain coccus-like bodies. Such bodies have also been described in rabies and their precise nature is unknown. They have not been found in poliomyelitis material taken from human cases.

In 1913 Flexner and Noguchi ([76]) described the cultivation of the virus of poliomyelitis. The medium consisted of human ascitic fluid to which was added a fragment of sterile fresh tissue. In the initial cultures the exclusion of oxygen is necessary but it is sufficient to cover the liquid with paraffin oil for this purpose. Also cultures were obtained without fresh rabbit tissue by using fragments of poliomyelitis brain in ascitic fluid. Brain tissue extract and sheep serum water served nearly as well as ascitic fluid, especially when fresh rabbit tissue was added to the medium.

The supposed virus of poliomyelitis stains by both Giemsa and Gram methods and appears in stained smears as variable numbers of minute globoid bodies, arranged in pairs, or short chains, or in small aggregated masses. In the fluid culture the pairs and chains predominate. Once growth has been obtained in fluid medium subcultures can be made on solid medium consisting of agar, ascitic fluid, and a fragment of sterile tissue. On solid medium the organisms develop as pairs and as aggregated groups. Cultures of the supposed poliomyelitis virus were obtained by these authors from fresh poliomyelitic brains (monkeys), from filtrates prepared from infected brains, and from glycerinated poliomyelitic brains.

The individual organisms are said to average about 0.2 micron in diameter, the limits of visible bodies being 0.15 to 0.3 of a micron. The minute globoid bodies usually appear in cultures by the sixth or seventh day. Growth begins slowly but increases rapidly later on and is usually complete by the eighth to the twelfth day. The cultures remain unchanged for several days in the incubator and are preserved for several weeks in the ice box.

The virus of poliomyelitis is sensitive to ordinary disinfectants

being destroyed by a 1:500 solution of potassium permanganate; 1 per cent menthol in oil; 0.5 per cent salol; 5 per cent boric acid; and one per cent hydrogen peroxide. The virus remains virulent in milk and water for about thirty days according to Levaditi and Pasti (77). The virus cultivated by Flexner and Noguchi is open to grave doubt as being the cause of this disease and must await further confirmation.

INCUBATION PERIOD

The incubation period is usually short, from one to three days, up to fourteen days, with many instances of seven days. Aycock and Eaton (78) have studied the disease in families and judging from secondary cases which become infected they estimate the incubation period to be ten days to eighteen days with the average at fourteen days. The experimental disease in monkeys demonstrated, in the hands of Flexner and Lewis, an average incubation period of 9.82 days. This was calculated from the time of inoculation until the first symptoms of paralysis occurred. It is not thought that the incubation period in human beings varies much from that in monkeys.

SYMPTOMS

In monkeys there is no immediate effect following inoculation. Nothing unsual is noticed until six to forty-eight hours preceding the onset of paralysis. The animals then may show certain prodromal manifestations. These consist of nervousness and excitability, tremor of the head, face or limbs, shifting gaze, hairs somewhat erect, and the animals prefer to remain quiet. The paralysis develops suddenly. Flexner and Lewis state "In general it may be stated that any of the larger groups of voluntary muscles may be first involved." In 81 animals inoculated by these authors, 40 monkeys developed paralysis in the left leg, 21 in the left arm, 10 in all four limbs, and 8 monkeys had bulbar and cerebral symptoms. With the development of paralysis in a large group of muscles other muscles may be found weak or paralyzed. The paralysis is associated with marked incoordination resulting in violent pseudo-convulsions; epileptiform convulsions with tonic and clonic muscle-spasms; and finally, according to Flexner and Lewis, sudden death with the apoplectiform type. These authors state that death has occurred within thirty minutes of the first appearance of cerebral symptoms.

In the naturally occurring disease in human beings the disease comes on suddenly and is characterized by fever, irritability, and

in many cases with nausea and vomiting. Paralysis usually appears within a few days (three or four). In some cases the paralysis is the first symptom noted. Abortive attacks without paralysis may occur in epidemics. During the acute stages of the disease the spinal fluid contains an increased number of cells (usually 200 or more) and an increase in globulin. Paralysis usually remains stationary for a few weeks, improvement is gradual but in some cases recovery takes place within a few months. Residual paralysis is usually permanent but improvement may follow proper treatment.

ANIMALS SUSCEPTIBLE TO THE VIRUS

Man is apparently the natural host for infantile paralysis. Monkeys of many different kinds are susceptible to the virus. Flexner and Lewis were unable to infect guinea-pigs, rabbits, horses, calves, goats, pigs, sheep, rats, mice, dogs or cats with this virus. Man and monkeys alone remain susceptible.

IMMUNITY

One attack of infantile paralysis confers a high degree of immunity. Second attacks have been reported but are rare. As mentioned above Flexner and Lewis found that monkeys which had recovered from an attack of the disease were found to have developed immunity. The serum of immune monkeys possesses virucidal properties for the virus in vitro. There is no racial immunity to poliomyelitis although the majority of cases have occurred in whites. Various preparations of infected nerve tissue have been tried for vaccination, such as dessicated cord, heated cord emulsions, chemically treated emulsions, etc., but none of these methods have been sufficiently established to warrant their use in human beings. A serum in horses is said to have been prepared but its preventive and treatment qualities have not been studied sufficiently to make any statement regarding it. More recently convalescent human serum has been employed with what appears to be very encouraging results.

TRANSMISSION

There are many theories regarding the transmission of this disease. There is evidence that the disease is spread from person to person and that healthy carriers of the virus may exist. Flexner and Amoss ([79]) have shown that the virus is present in the nasopharynx of both monkeys and human cases of infantile paralysis early in the course of the disease. Other investigators have also found

the nasopharynx of monkeys infected following experimental inoculation (Osgood and Lucas). Rosenou, Sheppard and Amos ([80]) were unable to demonstrate the virus in the nasal or oral cavities in convalescent cases. Amoss and Taylor ([81]) were able to produce infection by placing the virus upon this membrane.

Other theories of transmission have been considered such as the insect-borne theory, milk-borne infection, air-borne theory, the animal-reservoir theory, transmission through wounds, etc.

Rosenau and Brues ([82]) have demonstrated that the virus may be transmitted from monkey to monkey through the bite of the stable fly. This work was confirmed by Anderson and Frost ([83]). Epidemics have been described as being due to infected milk supply (1916 and 1925). It is possible to induce infection by way of the gastro-intestinal tract, but it is not thought that infection usually takes place in this way. Neustaedter and Thro ([84]) have been able to induce infection in monkeys with dust collected from sick rooms and suggest this mode of transmission in certain cases. In regard to a possible animal reservoir for the virus of poliomyelitis there is at present no evidence of it and the theory of infection through wounds possesses nothing in its favor.

For the present it seems best to regard poliomyelitis as a contact disease though many features of the disease cannot be explained upon this basis. Future epidemics may give us more definite information upon this point.

