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RÖMER

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Hampstead.

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(HEINE-MEDIN DISEASE)

BY

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Translator's Preface.

It appears highly probable that the disease known as Epidemic Infantile Paralysis will become more and more menacing to the community in England as well as in other countries. In its sporadic form the disease has been recognized for a long time; its effects on isolated lives have been so deplorable that it has come to be regarded as perhaps the most feared of all the diseases of childhood. But now we are face to face with a change in the way in which the virus attacks the human race; the disease has become epidemic in its incidence. The history of this remarkable disturbance of the balance between the attack of the virus and the power of effective resistance in human beings is told in the present book. Written as it is by an author who not only has made practical use of the discovery that the disease is communicable to monkeys, but also possesses in a high degree the sense of historical perspective, the book contains the results of his experimental work, and describes fully the difficulties which have stood and still stand in the way of advance in the elucidation of the problems presented by the disease both in its scientific and public health aspects. Under these circumstances it appears advisable to bring the work within reach of a larger public in this country.

At the moment of going to press the report on the Swedish epidemic of 1911 has appeared; it marks a further advance in the study of the disease, and is a brilliant vindication of the claims which Professor Römer has put forward in this book on behalf of the experimental method of investigation.

London, 1913.

Preface.

The occurrence of cases of epidemic infantile paralysis, the so-called Heine-Medin disease, in Marburg, Hesse-Nassau, gave me the opportunity of making investigations into the etiology of this disease. A considerable portion of these studies has already been published, in the form of short articles, in the *Münchener med. Wochenschrift*, and in communications to the Medical Society of Marburg. The present work was intended originally not for publication, but merely as an arrangement of the various above-mentioned isolated articles and lectures in a definite and logical form. As the work proceeded, however, the plan became wider, and the book gradually assumed its present form. The material itself increased in two directions.

In the first place I soon recognized that the collation of my own humble experimental results alone would give but a feeble representation of the stage which has been reached in the study of poliomyelitis. Such an experience must fall to the lot of any experimental investigator of poliomyelitis who endeavours to give form to his results and, in so doing, makes use of those results alone. This may be easily understood when one considers, that so far the only results which have been of any value in this field of research have depended upon the use of monkeys, and, further, that the cost of procuring and keeping these animals sets very definite limits to the extent of the investigation. Consequently I was obliged to make use of the work of other experimenters, who have attacked the problem with so much success during the last two years, in order to arrive at an even approximate idea of the present state of the question.

It was pointed out to me by friends that a review of the present state of our knowledge would be of interest to a wider public, and in carrying out this idea I found my material increasing in another direction. The experimental work not only involved necessarily a wide study of the literature, but threw new light on the numerous previous labours undertaken in the investigation of infantile paralysis. I have endeavoured, therefore, to bring before the reader in an orderly manner the mass of scattered material which is to be found in the literature of this and other countries, much of which is accessible only with difficulty. In starting from the idea that a comprehensive representation of the development of our knowledge of Heine-Medin disease up to the present day will be of interest to the reader, I am guided by my own experience. In the summer of

1909, when reports of the epidemic occurrence of poliomyelitis in Germany appeared, I must admit that the disease was relatively but little known to me. It is true that, from the time when I was a student, the classical picture of infantile paralysis, as described in the excellent monograph by Heine, was known to me, and reports of the epidemic occurrence of the disease had reached me from time to time. But, as easily happens when one is not immediately concerned with a question, I had not realized that since 1890 our conception of the disease had altered considerably from that contained in most text-books. Consequently, when the epidemic of 1909 once more drew attention to the disease, it was to me more or less of a novelty. I think I do no injustice to my colleagues in the profession if I assume that they also had but a passing acquaintance with the disease, particularly in such districts where it had not assumed epidemic proportions. The following book, therefore, may be perhaps of value; the more so as it seems by no means likely that we are at the end of our experience of this particular pest. The latest reports from Berlin give cause for the fear that further outbreaks are to be expected.

To the friendly co-operation of Professor Dr. Eduard Müller, the Director of the Medical Polyclinic in this town, whose clinical and epidemiological investigations I was able to follow step by step, and to supplement along experimental lines, I owe the fact that I was enabled quickly to become acquainted with the clinical picture, the epidemiological character and the general significance of the apparently new disease.

In the following pages I have endeavoured to avoid all that savours of a text-book; they form a *résumé* of my studies. This has been all the easier because, in spite of all the progress which has been made, there are still so many obscure points in the disease, that it is more attractive to discuss the problems which remain than to lose oneself in the description of those already solved. By always drawing attention to the work which remains to be done I hope that I have succeeded in avoiding the tedium which attaches necessarily to a book which is made up largely of references. If I have not succeeded, after all, I ask the reader not to take the will for the deed, but to reckon the will to the deed in my favour.

In the purely experimental part of this work I have had the pleasure of the extremely intelligent and untiring assistance of Dr. Joseph, the present assistant in the bacteriological department of the Hoechst Dye Works.

P. H. Römer.

Marburg.

Contents.

CHAPTER I.

The Development of our Knowledge of the Nature of the Disease of Heine and Medin.