PATHOLOGY

The anatomical changes found in monkeys have already been briefly described. In human beings the lesions are not only in the nervous tissues but also in the parenchymatous organs and lymphoid structures. In the nervous system the virus attacks the meninges particularly of the cord and medulla. There is a cellular inflammation of the pia most marked around the blood vessels. The walls of the vessels are also infiltrated and their lumen narrowed. The vessels entering the nerve tissue are also affected. Anemia, edema and hemorrhages result. The secondary degenerative changes in the nerve cells of the pons, medulla, cerebrum and cord, are secondary to the lesions in the vessels. Transient paralysis may be due to edema or temporary vascular obstruction from pressure. Permanent paralysis is due to degeneration and actual destruction of the ganglion cells. Any part of the central nervous system may be involved. The symptoms depend upon the extent of this involvement. The changes are chiefly in the gray matter of the anterior horns and

consist of acute degeneration. The nerve cells may disappear entirely being replaced by leucocytes. Round-cell infiltration may be noted in the posterior horns, the columns of Clarke, and the white matter of the cord. Similar changes are also noted in the spinal ganglia. Also in some cases similar lesions may be found in the pons, medulla, cerebellum, and cerebrum. Lesions may be found in other organs such as broncho-pneumonia, acute parenchymatous degeneration of the liver and kidneys. The thymus, Peyer's patches, and mesenteric lymph glands may be swollen. Gross changes at autopsy are found in the spinal cord, ganglia and muscles. The affected part of cord may be smaller than normal, the anterior nerve roots are degenerated, the affected muscles atrophied. The affected limb may be shorter and the bones may even be smaller than those upon the normal side.

PREVENTION

Isolation of cases of this disease is indicated. All discharges should be properly disinfected. All articles with which the patient has come in contact should be sterilized. Visitors should not be permitted. Prophylatic pasteurization of milk is indicated. In general common-sense methods of prevention apply. No definite program has as yet been formulated by epidemiologists for the prevention of this disease and probably will not be until more definite knowledge of its mode of spread and transmission is available.

RABIES—LYSSA

(Canine Madness, Hydrophobia); Wutkrankheit, Tollwut (German); La Rage (French); Rabbia (Italian)

DEFINITION

Rabies is an acute, rapidly fatal infection of the central nervous system. Highly specific it is a disease primarily of animals and is transmitted direct from one animal to another through a wound usually produced by biting. It is most prevalent among carnivora but it is infectious for nearly all mammalia. Rabies is communicated to man from lower animals by means of infectious saliva introduced into the tissues through a biting wound or through small abrasions in the skin of the host. The disease in man is most commonly transmitted by dogs.

HISTORY

Although the actual virus of Rabies has not been demonstrated in the saliva of infected dogs up to the present time, it was demon-

strated by Zinke as early as 1804 that the saliva of rabid dogs is infectious. Seventy-five years elapsed after this discovery before Galtier ([85]) was able to show that the disease could be transmitted to rabbits through artificial inoculation (1879). In 1881, Pasteur ([86]) with Chamberland and Roux found that the virus has a special affinity for the central nervous system. The work which followed this discovery by Pasteur and his collaborators from 1881 to 1888 will remain forever as a classical achievement in the science of modern medicine. During these years the method of immunization, now in general use through the world, was perfected by Pasteur, Roux, Chamberland and Thuillier. The story of this magnificient contribution to medical science is beautifully portrayed in mosaic in the tomb of Pasteur at the Institute Pasteur which stands as a monument to his brilliant work. It was not until 1903 that Remlinger ([87]) demonstrated the filterability of the rabies virus. This was confirmed in 1904 by Berterelli and Volpino ([88]) and later in 1913 in the United States by Poor and Steinhardt ([89]). Negri ([90]), an Italian of Parvia, Italy, in 1903 described bodies found in the cells of the central nervous system, especially in the large ganglion cells of the hippocampus major and in the Purkinje cells, which now bear his name. Negri's work has been amply confirmed by Volpino ([91]), Da Mato ([92]), Berterelli ([93]), Bosc ([94]), Poor ([95]) and other investigators. In 1913 Noguchi reported the cultivation of Negri bodies but his work has not been confirmed up to the present time.

DISTRIBUTION OF THE DISEASE

Rabies exists practically all over the world. It is most common in France, Belgium, Russia, certain parts of the United States and in the Philippine Islands. It is said never to have been present in Australia and for more than fifty years has not been known in Denmark, Sweden and Norway. Rabies was eradicated from England up until the World War and then again reappeared. It is said to have been again introduced by dogs carried in aeroplanes. One of the largest rabies clinic known to the author is in the Philippine Islands where there is a daily clinic at the Bureau of Science of about sixty patients reporting for immunization.

INCUBATION PERIOD

There is no disease in which the incubation period varies more markedly. The usual period of incubation is from two to eight weeks although cases in which symptoms did not develop until two years had elapsed are on record. Various explanations have been advanced

to explain the latency of the virus in the tissues. The most plausable theory perhaps is the time required for the virus to travel up the axis cylinder of the nerve trunk to the central nervous system. Favorable conditions may not exist for the multiplication of the virus at the time of infection and the virus remains dormant though alive, awaiting optium environment. Though purely theoretical this concept has its adherents. The incubation period also varies in animals, with the amount and virulence of the virus, with the extent and type of wound and particularly with the location of the wound with relation to its nerve supply. The average incubation period for various animals is usually given as follows: Man, 13 to 60 days; dogs, ten to forty days; cows, twenty-eight to fifty-six days; goats and sheep, twenty to twenty-eight days, pigs, ten to twenty-one days. For birds the incubation period ranges from fourteen to forty days.

SYMPTOMS OF THE DISEASE

Generally speaking, in dogs the first symptoms of the disease appear two to eight weeks after the wound. During the first stage of the disease (stadium prodromorum or melancholicum) there may be so little manifestation of symptoms that the condition is entirely unsuspected. The infected animal may be somewhat irritable and depressed, capricious or may avoid all noise and activity and hide away in some dark place. On the other hand the animal may appear mildly excited, moving from one place to another, scratch with the fore feet and without cause bark and bite at the air. Strange persons provoke growling and snapping and slight stimuli often cause the animal to become startled or jump up frightened. One may observe during these paroxysms dilatation of the pupils and slight respiratory disturbances. About this time the animal loses his appetite and later refuses all food. Difficulty in swallowing is quite characteristic and although the animal seeks water he is able to swallow very little of it. By this time salivation becomes manifest and increases. Sexual desire is increased and licking of the genitals is quite common. Within one to three days after onset symptoms the animal passes into the excitable stage, (stadium excitationis or acmes). The animal wants freedom, to be away from his usual surroundings. He will lick the ground, chew any object and develop a violent rage. Once loose the animal runs aimlessly often covering long distances and attacking people and animals along the way. The eyes are blood shot and in fighting with other animals the infected dog remains quiet though the normal animal howls and barks. Infected dogs when caged re-