Nomenclature.—Jakob v. Heine, who gave the first classical description of the disease, gave it the name, "Spinal Infantile Paralysis." He adopted this nomenclature because the cases which came under his observation were either children or adults who had been stricken with the disease during childhood; further, by a process of deductive reasoning carried out with great analytical clearness, he was convinced that the site of the lesion must be in the spinal cord. That this denomination was in general accurate is proved by the manner in which this name of the disease, which he was the first to differentiate as a clinical entity, has been preserved even to the present day. An attempt was made by the French writers to give currency to the terms "idiopathic" or "essential" infantile paralysis; but even at a time when the site of the lesion was not definitely proved these terms betrayed themselves as mere confessions of ignorance, and they rightly disappeared entirely when the spinal origin of the disease was clearly demonstrated.

When knowledge of the anatomical distribution of the fundamental pathological process advanced, a more exact anatomical term was added to the former appellation, in accordance with the tendency towards an anatomical nomenclature of diseases in general, and the name "Poliomyelitis Anterior Acuta" was coined, which expressed the favourite point of attack of the disease.

In the middle of the 'eighties observations on groups of cases, in a few instances of epidemics, of the disease began to accumulate, and in accordance with the newly gained knowledge the names "Epidemic Infantile Paralysis" and "Epidemic Poliomyelitis" came into use. But when Medin proved that the hypothesis of Strümpell and Pierre Marie was correct, that there was a connection between classical infantile paralysis and certain forms of encephalitis, these names were no longer satisfactory. According to these authors the same pathological agent may produce at one time, by affecting the spinal cord, the well-known disease described in a masterly manner by v. Heine, at another time, by affecting the brain, a cerebral paralysis.

In spite of these facts, however, the old term "Spinal Infantile Paralysis" held its ground, even though it was demonstrated that not infrequently adults were attacked by the disease. The name "Paralysie infantile," introduced by the French authors, hereby also lost all justification.

There were three reasons why the name "Spinal Infantile Paralysis" remained without a rival, besides the obvious historical one, *viz.*, the authority of v. Heine. In the first place it was doubted whether a disease which presented so constant and so definite a clinical picture as spinal paralysis could have a pathological cause identical with a disease showing such a remarkable difference from the clinical point of view as cerebral paralysis. Secondly, it was difficult to believe that a disease, which appeared to be a definite system disease of the spinal cord, could fall out of its *rôle* so far as to be bound to no system. Pathological investigation, which took place usually in cases of long standing (owing to the fact that fatal acute cases were inaccurately diagnosed), showed that the site of the lesion corresponded with the clinical picture and involved practically exclusively the grey matter of the anterior horns. Finally, the absence of any new, accurate, comprehensive, and simple term led to the retention of the old, even though it was recognized to be unsatisfactory.

In the meanwhile our knowledge of the histology of the disease had increased and changed; investigation of recent cases had shown that lesions were to be found in the medulla, pons, and cerebrum, as had been expected by the more acute clinicians. To call the disease a "myelitis" was unsatisfactory, and the term was applicable to only a fraction of the cases. After Rissler, Wickman, v. Harbitz and Scheel had proved that the disease did not limit itself to the grey matter, but usually involved the meninges and frequently the white matter of the cord and brain, the term "poliomyelitis" was clearly too narrow. These results having been confirmed on all hands, an attempt was made to give expression to the anatomical knowledge thus gained; the name "Meningo-myelo-encephalitis disseminata" was evolved. Besides the fact that such a name could not meet with general use, it was by no means free from objections.

It is to the credit of Wickman, whose work we shall discuss more fully later, that he drew attention to cases which were undoubtedly caused by the same virus as the cases of epidemic infantile paralysis, and yet showed no definite signs of paralysis. Clearly it would be ridiculous to call such cases paralysis; the term poliomyelitis might still be applicable to these abortive cases, because it appears likely that some degree of inflammation of the grey matter was present; yet anatomically this has not been clearly proved. Wickman found a way out of these manifold difficulties. He proposed the name "Heine-Medin" for this disease, which was so kaleidoscopic in its symptomatology, so variable from the point of view of pathological evidence, and the etiology of which was so entirely unknown at that time.

No one can object to the association of the names of these two men with the disease. Heine gave the first classical description of the disease, and Medin was the first to correlate the various types and provide us with a comprehensive view of the disease. It is true that such a name is unsatisfactory because, where possible, the name should express the essential character of any disease; but in the present instance our knowledge is insufficient to enable us to do this. We have seen what difficulties and perplexities stand in the way of any anatomical nomenclature, and it must be admitted that our knowledge of the question of etiology is still in its infancy. The wider the term now chosen, the less will be the likelihood that future researches will necessitate further change. On the other hand, there is no fear that the name "Heine-Medin" is so wide and indeterminate that diseases not belonging to this class will be included under it. By means of experiments with apes we are in possession of an infallible criterion to decide whether a particular doubtful case should or should not be classified as one of Heine-Medin disease. We therefore agree with Wickman and in future shall call all cases belonging to the group which he has established so brilliantly, both from its clinical as well as from its epidemiological aspect, cases of Heine-Medin disease. There are further practical advantages. During the epidemic, in answer to my question as to whether any connection could be traced between a particular case of infantile paralysis and previous cases, doctors have frequently replied in the negative because they have known of no cases of *paralysis*. If the name "Heine-Medin" be adopted, it is to be hoped that the discovery of Wickman will become more widely known, namely, that although paralysis is the outstanding feature of the disease it is very possibly by no means the most common feature.