main quiet but develop a violent rage when teased. Frequently their teeth are broken in grabbing the bars of the cage and attacking objects with which they are teased. Such animals have been known to bite red hot iron or burning coal. Stages of exhaustion follow such attacks and the animal falls down in unconsciousness for indefinite periods. About this time the early symptoms of paralysis appear. The larynx may first become paralyzed and is evidenced by the peculiar hoarse bark. Swallowing becomes very difficult as the inflammation increases and later there is degeneration of the 11th and 12th pairs of nerves. The animal refuses all food and drink and the sight of water may provoke an attack; hence the term hydrophobia. Circus movements have been noted in this stage. The paralysis gradually progresses and involves other parts of the body. The jaw muscles become paralyzed and the tongue hangs out, the saliva flowing out of the mouth in copious quantities. The eyes are full and the pupils dilated and the face has a peculiar cunning and troubled expression. Gradually as the paralysis spreads the animal becomes emaciated, the exhaustion increases and the patient dies in convulsions. During the excitable stage the temperature rises one to three degrees, but later during the paralytic stage the temperature is usually below normal. The pulse is rapid according to Blaine ([96]). Courmont and Lesieur ([97]) found that the polymorphonuclear leucocytes are gradually increased in the blood to the end of the disease. Nocard ([98]) states that the urine usually contains sugar.

While this description of the course of the disease in dogs may often be somewhat modified, the same course, with slight modifications, is seen in other infected animals such as the cat, horse, cattle, sheep, goats and swine. The disease has a course of from four to seven days but may last from eleven to thirteen days or in exceptional cases even longer. Artificially infected dogs have been known to recover from the disease but generally speaking, with few exceptions, the disease is fatal (Pasteur). Cases where dogs were still alive while persons bitten by them had already died from rabies, have been reported by Talko and Johne ([99]). Of the untreated persons bitten by rabid dogs, about 16 to 20 per cent die of rabies. According to Babes ([100]) 60 to 90 per cent die after bites of wolves. In human beings the symptoms of rabies are characterized first by depression, itching in and around the wound and fever. Soon the patient becomes uneasy, respiratory irregularities develop, swallowing becomes difficult and for all liquids there is a distinct aversion. Salivation becomes increased, and, with the increased reflex

excitability which develops, attacks of delirium appear. Finally paralysis begins to appear first of the muscles of the face, eyes and tongue, and gradually involving the trunk and limbs.

ANIMALS SUSCEPTIBLE TO RABIES

All mammals are susceptible. Birds have been known to contract the disease. Rabies is common in dogs, wolves, jackals, foxes and hyenas. According to Rosenau ([101]) the disease is comparatively rare in cats and skunks. The author, however, has observed one epidemic of rabies in cats in Texas which was rather extensive. The disease is considered to be much less frequent in cattle, horses, swine, goats and sheep, but it does occur with symptoms quite similar to those found in dogs. Rabies can be transmitted to guinea pigs and rats. Infected birds not infrequently recover, but in those in which the disease is fatal only two or three days elapse between the first symptoms and the development of paralysis and death.

THE VIRUS OF RABIES

That the filterability of the virus of rabies is beyond question has been amply demonstrated by Remblinger and confirmed by Berterelli and Volpina, by Poor and Steinhardt and others. The virus may appear in the saliva five days before the animal shows symptoms and has been demonstrated in the saliva of recovered dogs twenty days later. The virus is found in the tear glands, the adrenals, pancreas, the spermatic fluid, vitreous humor, urine, lymph, milk, spinal fluid, ventricular fluids and occasionally in the blood. It is distributed throughout the central nervous system and in the peripheral nerves supplying affected parts of the body.

The virus of rabies is supposed to have been cultivated by Noguchi ([102]) in 1913. Noguchi placed small pieces of brain tissue from rabid animals with pieces of kidney of healthy rabbits into ascitic fluid. After incubation at 37 degress C. and after several generations, he found minute pleomorphic bodies which stained red with Giemsa's method. Inoculation of this material into susceptible rabbits produced typical rabies. These experiments have not been confirmed by other investigators. Volpius ([103]) as well as Kraus ([104]) have observed similar bodies in sterile ascitic fluid and conclude that they are identical with lipoid droplets. The experiments of Pfeiler and Klump ([105]) who described the cultivation of rabies in peptone containing Martin's broth have not been confirmed.

RESISTANCE OF THE VIRUS

The virus in nerve tissue, when protected from light and dried at 20 to 22 degrees C. dies in from five to eight days. It is destroyed by sunlight in about forty hours when exposed on glass slides in thin layers. It is quite resistant to putrefaction. Glycerin preserves the virus. The virus is resistant to freezing but is destroyed when exposed to 60 degrees C. for one-half hour. Five per cent phenol destroys the virus in about seven days though it resists 0.5 per cent phenol. Cumming ([106]) has shown that the virus is destroyed in about three hours by various aldehyde compounds. The virus is destroyed by 0.08 per cent formaldehyde within two hours, and by a 1:1000 solution of bichlorid of mercury or iodin within one hour.

PATHOLOGY (CELL INCLUSIONS—NEGRI BODIES)

At autopsy, in carnivorous animals, the stomach may be found contracted and empty or filled with foreign substances such as straw, hay, sand, pieces of wood, stones, bones, hair, leather, feathers etc. The mucous membrane of the stomach is injected and the rugae show hemorrhages and erosions. Foreign bodies may also be found in the oesophagus or intestines. There may also be present a catarrhal inflammation of the respiratory organs, hyperemia of the salivary glands, the liver, spleen and kidneys and an edematous inflammation of the meninges and of the gray matter of the brain. Schaffer ([107]) recently studied the changes in the central nervous system in six cases of hydrophobia in man. He found cellular infiltration with either capillary or large hemorrhages in the segment of the spinal-cord where the nerves coming from the place of infection enter, in the perivascular lymph spaces, in the walls of the vessels of the gray matter of the anterior horn, in the vicinity of the central canal and also along the connective tissue trabeculae of the white substance. In the nerve cells he found fibrillation, hyaline and vascular degeneration, granular disintegration and pigmentation atrophy of the cellular bodies. In the medulla, below the floor of the fourth ventricle and around the origin of the 12th, 10th and 7th pairs of nerves, there were found hyperemia, perivascular cellular infiltration and small hemorrhages. The nerve cells showed signs of degeneration. Slight hyperemia and cellular infiltration were found in the brain. Csokor and Dexter ([108]) attach great importance to small foci of inflammation in the brain and to the perivascular cellular infiltration but Trolldenier found that these lesions are absent in about

Yet Galtier ([118]) observed intermittent rabies in two dogs and Lignieres ([119]) in one dog. After the first attack a marked improvement followed, in 36, 27 and 28 days, respectively; however, an aggravation with fatal termination resulted. Recovery of dogs from rabies has already been noted. There also seems to exist some degree of immunity in man against the virus of rabies as evidenced by the fact that of all persons having been bitten by rabid dogs, such cases not receiving any protective treatment, only sixteen to twenty per cent develop the disease.