The nomenclature proposed by Wickman will be used in this book; at the same time, for practical reasons, the exciting cause of Heine-Medin disease will be referred to as "Poliomyelitis Virus" (abbreviated: p.m. virus). This term expresses one of the most important characteristics of the virus, which has not been isolated as yet, namely, its tendency to attack the grey matter of the spinal cord. We do not scruple to speak of the virus and bacillus of tuberculosis, even though we know that on occasion Koch's bacillus does not form tubercles.

Historical Retrospect.—As in most directions in medicine, we owe our knowledge of the disease of Heine and Medin to a few exceptional men. The extent of our indebtedness to them will be particularized in the chapters which deal separately with the clinical aspect, the etiology, the epidemiology, and the pathogenesis of the disease. Others have done much in a small way to fill the gaps left by the men of wide views and imagination, but as time progresses their work will become more and more of an anonymous character.

At the beginning of the history of the disease one name stands

out, that of Jakob v. Heine. It is to his credit that he isolated a type of flaccid atrophic paralysis from the chaos of the multitudinous forms of paralysis affecting children. He chose the name "Spinal Infantile Paralysis" because of the supposed site of the lesion. His excellent description remained for years the basis of all the accounts of the disease in the text-books, and for a long time, with the exception of the discovery of the changes in the electrical reactions by Duchenne and Erb, no important addition was made to it by other observers. It was not until the occurrence of the great Swedish epidemics that Medin and Wickman discovered that the disease "Spinal Infantile Paralysis" was only the common symptom-complex produced by a disease which more rarely appeared in a bulbar, cerebral, polyneuritic, ataxic, meningitic or abortive form, or as Landry's paralysis. Owing to the length of time which had elapsed, during which the disease had been considered as a fully described entity, the many-sided picture of the disease drawn by the Swedish authors was surprising and novel. Many considered that the disease so described had nothing to do with Heine's disease, while others fell back upon the hypothesis that the disease had changed in the manner of its manifestation. As a matter of fact, the only change which had taken place was in the extent of our knowledge. It is necessary to recognize this important fact in estimating the value of the contributions of the Swedish investigators. Their results have been confirmed by all the painstaking work which has been done in the more frequent epidemics of later years.

Pathological and anatomical investigations have advanced *pari passu* with the clinical, in this as in other departments of medicine. Heine placed the lesion in the spinal cord on theoretical grounds; the proof of the existence of an organic lesion was furnished later by microscopical investigation at the hands particularly of French authors (Prévost and Vulpian, Charcot and Joffroy, Roger and Damaschino), who called attention to the most important change of all, the atrophy of the ganglion cells. The French authors also pointed out the importance of the interstitial changes which occurred in the cord. Subsequently, pathological discussion raged round the question whether the parts primarily affected were the ganglion cells, as maintained by Charcot, or the supporting structures of the cord. It cannot be said even at the present day that this question has been decided finally one way or another. But the researches of Rissler in acute cases have enabled us to say definitely that the disease consists in a disseminated, infiltrative, inflammatory process, which may attack any portion of the central nervous system, but which shows a predilection for the spinal grey matter. Wickman particularly not only confirmed and extended our knowledge of the actual, demonstrable, pathological changes, but threw new light upon the question of the pathogenesis of the disease. Recent experiments with animals appear to be leading to a still more clear conception of the pathology and pathogenesis of Heine-Medin disease.

The history of the epidemiology is of more recent date; in the 'eighties endemic occurrence of the disease was noted, epidemics were observed only at the beginning of the 'nineties. The first epidemics served only to increase clinical knowledge of the disease. Wickman's thorough work on the epidemiology dates from 1907; he produced proof that the disease is contagious and his conclusions have been borne out in the main by subsequent investigators. Successful investigation of the etiology is of very recent date. Since Strümpell first came to the conclusion that the disease was due to an exogenous, living agent, and as a result of the confirmation of his views by subsequent epidemics, the etiological aspect has had similar justification and importance as the other aspects of the disease. After passing through several phases this work has now entered on a new path owing to the success of Landsteiner in transmitting the disease to apes. At present we are at the beginning of this line of research, but already important additions to our knowledge of the active agent have been made, the pathology and pathogenesis becoming better known thereby, while at the same time a further stage in the understanding of the epidemiology has been reached; finally, there is now some hope in the direction of actual combating of the disease, either by means of hygienic measures or of drugs.

This short *résumé* of the history of the disease of Heine and Medin bears out what I said at the beginning, that it resolves itself into a series of steps made by a few remarkable men. The clinical aspect is bound up with the names of Heine, Medin, and Wickman; pathological research from the purely descriptive point of view begins with Charcot's teaching that the ganglion cells are the elements primarily affected, and the critical histological studies of Wickman have been the most important subsequent additions to our knowledge in this field. Wickman must be regarded as the founder of the epidemiology, while Strümpell laid the foundations of the etiology of the disease by his brilliant hypothesis and Landsteiner has led the way in the elucidation of the etiology by means of his experiments on animals.

CHAPTER II.

The Symptomatology of the Disease in Man.

I.—HISTORICAL.