In general, however, considering the susceptible forms of life it may be said that comparatively little immunity exists and the necessity of giving protective immunization in inoculated cases, whether man or animals, is highly important.

According to Horowitz-Wlassowa ([120]) the serum of rabies infected or immunized rabbits gives fixations with the rabies virus (fixed virus as well as street virus). Fixation was not obtained with the serum of persons subjected to preventive treatment against rabies. Kraus and Michalka ([121]) suggest the use of boiled antigens in diagnostic tests in cases suspected of being rabies. The same authors ([122]) find that the complement fixation reaction, using both Koktoantigen and glycerol extract of the brain of rabbits infected with rabies, together with immune serums, is as specific as it has been with other filterable viruses reported by Kraus, Takaki *et al.* According to Nedrigailoff and Sawtschenko ([123]) the serum of men and animals that have died of rabies gives a specific reaction with an antigen prepared from the salivary glands of a rabid animal.

Artificial immunization may be carried out according to several methods. Details of these methods may be found in standard texts on hygiene and bacteriology. The various methods which have been used are as follows:

1. Protective vaccination with dried substance or spinal cord. Pasteur's method.
2. Protective vaccination with diluted virus. Hogyes' method.
3. Protective vaccination with desiccated-at-low-temperature virus. Harris method.
4. Protective vaccination with dialyzed virus. Cumming method.
5. Protective vaccination by intravenous injection of cerebral substance (for animals). Galtier's method. (Considered unsatisfactory.)
6. Serum immunization and vaccination. Babes and Lepp's method.
7. Protective vaccination with phenol-glycerinized virus. Umeno and Doi method.

Of all the methods of protective vaccination mentioned above the Pasteur method is still in most general use throughout the world. There are many modifications of this but the fundamentals rest upon the original Pasteur methods. It is impossible to compare results with the various methods cited although each has its adherents.

Artificial immunity appears in about two weeks after treatment and lasts for a varying period of time. In general it is thought that immunity conferred in this way lasts about a year although it is known that in some cases protection fails entirely and a small percentage of treated cases die of rabies. The immunity produced is not of the nature of an antitoxin. The serum of an immunized animal is virucidal for the virus of rabies in vitro, the immune bodies appearing in the blood about twenty days following the last injection of vaccine. Recently the writer ([124]) has called attention to the work of Kelser ([125]) in which this author was able to produce immunity in rabbits against the rabies virus by the use of a chloroform-treated tissue vaccine. It is possible that by this method Kelser has been able to produce a mitigated virus of low virulence which is capable of inducing immunity. These experiments have not as yet been confirmed.

CONTROL OF RABIES

Various control measures are advocated to keep this disease within bounds or to totally eradicate it. These measures are discussed in detail in standard texts on preventive medicine. In general they consist of (1) Laws regulating importation of dogs; (2) Muzzling; (3) Quarantine; (4) licencing; (5) education and responsibility, and (6) immunization. While protective vaccination of dogs (the most important reservoir of the virus of rabies) is just now becoming general throughout the world, this measure bids fair to alter most favorably the picture of this disease as a public-health problem.

COMMON COLDS—THE ACUTE CORYZAS

Under the heading of common colds we include a group of acute infections (exudative and catarrhal) of the nose, throat, larynx, trachea, and larger bronchi. In some cases the sinuses are involved. Epidemics of "colds" are common and the infection appears to spread with great ease. The infection may localize in one membrane such as the nose (rhinitis) or in the pharynx (pharyngitis) or two or more membranes may be involved. In some cases the sinuses, nasopharynx, throat, trachea, and larger bronchi may all be affected. "Common colds" are to be regarded as an acute infectious disease

and not merely as congestion of the respiratory membranes produced by drafts of cold air, changes in temperature, etc. Under normal circumstances the ciliated epithelium of the respiratory tract prevents, to a large degree, the entrance of bacteria from without. However, this mechanism is not perfect and untold numbers of microbes enter the respiratory tract. Also it is now known that the lacrymal and nasal secretions exert a mild germicidal action and this is likewise true for the saliva. There is some evidence that the secretions from other mucous membranes of the respiratory tract possess bacteriocidal properties. The mechanical and chemical nature of the mucous membranes of the respiratory tract then tends to prevent infection under normal conditions. Why then are colds so prevalent? It is estimated that about ten per cent of human beings are at all times affected by "common colds" of a greater or lesser degree. Undoubtedly there are many predisposing causes to the development of "common colds" but the chief reason common colds are so prevalent is the fact that they are due to acute infections caused by one or more specific infectious agents.

The "common cold" has attracted more attention in recent years than ever before. The medical profession and the public at large have begun to realize the importance of this disease especially in its relation to epidemic influenza and pneumonia and its economic importance to the nation in the enormous loss of working hours which results from these infections.

Bacteriologists have long been concerned with the problem of the common cold and many attempts have been made to isolate the causative organism. At various times such microbes as pneumococci, influenza bacillus, streptococci (both hemolytic and viridans), staphylococci, micrococcus catarrhalis, and diphtheroids have been cultured from the respiratory tract of cases of "common colds." Of the relation of any of these bacterial forms to colds little is known. So far there is no direct evidence that any of these bacteria should be incriminated as the single etiological factor of these infections.

Huter ([126]) in 1873 first described a micrococcus as the cause of common colds. In 1888 Hajek ([127]) reported the presence of a large diplococcus (Diplococcus coryzae) found in the early stages of acute colds. Paulsen ([128]) in 1890 examined a number of cases of common colds and found various cocci and bacilli in the nose and throats of these patients. Cautley ([129]) a few years later discovered the presence of a diphtheroid bacillus in seven out of eight cases of colds of various types. He believed this organism to be the cause

of acute colds and designated it B. coryzae segmentosus. Benham (130) quotes Gordon as having found Cautley's bacillus in seven cases of colds. With this organism Gordon was able to produce illness in guinea pigs from which they recovered after a few days. Benham also quotes White as having found Cautley's bacillus in seventeen out of twenty-one cases although inoculation experiments on guinea pigs, rabbits, and monkeys were negative.

In 1906 Benham found a diphtheroid organism, which he believed to be identical with Cautley's organism, in twenty out of twenty-one cases of colds. He named this organism Bacillus septus. Micrococcus catarrhalis was also present in several of Benham's cases. In 1902 Gohn and Pfeiffer (131) found the micrococcus catarrhalis in 81 out of 140 cases of infection of the respiratory tract. These authors regarded the presence of this organism in respiratory infections as a saprophyte which, under favorable conditions, gives rise to an acute infection. Bezancon and de Jong (132) during an epidemic of influenza in Paris in 1905 found various organisms present in the respiratory tract. Among these were micrococcus catarrhalis, Micrococcus paratetragenus, the pneumococcus, Friedlander's bacillus, staphylococcus, streptococcus, and diphtheroids. During the same year Dunn and Gordon (133) pointed out the etiological importance of the M. catarrhalis in an epidemic in Hertfordshire, England while Allen (134) during the following year isolated M. catarrhalis from several cases of "common colds" in the same country. Neumann (135) in 1902, as a result of his extensive studies on the etiology of common colds, concluded that diphtheroids and pneumococci, and perhaps other organisms, could produce colds. This investigator found the micrococcus pyogenes albus present in 86 to 90 per cent, diphtheroids in 98 per cent. He states that 78 strains of diphtheroids isolated by him were found to be non-pathogenic when inoculated into guinea pigs although pathogenic strains of this organism were found in infected cases. Both Lingelsheim (136) and Barnes (137) have shown that streptococci may cause infections of the nose, pharynx and tonsils. The streptococcus has, of course, long been established as an etiological agent in epidemic sore throat. Mathers (138) in 1917 and Floyd (139) in 1920 described streptococci and staphylococci in relation to epidemics of acute respiratory infections occurring in Chicago and Boston.

In 1920 in the Boylston prize essay, Mudd, Grant and Goldman (140) have reviewed the entire literature on the acute respiratory infections and after a careful analysis of the various bacteriologic find-

ings state: "Since the early days of bacteriology, attempt has been made by the several proponents and opponents of the infectious theory to refer the "common cold" on the one hand to the action of a specific microorganism, and on the other hand to various environmental and constitutional causes, such as exposure to changes of temperature, the "lithemic diathesis" and what not. Although perhaps laudable as philosophic ideals, such efforts to explain the many phenomena involved by a single cause are less deserving scientifically, and have met with just failure. The common cold is, as a matter of fact, in most instances the result of a local infection, but there are many types of cold and many infectious agents responsible for them; and the effect of various constitutional and environmental factors in determining infection is often of great importance. Furthermore there are many acute inflammations of the upper respiratory tract not primarily due to the local action of microorganisms, but rather to local expression of chemical or mechanical irritation, of thermal trauma, of nervous reflexes, of drug intoxications, of constitutional disease, or anaphylaxis".

In 1913 Tunnicliff ([141]) investigated 82 cases of common colds in Chicago and from 92 per cent she isolated a bacillus to which she gave the name B. rhinitis. Also this investigator found the same organism in 90 per cent of 20 cases of chronic colds (rhinitis). In normal throats she was able to produce a slight inflammation with the B. rhinitis and the organism was recovered in most cases from the artificially infected throats 18 to 20 hours after inoculation and in a few cases two or three days later. Tunnicliff vaccinated two volunteers with this organism and from variations in the opsonic index she believed that there was evidence that this organism is the cause of common colds.

Kruse ([142]) in 1914 filtered the nasal secretion from a case having acute coryza and then placed a few drops of the filtrate upon the nasal mucous membranes of 12 volunteers. In four of these cases acute colds developed. The period of incubation in the positive "takes" ranged between one and four days. In this experiment the infected nasal secretions were diluted 15 times with salt solution. In another experiment Kruse diluted the infected nasal secretions from an acute coryza patient with twenty times its volume before filtration. In the test experiment with this filtrate 36 students were inoculated and 42 per cent developed acute symptoms of coryza within one to four days.

The experiments of Kruse were repeated by Foster ([143]) in 1915.

This investigator confirmed the presence of a filterable virus in the nasal secretions of cases of acute colds. Material taken from a case of acute coryza, diluted and passed through Berkefeld N filters, when inoculated into nasal cavities of ten soldiers produced symptoms within eight to thirty hours in nine instances. In seven of Foster's cases the symptoms of acute coryza were definite and clear cut; two reacted questionably, while one case exhibited no symptoms. Foster states: "The initial symptoms, as a rule, were dryness of the nose and throat and attacks of sneezing, dull frontal headache and a sensation of pain and fulness over the frontal sinuses. Several of the men complained of alternate sensations of chilliness and flushing. There was copious rhinorrhea, usually on the second day, in a majority of the cases. Six of the subjects exhibited a slight rise in temperature—99.2—100 F. and in these cases the pulse was accelerated. Tinnitus aurium or slight impairment of hearing was recorded in four instances; sore throat in 5; cough in 5; and aching pains in the back or extremities in 4. One of the men complained of parotid tenderness and pain on moving the jaw; in another case a marked crop of herpes labialis was noted. The duration of the symptoms varied 3 to 6 days—usually 5."

Foster was unable to obtain growth of any organisms from early cultures of his filtrates but under the darkfield microscope he noted myriads of extremely active, minute bodies occurring singly, in pairs, and in masses varying in size. In older cultures (14 days) of his material Foster found minute coccoid bodies which varied in size from those which were barely visible to bodies larger than staphylococci. The larger bodies often showed smaller bodies adhering to them. This microbe stained with Giemsa but not well with ordinary laboratory stains. The predominating type noted by Foster was a small globoid body measuring 0.2 to 0.3 of a micron in diameter. In conclusion Foster states: It becomes evident at once that this microorganism differs markedly from any known organism with the possible exception of the "globoid bodies" described by Flexner and Noguchi, and believed by them to be the causative factor in poliomyelitis. An extremely pleomorphic streptococcus, the minute forms of which bear some resemblance to this micro-organism has recently been described in connection with poliomyelitis, also, by Mathers ([144]), Rosenow, Towne and Wheeler ([145]), and Nuzum and Herzog ([146])". Later Foster compared his microbe isolated from cases of common colds with the organism described by Flexner and Noguchi for poliomyelitis and also with the streptococcus described by Rosenow, Towne

and Wheeler. His examination showed that the organism isolated from common colds differs from the poliomyelitis virus in that the former is subject to many variations in size and the larger forms show evidence of budding, neither of which is true for the Flexner-Noguchi virus of poliomyelitis. With regard to the streptococcus Foster found that his organism showed little tendency to chain formation, and the pleomorphic forms, common to the streptococcus, were absent.

Foster was also able to demonstrate that his cultures were filterable through Berkfeld N filters and that filtrates of the cultivated organisms in the second generation are infective when tested upon volunteers.