The Period before Heine.—It was not possible that such a disease could have been overlooked by the medical profession before Heine's time. The credit of having described cases is generally given to the Englishman, Underwood, who flourished about the middle of the eighteenth century. According to Seeligmüller's critical analysis of the report it appears that it was inaccurate and did not differentiate between the paralysis due to spinal infantile palsy and that due to other spinal lesions, *e.g.*, vertebral caries. The German, Jörg (1816), wrote the first description to which exception cannot be taken. His description is as follows:—

> The little girl was born healthy, although the mother was by no means strong. When a few weeks old the child suffered from some violent fever, of the nature of which the parents could tell me nothing, but which seemed to have been caused by a chill and to be of the nature of those typhoid fevers to which children are so subject and which make such devastating inroads on their whole economy. The illness lasted a long time, and the parents and the doctor despaired of all hope. In spite of this the child gradually recovered from the fever, although she remained for a long time wasted and weak. About the same time the mother suffered from some illness of which she very nearly died and the child consequently was left to the care of strangers. When the mother had recovered sufficiently to resume the care of the child she noticed that it did not move its feet properly; it became more and more clear that the feet were becoming clubbed.

Heine, who referred to this case of Jörg, also called attention to an observation of Brück (1839), who mentions the case of a boy who developed contractures of all limbs after infantile paralysis. The case reported by Badham (1836), quoted in full by Heine, probably does not belong to this group; indeed, the author himself regarded the paralysis as of cerebral origin. The communications of Badham, however, are of importance inasmuch as they were the cause of the first publications of Heine. Badham wrote "What is the cause of this paralysis? Of what nature is it? What is to

be done against it? The author would be glad to know the answers to these questions and he calls upon the medical men of all nations to publish their experiences and views in this important matter." In too modest a fashion Heine prays that his publication "may not be taken to be an answer to the questions put before the medical world by the English doctor." As a matter of fact, however, Heine's first monograph contains as complete an answer to these questions as was possible, considering the standpoint of medicine at that time and the amount of material which was at his disposal.

Heine's Work.—The method of Heine throws much light on the methods involved in all successful investigations. It follows in the main a procedure opposite to that used by Medin, which we shall consider later. Heine collected cases of a definite type out of the numerous records of paralysis in children, and raised this type, the flaccid atrophic spinal type, into a definite clinical entity. We know now that the cases selected by Heine did not exhaust his material from the etiological point of view, and that consequently his classification was too narrow. This does not detract from the value of Heine's services, which lay in the differentiation of a type from amongst the medley of inco-ordinated observations of which his material was composed. He had succeeded in discovering the most common form of the disease and his work is a standing example of the value of applying an arbitrary principle in a schematic and orderly way to a mass of clinical observations; the result may not give a complete explanation of all the appearances, but it undoubtedly leads to a widening of our conception of the disease and to an actual increase of knowledge.

In the text-books and in many modern monographs Heine is given credit for being the classical observer of the symptomatology of the chronic stage of infantile paralysis. But it must not be forgotten that he was well aware of the acute stage; he writes: "Two stages can be made out at once, a primary acute stage and a secondary chronic one; the two stages merge into one another without any definite dividing line." He gives the following description of the acute stage:—

> The disease attacks children who are healthy and well developed at the age of from 6 to 36 months. Usually they have suffered from no illness previously, in some cases they have been somewhat unwell for a short time. The incidence is sudden, occurring with fever, congestion of the head, restlessness, and, in short, symptoms of general irritation. At the same time there are signs of difficulties in dentition, the children put their hands to their mouths, from which saliva pours, the gums are swollen in places and are hot, sleep is restless, broken by paroxysmal cries, and the eyelids are only half closed. Sometimes the disease begins with vomiting, diarrhœa, or the appearances of acute rheumatism. Rarely one of the exanthemata seems to be at the root of the matter. Subsequently there may be more or less severe convulsions, which may recur. In two children, whom I treated later, the illness began suddenly with convulsions, collapse, frothing at the mouth and nose, and lividity. In other cases the paralysis appears after

only slight general symptoms of fever which may be overlooked; the child goes to bed apparently healthy and is found paralysed in the morning. This mild type of onset is the more common form and often leads both the doctor and the parents to take too hopeful a view of the illness. The danger to life in such cases is very slight, but there is no doubt that in the more violent cases the child is in considerable danger, although no directly fatal case has come to my knowledge. The convulsions are limited to a single attack in most cases, but rarely the initial attack is followed by several minor paroxysms. After the convulsions the child lies quiet, pale and exhausted, looking about the room as if just awakened from a sleep—[in the First Edition Heine writes "paralysis suspendit convulsiones"] and it appears to the parents as if convalescence will be rapid until they find on lifting the child that it is paralysed. The lower extremities are most frequently affected; often in conjunction with the muscles of the trunk, so that the patient not only loses the power of walking, but even of sitting up and of holding up the head. Frequently one leg is affected, but without the corresponding arm, as in the hemiplegic type of the disease; a few separate muscles may be affected in each leg. In the rarest cases one arm and shoulder being affected the limb hangs by the side, while the lower extremities remain quite untouched. The bladder and rectum are sometimes weakened for a time, but never permanently affected. With the occurrence of paralysis the first stage of the disease is finished and it passes into its second stage.

This description, in my opinion, is still worth recalling in the light of our subsequent knowledge. It is true that Heine depicts the acute stage mainly from facts obtained from the history of the cases, but this scarcely diminishes the value of his statement, as the obtaining of a good history is one of the most important parts of clinical examination and is an art in itself which is by no means understood by everybody. Eduard Müller has lately called attention to the great importance of a good history in just these cases; further, the doctor rarely has an opportunity of observing the acute stage of the disease, except during an epidemic. Even as late as the year 1878, we find Seeligmüller complaining that there was but one description of the acute stage in the literature, that written by Dr. Ehrenhaus, an assistant of Dr. Henoch.

Heine may be considered the founder of the symptomatology of both the acute and chronic stages of the disease. Following on a short communication to the Society for the Study of Natural History at Freiburg, in 1838, his first monograph appeared in 1840. In this he describes fourteen cases of paraplegia, seven cases of "hemiplegia," which term he uses to connote paralysis of *one* extremity, *i.e.*, cases which we should call monoplegia, and six cases of partial paralysis. In the same monograph he describes four cases of paralysis due to cerebral lesion, which he differentiates sharply from the rest by laying stress on the spastic nature of the paralysis; he thus lays the foundation of his classification of the paralyses according to their spastic or non-spastic character, which classification has been adhered to down to the present day. The

correctness and comparative completeness of his description is generally admitted; in particular he called attention to the absence of sensory disturbance and to the fact of recovery taking place from even extensive paralysis. He says also: "The gradual reduction of the paralysis, both in extent and in intensity, gives ground for the belief that it is due to the gradual re-absorption of exudate around the nervous elements, whereby the latter are partially relieved from pressure." This shows that he had some idea of the nature of the pathological process involved. He recognized that the mental condition of his patients was good ("some of them showed much talent"), and he describes with great clearness the paralysis, the atrophy, the contractures, the delayed growth of bone and the other deformities. From the point of view of etiology, he believes that delayed and difficult dentition is to be blamed. Finally, he showed the way towards the correct orthopædic treatment of the permanently paralysed.

It is surely of value to save from oblivion the life-history of so remarkable a man. By the courtesy of Dr. Sick, the Director of the Municipal Hospital of Stuttgart, I am in possession of the *Proceedings of the Würtemberg Medical Society;* in vol. 1, 1880, there are to be found the following biographical notes:—

"Jakob Heine was born April 16, 1800, at Lauterbach, a village in the Black Forest. His father kept an inn, and was also a farmer. At first he attended the village school, but he soon showed desire for a wider education. When aged 13 he tried to enter the Gymnasium at Rottweil, but was not accepted as he was already too old. For some time he followed his father's occupation. The desire for a scientific training left him no peace, and at the age of 21 he entered the classical school at Altirsbach, where he worked side by side with boys from 8 to 14 years old. In the autumn of 1822 he entered the Gymnasium at Rottweil, and in a short time, by untiring effort, he passed his examination. In 1823 he entered the University of Würzburg, where the influence of his uncle Heine, 'the Father of Orthopædics,' soon caused him to give up theology for medicine. He carried on his studies with great assiduity and under many difficulties. He acted for a time as assistant to Schönlein, and in the surgical clinic of Textor; he was also prosector of anatomy. He graduated in Würzburg, and passed the Würtemberg State Examination at Tübingen in 1829. Shortly afterwards he was asked to arrange a State orthopædic hospital. He chose the town of Cannstadt, where he opened the institution in 1829. As so often happens when a new special hospital is founded, the patients who appeared wanting orthopædic treatment seemed literally to spring out of the ground, and enlargement of the hospital speedily became necessary. Heine married Henriette Camerer, daughter of the Director of the Catholic Council in Stuttgart, in 1831. Patients of all countries and of all ranks came in great numbers to his institution.

"Apart from the two monographs which appeared in 1840 and 1860 Heine did not write anything.

"He received many personal honours. In 1830, as a result of the immediate success of his institution, he was given the freedom of the town of Cannstadt and the title Hofrat. Later he obtained the title Geheimer Hofrat, and was the recipient of many Orders. He retired into private life

in 1865. He had the proud pleasure of seeing one of his sons become surgeon and lecturer at the University of Prague, although he had the sorrow of seeing this same son die before him in 1877. Heine died November 12, 1879, in Cannstadt. His life was that of a man of manly character who rejoiced in overcoming obstacles; he is said to have 'had good luck,' but, as a matter of fact, his success was due to his magnificent energy and self-confidence."

The best clinicians, Romberg, Bardeleben, Duchenne, and Rilliet praised his work. Rilliet and Barthez, who wrote on infantile spinal paralysis in 1843, did not know of his work at that time and used the term "essential infantile paralysis" because they were unable to find any changes in the spinal cord *post mortem*. In a later work (1851) they recognized the importance of Heine's work, but again rejected the term "spinal," owing to their repeated negative results at autopsies.

In England attention was turned to the paralyses of children. In 1850, Kennedy described cases of "temporary paralysis" in which, however, there is some doubt as to whether they were due to the same cause as Heine's cases. The English physician, West, coined the term "paralysis of the morning" in 1852; this term was used for a long time, although, judged by the standard of our present knowledge, it has little to recommend it. In 1860, Heine's second monograph appeared; in it he gives records of 150 further cases, and localizes the lesion in the spinal cord with certainty by purely deductive reasoning. We shall return to this point later.

From Heine to Medin.—The next thirty years did not add much to the clinical knowledge of the disease. Of importance was the demonstration of the change in the faradic reactions of the muscles by Duchenne, and his conclusion from this that the disease was spinal in its localization. He invented the name "Paralysie atrophique graisseuse de l'enfance," which was but little used. Erb followed with observations on the changes in the galvanic reactions and formulated his theory of the "reaction of degeneration." Otherwise, as far as progress in the field of clinical investigation was concerned, the period produced nothing. The text-books of the time followed Heine's description, with the addition of the results of investigations of Duchenne and Erb. Many isolated observations were put on record during the years 1860 to 1890, which tended more and more to show that the description given by Heine was becoming too narrow and that the conception of the disease needed broadening. However, nothing definite was achieved, firstly, because the several observations remained isolated, and, secondly, because at that time men's energies were directed mainly in the direction of topographical diagnosis. The man with true scientific insight had not arrived.