The question naturally arises as to whether this microbe might not exist in symbiosis with a true ultra virus of common colds. No instance of such a phenomenon however is known (with the exception of Hog cholera). Again the organism described by Foster might be a stage in the life cycle of an ultravirus and modern investigation upon the filterable forms of bacteria (tubercle bacillus, streptococci, etc.) lend support to this concept. In this connection Foster recalls the work of Hurt, Lakin, and Benians in which these authors suggest that epidemic meningitis may be due to an ultravirus while the meningococcus found in the spinal fluid of these cases represents "a late phase in the life history of an unidentified micro-organism that is the true infective organism". These authors demonstrated that it was possible to obtain a pathogenic virus from the spinal fluid of acute cases of epidemic meningitis after the spinal fluid is passed through a Chamberland F filter.

In support of this theory Foster points out that the microbe isolated by him from cases of common colds shows a considerable variation in size and further that from 7 to 14 days are needed in order to obtain growth of the virus. The virus is cultivated under anaerobic conditions. In conclusion Foster says "Although conclusive proof of its nature has not been adduced, the experiments suggest that the micro-organism described bears a definite relation to the true infective agent of common colds". It should be pointed out however that Foster's controls are not entirely acceptable.

Mudd, Grant, and Goldman in the Boylston prize essay after a careful survey of all the important investigations which have been made on the etiology of the "common cold" further state: "A filterable virus seems without question to be the causative agent in the coryza of one fairly well defined type. . . . . (1) A common and

fairly well defined clinical entity, an acute coryza, exists, probably with the filterable virus of Kruse and Foster as its causative agent. This affection is readily communicable and probably does not depend to any great extent upon the action of exciting factors in depressing the resistance of the subject. (2) A heterogenous group of pure and mixed infections of the nose, pharynx and tonsils exists with various clinical pictures . . . . . some closely approaching that of Foster, others mere circumscribed inflammations . . . . . and with any one of a considerable number of bacteria capable, under appropriate circumstances, of acting as causative agents."

Of all the bacterial forms which have been described by the various investigators it appears that the pneumococcus, streptococcus, B. diphtheriae, B. rhinitis, Pfeiffer's bacillus and Friedlander's bacillus have the best claims to etiological import in relation to the acute respiratory infections.

While it is well recognized then that the "common cold" is to be regarded as an infectious disease, authorities are also agreed that there are a number of predisposing factors in the development of such an infection. Furthermore there may be symptoms of coryza which are not related to infection but which may be caused by one or more of these factors. It has long been thought by the layman and by physicians that drafts of cold air may cause colds. Chilling of the body surface, particularly one portion of the body surface, is now thought to be a predisposing cause in the development of colds. In fact, the general statement may be made that anything which lowers the resistance of the host may predispose to infection. Practically all texts are agreed on this thesis. It follows then that exposure to cold drafts contributes to the development of colds. Mudd, Grant, and Goldman have shown that the chilling of the body surface causes reflex vasoconstriction and ischemia of the mucous membranes of the nasal cavity, nasopharynx, palate, oropharynx, and palatine tonsils. These authors believe that ischemia may be the means of lowering the local resistance to infection. Rosenau (147) states "Chilling causes vasomotor contraction of the capillaries of the skin, which is doubtless designed to conserve body temperature; coincidently there is turgidity of the erectile tissue of the mucous membrane of the turbinates, which is probably a defensive action. This congestion partly closes the nose and causes snuffling and increased secretion, which is ordinarily called a cold. A great variety of mechanical, chemical and even psychic stimuli will produce congestion of the cavernous tissue over the turbinate; in fact, the mucous membrane

of the nose may become very sensitive, even hypersusceptible. Anaphylactic reactions to pollen and proteins are common manifestations of the nasal mucosa."

Vaughan ([148]) states in this connection "In our opinion, the acute coryzas are most rationally explained on the ground that they are due to protein sensitization. They may be caused by any protein, living or dead, organized or unorganized, particulate or in solution. Omitting from consideration Foster's theoretical globoid bodies, suspected in his subcultures, his experiments and those of Kruse are most easily explained on the ground of protein sensitization. These experiments are practically duplications of the ophthalmic tuberculin test. A minute trace of tuberculin dropped into the eye of a patient in the early stages of tuberculosis causes an exudative inflammatory action. In all probability, Foster's soldiers had been previously sensitized to the same protein which existed in his nasal secretions and in those of his laboratory assistant. If this be true, it could not be otherwise than that an inflammatory reaction would result within a few hours after the application of this protein to the nasal mucous membrane of these soldiers."

When writing the above, Vaughan was not aware of the later work of Foster in cultivating the micro-organism with which he was able to produce colds in volunteers. Perhaps the main thesis of his theory of the origin of colds he would have stated notwithstanding. However in view of Foster's work, confirming and extending as it does the experiments of Kruse, and further in view of the recent studies of Olitsky and Gates ([146]) on a filterable agent which they believe to be the cause of influenza, science is not ready to accept Vaughan's theory of sensitization as the only explanation for common colds. Neither, for that matter, are we willing, without more conclusive data, ready to accept the filterable virus origin of colds and influenza. We must, however, in the broad interests of science, give these theories and experiments serious consideration.

Under present conditions, in view of all we have been able to learn by experimental work and though observation, we are inclined to agree with Mudd, Grand and Goldman that a clinical entity exists in the form of the infectious cold. Similarly it is well known that coryza is common in some people who become sensitized to various proteins. Consequently a classification of "colds" might be suggested as follows:

(1) Common colds which are due to infectious agents.
  (*a*) Various pathogenic bacteria
  (*b*) Filterable viruses.

(2) Colds which are due to local sentitization to various proteins.

To these groups should be added those predisposing causes which, in and of themselves, are not the cause of cold but contribute to the development of colds by creating favorable conditions for infection by micro-organisms or sensitization to various proteins other than infectious agents. Under this heading we should include (1) drafts of cold air which produce a chilling of the body surface; (2) chemical or mechanical irritation; (3) thermal trauma; (4) nervous reflexes; (5) drug intoxications; (6) constitutional diseases; and (7) psychic influences, etc. In general any factor which may lower the resistance of the host to infection or lead to specific sensitization may be regarded as a predisposing cause in the development of common colds.

While the subject of the common cold is now recognized to be one of the most important problems from the standpoint of the health of the human race, there still remains much work to be done in careful investigative work of its cause or causes. We are inclined to feel that the work of Foster and Kruse has given us fairly convincing evidence that at least one type of "cold" *may* be due to a filterable virus and that future investigative work should be done along these lines to enable us to better understand the nature of these agents and the mechanism by which such infection takes place.

INFLUENZA
(Epidemic Influenza; La Grippe; Grip)

DEFINITION

Influenza is an acute, highly communicable, febrile disease, characterized by catarrh of the respiratory tract and in some cases of the alimentary tract, by pains in the head and musculature, by its tendency to bronchial and pneumonic complications, and by its occurrence in epidemic and pandemic form. The disease is also notable for its sudden onset and extreme prostration. The cause of influenza has not been definitely determined but it has been thought to be due to a minute filterable virus, *bacterium pneumosintes*, described by Olitsky and Gates [150].