Among these observations, which showed that the limit drawn by Heine was too narrow, were some which proved that the disease might attack adults. Such were those of Meyer (1860), Duchenne *fils* (1864), and particularly the elder Duchenne, Erb and Charcot,

who based their conclusions on positive anatomical evidence. Others were Schultze, 1878; Friedländer, 1882; Leri and Wilson, Rissler, 1888; Leegaard, 1889; Williamson, v. Kahlden, Middleton, Jagic, Röder and Bickel, Sherman and Spiller, Taylor, van Gehuchten.

Some observers pointed out the similarity or even the identity of the pathological processes in infantile paralysis and Landry's disease. These were Petit *fils*, Zimmermann, who in 1885 examined a case of Landry's paralysis and came to the conclusion that this disease and infantile paralysis formed only different degrees of one and the same disease; Buss in 1887, and particularly Raymond.

In other directions also the accepted idea of the disease began to fall in pieces. Erb recognized that there are cases of paralysis which are identical with infantile paralysis and which end in complete recovery; Duchenne in 1855, Volkmann in 1870, and Frey in 1874, had already described similar cases. The similarity between certain forms of paralysis due to medullary and pontine lesions and anterior poliomyelitis was put on record. Eisenlohr, in 1880, described some typical cases. But it was Oppenheim who in 1883 formulated clearly an "encephalitis pontinea," which was in close relationship to infantile paralysis. Thus we see how the original conception of the disease gradually became widened; but, owing to the absence of any criterion by which the several varieties could be judged and included or excluded in the general group, no definite restatement of the position was possible.

The most important advance was made by Strümpell; he placed certain cerebral palsies in the same group with the spinal infantile palsies. The importance of this step lies in the appearance of a new etiological standpoint, by which Strümpell justified his classification, and which was accepted later by Jendrassik and Pierre Marie. Strümpell also connected etiologically certain forms of neuritis with poliomyelitis. I have no doubt that if Strümpell had had the opportunity of observing an epidemic he would have antedated the discoveries made by Medin. His arguments seem to me to be of such importance as to merit quotation. In 1884 he wrote:—

> Even the general course of these diseases shows great similarity. Multiple neuritis and poliomyelitis appear in similar varieties; they show the same gradation between the acute and the chronic forms. Both affect principally the motor tracts, although owing to the peripheral nerves being affected in the one and the spinal cord in the other there are many minor differences in the symptoms. It follows that the purely anatomical classification between neuritis, poliomyelitis, and acute encephalitis, which is now in vogue must be looked upon as an artificial one. It seems to us worth while to consider whether all these diseases may not be brought under one etiological heading, and whether they may not be considered to be different local manifestations of the same disease, or at least of very closely allied diseases. In this connection one might apply the analogy between croup and faucial diphtheria to the diseases, multiple neuritis and

poliomyelitis. It is only of late years that the former diseases have been recognized as arising from the same cause, whereas for many years a purely artificial distinction was made between them.

In the year 1885 he writes:—

Both diseases tend to attack previously healthy children in infancy. They present a stage of acute invasion in which they can scarcely be differentiated; this leaves a paralysis behind it which in both diseases affects the motor tracts, in the case of poliomyelitis the grey matter of the cord, in the case of the hemiplegic palsies undoubtedly the brain; this resultant palsy is naturally of different kinds, but the differences are due merely to the localization of the disease and not to any difference of the essential nature of it. In any case the analogy between the two diseases is remarkable in that in both cases it is the grey matter which is affected. That in the hemiplegic cases the cortex of the brain is affected is proved by the distribution of the paralysis, the occurrence of epileptic attacks and athetosis afterwards, and, from the anatomical aspect, by the results of microscopical examination. In these cases porencephaly is found which is not of the kind present in cases of congenital defect, but which still shows evidences of its inflammatory origin; further, this porencephaly is found in the central convolutions, that is to say, in the motor regions. The appearances are precisely similar to those found in the anterior horns after an attack of poliomyelitis. There is at present no record of pathological investigation of the acute stage of either disease.

It seems to me to be justifiable to class acute encephalitis as a by no means rare variety of acute anterior poliomyelitis. Personally, I lean towards the opinion that the two diseases are of the same essential type, or are even identical, inasmuch as both are due to the same agent, possibly of an infective nature, which attacks sometimes the grey matter of the cord and at others the cerebral cortex. In order to express this relationship in the nomenclature, I should recommend that this particular form of hemiplegia should be called cerebral infantile paralysis or polioencephalitis acuta in contradistinction to spinal infantile paralysis or poliomyelitis acuta. The diagnosis of the former is arrived at easily by means of careful investigation; at the same time the existence of hemiplegia in children due to other causes must not be lost sight of.