HISTORY

Vaughan [148] states that "What appears to be the first recorded instance of an influenza epidemic is referred to in Livy in 412 B.C." While according to this author these early reports are not

authentic, they appear to be influenza because of their sudden onset and wide distribution. Vaughan quotes Hirsch as looking upon the year 1173 as witnessing the first epidemic of which authentic reports are available. Influenza during that year spread over Italy, Germany and England. This author states that the first great pandemic of the disease occurred in 1510. At this time influenza spread from Malta to Sicily, thence into Spain, Italy Hungary, Germany, France and England. The symptoms of the disease consisted of fever, cough, hoarseness, headache, anorexia, insomnia, pains in the stomach, kidneys and legs. Symptomatically then this pandemic may have been due to influenza. From that time on history records numerous pandemics of the disease. Great pandemics are known to have occurred in 1590, 1732, 1781, 1830, 1833, 1836, 1847, 1850–51, 1855, 1857–58, 1874–75 and 1889. In North America epidemics have occurred since 1557. Vaughan records the various epidemics as follows: 1557, 1580, 1647, 1732, 1737, 1760, 1780, 1789, 1805, 1824, 1830, 1836, 1843, 1850, 1860, 1863, 1873, 1874, 1879, 1889, 1891, 1916, 1918. The last great pandemic occurred in 1918–19 and again in the winter of 1919–20. The disease entered America in September of 1918. Thousands of men were mobilized in the army camps and the disease swept through these hordes of men like a tidal wave leaving great numbers of dead in its wake. In this epidemic the disease had its highest mortality in the age group of 20 to 35 years (though the disease was by no means confined to this group) and for that reason greater mortality resulted in the army than in civilian life. During this year the disease spread all over the world to pandemic proportions and is considered the most severe outbreak of influenza in the history of all time. According to Vaughan (Warren) the 1918 pandemic had its origin in the United States and the virulence of the organism was enhanced by passage to and from Europe. The common complication of the disease in this epidemic was pneumonia. The pneumonia rate was somewhat higher among colored troops than among white troops as was also the death rate. Out of 1,439,000 men under arms in the United States, Vaughan states that 338,343 had influenza, or 22.6 per cent. The death rate among these troops during epidemic was 1.56 per cent. In the American expeditionary Forces abroad there were 1,745,000 men under arms and of this number 77,828 had influenza. The death rate in this group was only .48 per cent. This has been explained by the fact that the soldiers in Europe were seasoned men . . . . having come from camps where influenza had

been present and so had acquired some immunity to the disease. While the mortality in civilian life during this epidemic was lower than in the army, it was greater in the cities than in rural communities. Undoubtedly the crowding of human beings contributes to the great spread of the disease. It is thought that the disease is spread from person to person through coughing, sneezing, and by droplet infection from the mouth, nose, and throat of infected persons. Carriers of the virus of influenza may transmit the disease to healthy persons though they themselves may be unaffected by it. Dust may transmit the disease from infected persons to healthy persons, but for the most part the disease is probably disseminated from person to person. A comprehensive analysis of the last great pandemic of influenza is given by Vaughan and for a detailed analysis the reader is referred to his work.

DISTRIBUTION

Influenza may occur in pandemic form and exist practically all over the world wherever man, its natural host, exists. Small epidemics are undoubtedly in existence in some parts of the world at all times. Periodically the disease reaches pandemic proportions and must be explained either by a diminution of the normal resistance or immunity of the host, or by an increase in the virulence of the virus, or perhaps a combination of both.

THE VIRUS OF INFLUENZA

In 1892 Pfeiffer ([151]) discovered the influenza bacillus in 31 cases of clinical influenza. The bacillus was present in smears from the pharynx and sputum. This organism is a small, Gram-negative, non-motile, hemoglobinophilic, bacillus which grows aerobically at 37° C. on blood agar. Various investigators have found this organism, almost constantly in the throats of influenza cases. It is present in about thirty per cent of normal throats and also occurs in cases of measles, whooping cough and in other infectious diseases. Pfeiffer claims to have produced influenza in a few instances in monkeys, and a typical form of the disease in rabbits. It is interesting to note that during the 1918 epidemic a variety of organisms were reported from the different army camps in the United States as being the predominating organism in the cases of influenza in those particular localities. In some instances staphylococci predominated, in other cases it was a streptococcus or a pneumococcus, while in others the Pfeiffer bacillus was the most common organism found. All of these observations have led to the opinion that the influenza bacillus

of Pfeiffer may be only a secondary invader and while not the actual cause of influenza, it may become exceedingly virulent, and as a secondary invader contribute to the most severe complications (pneumonia) of the disease. Even now opinion remains divided as to the role the influenza bacillus plays in epidemic influenza. Some authorities still believe in its etiologic significance and the question remains unsettled. After the discovery by Pfeiffer of the influenza bacillus this investigator found in three cases of broncho-pneumonia following diphtheria in children a similar bacillus, although somewhat larger, which he designated pseudo influenza bacillus. Whether this organism, represents still another strain of the influenza bacillus and possesses any relation to epidemic influenza is not known.

In 1918 Park and Williams ([152]) made a survey of the presence of the Pfeiffer bacillus at the beginning of the influenza epidemic in New York City. Their results are tabulated below.

TABLE

Influenza Bacillus

Group	Present	Absent	per cent Present
	Influenza cases or associates		
Hospital cases	160	40	80
Marines	30	0	100
Home for children	47	1	98
	Autopsy of Influenza cases		
Lungs	24	6	80
Tracheas	26	1	96
Heart's blood	3	27	10
	Controls		
Nurses-contacts	4	6	40
Nurses-noncontacts	1	7	9
Measles	4	2	67
Admission ward	4	5	41
Home for girls (isolated)	2	32	6
Preventorium (not isolated)	14	25	33

These results show that a greater percentage of influenza cases harbor the influenza bacillus than do presumably healthy persons, yet they indicate the presence of this organism in normal persons. The etiologic significance of the influenza bacillus is exceedingly difficult to determine in that one set of experiments may indicate its relation to the disease while another set of examinations may tend to indicate its unimportance. The very nature of influenza presents difficulties which make the etiologic significance of this organism difficult to determine. For example, we do not know the relation of influenza to the "common cold", to "grip", "catarrhal fever", so-called "in-

testinal influenza", etc., although with regard to the latter it is thought that true influenza may manifest itself predominately, in some cases, as an intestinal form. While a vast amount of experimental work purporting to establish the influenza bacillus as the actual cause of influenza, such as the experimental production by Blake and Cecil (153) of a respiratory disease in monkeys with this organism, which they state is typical of influenza in man, we must conclude that the question still remains unsettled.