These different observations prepared the way for Medin. The first great Swedish epidemic enabled him to place on a firm basis the relationship between the various types of this disease, which until then had been classed as strictly separate entities. He observed not only the classical spinal form as well as the cerebral and the polyneuritic forms (thereby confirming the brilliant theory of Strümpell), but also the bulbar form and cases of a peculiar ataxia. All these could be traced as occurring in considerable numbers within the same epidemic, and so were doubtless due to the same cause. Heine's classical description of the simple spinal form was thus amplified; the disease appeared to be one attacking the whole nervous system in a patchy, disseminated manner, and producing, according to its particular localization, a kaleidoscopic variety of clinical pictures. At the Berlin Congress, where Medin published his results, Heubner recognized at once their fundamental

importance. Medin, the first to have the opportunity of observing the acute stage of the disease, thus became the founder of the symptomatology of this stage.

Medin to Wickman.—In the following years there occurred several smaller epidemics which enabled Medin's observations to be confirmed. Hoffmann, in 1894, observed a brother and sister, the one suffering from the spinal, the other from the cerebral form. Calabrese also identified the cerebral and spinal types. Zappert observed the Austrian epidemic of 1898 and found an increasing number of cerebral cases.

Besides many confirmatory observations, there were many which opened up new ground. Duquennoy (1898) noted a particularly painful type. Schultze, Auerbach, also Caverley and Macphail in an epidemic, noted the frequent involvement of the meninges; unfortunately, these observers fell into the error of confounding the disease with cerebro-spinal meningitis.

The clinical studies of Wickman form the completion of this period. By his wonderful histological work he made important additions to our knowledge and he described a meningitic form, also a type simulating Landry's disease and particularly an abortive form of the disease. His work was fully corroborated during the epidemics of 1908 and 1909 by Leegaard in Norway and by Zappert in Austria; Eduard Müller made an exhaustive clinical study of the epidemic in Hesse.

The names Heine, Medin, and Wickman mark the commencement of three important periods in the history of our knowledge of this disease.

II.—THE SYMPTOMATOLOGY IN MAN.

I have neither the intention nor the capacity to give a complete description of the symptomatology. I intend to give merely a short sketch of the subject as worked out by Wickman and Eduard Müller, in order that the reader may be in a position to institute direct comparisons with the clinical picture seen in the case of apes, which I shall describe later. For more complete information I refer the reader to the monographs written by Wickman and Eduard Müller.

Period of Incubation.—This lasts at least five days; it is usually not more than ten days, and its average duration is about a week. Wickman suggests the possibility that it may last only one day, but his conclusion rests upon an inadequate interpretation of certain epidemiological observations. I may mention here that the incubation period in apes may be much longer and that this may be the case also in man.

Prodromal Symptoms.—The disease does occur suddenly without any prodromal symptoms (the "paralysis of the morning"), but this is exceedingly rare; usually, there are symptoms for a variable length of time, one to seven days. The most common

is fever of no great degree, which is sometimes remittent, sometimes continuous. The degree of fever and the severity of the prodromal symptoms generally bear no relation to the amount of subsequent paralysis. The frequency of the pulse is increased, and more than proportionately to the temperature; Eduard Müller suggests that this may be due to implication of the bulbar centres. Finally, there is general malaise. Occasionally a rash is seen, very rarely herpes labialis (an important differential point with regard to cerebro-spinal meningitis) and herpes zoster. Some authors are inclined to include herpes zoster as one type of the disease; we shall return to this point later.

Quite frequently the respiratory tract is affected; the patient suffers from coryza with conjunctivitis, from bronchitis or even from broncho-pneumonia. In some epidemics, *e.g.*, in our Hessian one, the respiratory tract is much more frequently involved than the alimentary tract, which in other epidemics is a favourite seat of the initial symptoms; vomiting, diarrhœa or constipation may occur. Examination of the blood shows leucopenia (Eduard Müller), which is of much diagnostic value in certain cases.

The most important prodromal symptoms are those connected with the nervous system. Without any definite psychical disturbance there is a certain degree of somnolence; rarely convulsions and tremors occur (they are noted more frequently by the older writers); of particular importance is a general tenderness of the whole person; this is characteristic and was observed by Heine, Duchenne, and others. Even a light touch causes pain which is increased by passive movement, particularly if the spine be involved in the movement. Spontaneous pain occurs in the limbs and in the neck and back; the spine feels stiff. There may be some tenderness to pressure of the nerve trunks. The cause of most of the sensory symptoms lies in the involvement of the pia mater. Excessive sweating is a characteristic and has been observed by many authors; Müller has found it in three-quarters of his cases; it may be due to involvement of the spinal sweat centres, which are said to exist in the anterior horns of the grey matter.

It may be said that the initial symptoms present no definite diagnostic picture; according to the predominance of any one group of symptoms, the appearances may be meningeal, gastro-intestinal, respiratory, or merely generally febrile in type.

Stage of Paralysis.—This stage is characterized by an extraordinary variety of symptoms. The following classification of types, as proposed by Wickman, cannot be made to fit every case, because so many are intermediate between two types. It has been suggested that Wickman's classification should be simplified, but I cannot see any good reason why this should be done.

(*a*) *Abortive Type.*—Some of the earlier authors, Briegleb, Pasteur, Medin, and Leegaard, observed cases of general fever which were in close contact with cases of definite infantile paralysis; but it was Wickman who first clearly proved the connection

between the two groups of cases and brought into prominence the abortive type of the disease. This type consists essentially of the prodromal symptoms, which clear up without any paralysis. Cases do occur which lie between the true abortive and the spinal type; in these there may be a slight temporary weakness of one muscle or group of muscles, or there may be merely a temporary loss of a deep reflex—the "rudimentary poliomyelitis" of Eduard Müller.