Other investigators in searching for the etiologic agent of influenza have considered the possibility of a filterable virus as the cause of this disease. This is suggested by the extreme infectiousness of the disease, by the lack of uniform bacteriologic findings particularly in the mild early cases, but also in the older cases, and by the similarity of mild influenza to the common cold which has been thought by Kruse (142), Foster (143), and others to be caused by a filter-passing virus.

Nicolle and Lebailly (154) in 1918 reported their work on mice and guinea pigs in which they inoculated blood and secretions from cases of influenza, or uncomplicated grippe. Their results were negative. These investigators then inoculated secretions from the nose and mouth of a typical case into the conjunctiva and nasal cavities of several monkeys. Both filtered and unfiltered secretions were inoculated. At the same time two healthy human beings were inoculated. The monkeys became sick with a temperature of 40° C., depression, and diarrhoea within six days and the human subjects exhibited similar symptoms about the same time. The human subjects were inoculated subcutaneously. The writer has noted that normal monkeys may have a temperature of 40 degrees C. especially when frightened and excited. During the same year Dujarric de la Rivière (155) injected himself intravenously with 4 c. c. of blood taken from four cases of influenza, diluted and filtered, and three days later developed a temperature of 38° C. accompanied by intense headache, chills, pains in the limbs, and weakness. After about five days he rapidly improved but remained subsequently immune of filtered sputum taken from influenza cases which was sprayed into his nose and throat. About the same time Selter (156) sprayed his own throat and that of another human subject with filtered secretions taken from a patient having early influenza. Both Selter and his subject developed mild attacks of influenza. At this time Binder and Prell (157) described certain minute coccoid bodies in the tissues of influenza patients similar to those described by Noguchi in poliomyelitis. These bodies were stained with iron hematoxylin and Giemsa but were

Gram-negative. They presented evidence that these bodies could be cultivated but were inclined to treat their etiologic significance with conservatism. Similar bodies were later described by Angerer ([158]) which he claimed to have cultivated direct from the serum of human cases of influenza.

In 1918 Bradford, Bashford, and Wilson ([159]) produced symptoms in guinea pigs and monkeys with filtered material taken from cases of Trench fever and influenza. In anaerobic cultures they found small Gram-positive bodies which they believed to be the causative agents. In the following year Arkwright ([160]) reported that in his hands the cultures of Wilson proved negative when inoculated into three volunteers. During the same year Yamanouchi, Sakakami, and Iwashima ([161]) injected emulsions, and filtrates of emulsion made of the sputa from 43 cases of influenza, into the nose and throat of 24 volunteers. These authors state that six of the volunteers, who had previously had influenza, were immune and showed no symptoms following the inoculation but all of the remaining 18 developed the disease within two or three days. Furthermore filtered blood taken from influenza patients produced the disease in healthy volunteers. These investigators were unable to produce symptoms by injecting Pfeiffer's bacillus, or this organism mixed with pneumococci, streptococci, and staphylococci into the nose and throat of 14 healthy volunteers who had never had the disease.

In 1919 Lister and Taylor ([162]) produced only negative results in monkeys and human beings following the injection of filtered material taken from the lungs and throats of influenza cases. Wahl, White, and Lyall ([163]) during the same year obtained negative results following a similar procedure. Leschke ([164]), on the other hand, permitted a number of people to inhale the vapor from lung filtrates taken from typical cases of influenza and incubated for several days, and all of his subjects developed typical influenza.

An attempt to induce the disease with filtered nasal secretions into healthy human subjects met with failure in the hands of Rosenau ([165]) and McCoy ([166]) in experiments undertaken by the United States Public Health Service and the U. S. Navy in 1919.

From 1920 to 1923 Olitsky and Gates published a series of papers dealing with a filterable virus obtained from influenza cases. These authors used filtered and unfiltered influenza secretions. Intratracheal inoculations were made directly into the lung tissue of rabbits with unfiltered nasopharyngeal washings, the filtered washings, lung tissue suspensions (filtered and unfiltered) from previously inoculated rabbits, and lung tissue which had been preserved in 50 per

cent glycerine. The injections were made into rabbits with an intratracheal catheter and about 3 cc. of material were administered at each injection. Within 24 to 48 hours following the inoculations the rabbits began to show symptoms. The first symptoms consisted of fever and general indisposition. A conjunctivitis and leukopenia then developed. Except in complicated cases the rabbits always recovered after about three days. Clinical and pathological effects were produced in series through fifteen rabbits inoculated with ground lung tissue from a rabbit previously infected. Glycerinated material from one rabbit was passed through a series of ten rabbits producing typical symptoms of the disease in all. The infectious agent described by Olitsky and Gates is filterable through both Berkefeld "V" and "N" candles.

When infected animals were killed during the period of illness these authors found that the lungs were enlarged and edematous, and in some cases hemorrhagic. Hemorrhagic foci and alveolar exudate were found on microscopical examination.

It should be pointed out however that hemorrhagic lesions in the lungs of rabbits may occur in normal animals which have not been infected experimentally. Branham ([167]) has shown that hemorrhagic lesions in the lungs are almost constantly found when the animals are killed by a blow on the back of the neck. This author believes that the mode of death has something to do with the occurrence of these hemorrhages. Maitland, Cowan, and Detweiller ([168]) had previously suggested this possibility.

Later Olitsky and Gates were able to cultivate from the filtered washings taken from influenza patients a minute bacilloid body which they have designated bacterium pneumosintes. This organism they have also isolated from the lungs of infected rabbits. This organism is a minute Gram-negative, anaerobic bacillus-like body which is easily cultivated but which loses its virulence rapidly under artificial cultivation. The microbe appears larger after prolonged cultivation but cultures are still obtained from filtrates.

In summing up a discussion on the etiology of influenza in a paper on the etiology and epidemiology of influenza (1922) Zinsser ([169]) states: "This leaves the entire subject in a very unsatisfactory condition. The temptation to draw definite conclusions from material of this kind is always a strong one. But to profess certainty when available evidence does not justify conclusions is as serious an error as to put forth inconclusive experimental work, and would serve merely to mask the truth. . . . The problem of influenza etiology will not, in our opinion, be solved at times when influenza

This is true especially during great epidemics. In the household or small hospital, isolation may be practiced and may prevent further spread of the infection. Quarantine was practiced in several army units during the epidemic of 1918 as well as in civil communities and while the spread of the disease was delayed, the disease eventually spread over such barriers. Masks to be worn over the lower part of the face to prevent the spread of secretions from the respiratory tract have been employed without demonstrable effect. Complications seem to be increased in hospitalized cases and in general this measure does not lessen the morbidity or mortality of the disease. Closing of school has not led to a reduction in the number of cases of the disease nor has the use of nose and throat sprays and gargles. Perhaps the only measure which has any effect in preventing the spread of influenza is to avoid crowded places such as the theatre, churches, etc., during an epidemic. Undoubtedly large gatherings of people contribute not a little to the spread of this disease. General hygienic measures are, of course, indicated as in the case of any other communicable disease.

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