The proportion of abortive to paralytic cases varies in different epidemics and in the several foci of the same epidemic. Wickman himself has recorded figures varying from 35 per cent. to 56 per cent. Müller believes that about 50 per cent. of all cases are abortive. The etiological identity of the abortive and paralytic cases is proved by the simultaneous occurrence of both types in the same family, and latterly by the serum test (*vide* Chapter VI).

(*b*) *Spinal Types.*—These, forming the classical spinal infantile paralysis, together with the abortive type, make up the great bulk of the cases. They are characterized by the occurrence of paralysis either during or subsequent to the febrile attack. At first there is only paresis, but this quickly develops into paralysis. The extent of the paralysis, the muscle groups involved, and the degree of loss of function, all vary within very wide limits. Most frequently the lower limbs are attacked, particularly the peronei and the quadriceps, next often the shoulder muscles. The muscles of the buttocks, which are involved in two-thirds of the cases, according to Eduard Müller, and the abdominal muscles are often affected but frequently overlooked. Not infrequently the intercostals are attacked, the diaphragm more rarely, and the muscles of the back and neck least of all. In short, any and every muscle may be affected, but those of the lower extremities most frequently of all. The paralysis is of the flaccid type, the tone of the muscles being diminished; the deep reflexes are depressed or abolished; the electrical reactions show quantitative diminution of excitability and a partial or complete reaction of degeneration; muscular atrophy follows on the paralysis. At the commencement of the illness there may be an increase in the deep reflexes; Förster has even recorded the occurrence of ankle clonus. Müller considers that involvement of the pyramidal tracts is indicated hereby. The fact that flaccid paralysis does not occur is therefore of no diagnostic significance in excluding Heine-Medin disease. The degree of paralysis may vary from the mere loss of a deep reflex to the most complete flaccid paralysis.

Disturbances of micturition are rare during the paralytic stage, but a form of retention which is undoubtedly nervous in origin is frequent in the acute stage (Müller). Incontinence of either urine or fæces is exceedingly rare.

The essential characteristic of the disease is therefore a motor paralysis. Disturbance of sensation is of relatively small

importance. Loss of sensation to a greater or less degree has been observed, and Müller lays stress on relative thermanæsthesia and analgesia occurring frequently, if only transitorily, at the beginning of the disease; this may be due to some involvement of the posterior horns.

The stage of repair follows that of acute paralysis, and after about one to one and a half years the chronic stage begins. After

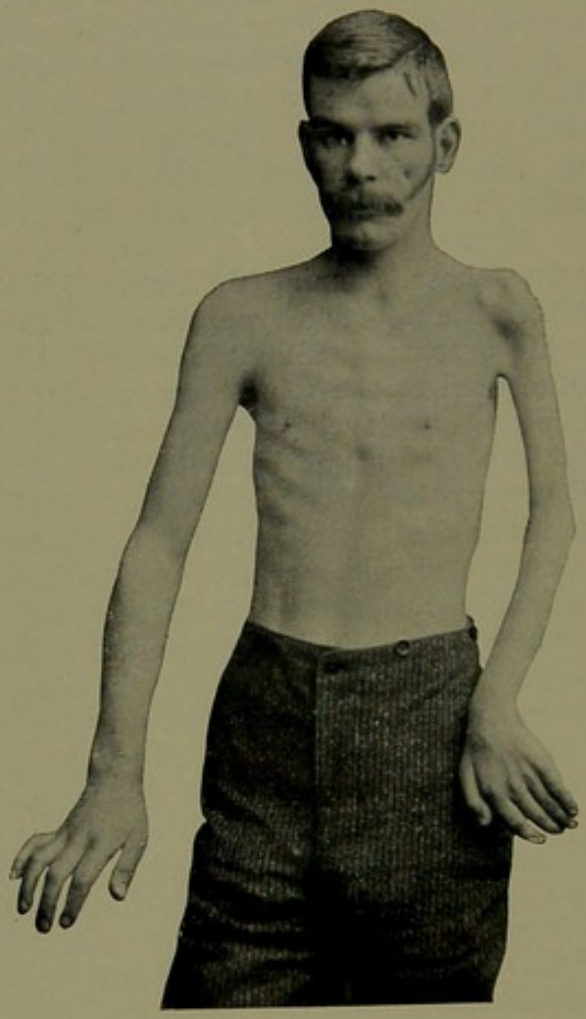


FIG. 1.

The spinal form of Heine-Medin disease with paralysis and atrophy of the left upper extremity dating from infancy. The muscles of the shoulder-girdle are most affected. (After Byrom Bramwell.)

this no further recovery of power is to be expected, and in young, growing individuals it is during this stage that deformities appear. There are also vasomotor disturbances, the limbs are cyanosed and cold and the muscular atrophy becomes marked (fig. 1).

The most common deformities are pes cavus and in children scoliosis (figs. 2 and 3).

Occasionally there is a recurrence of the disease occurring at an interval of some weeks or even months after the first attack (Medin, Leegaard, Neurath, Schwarz). But Müller has pointed out that every increase of paralysis occurring after an interval is not to be regarded as a recurrence of the primary disease, but is often due to tracts or centres which were damaged suddenly refusing to work.

(*c*) *A Type which simulates Landry's Disease.*—I have already mentioned certain isolated records of cases which point to the identity of Heine-Medin disease and Landry's disease. In the year 1859, Landry described a disease which began as a paralysis

FIG 2.

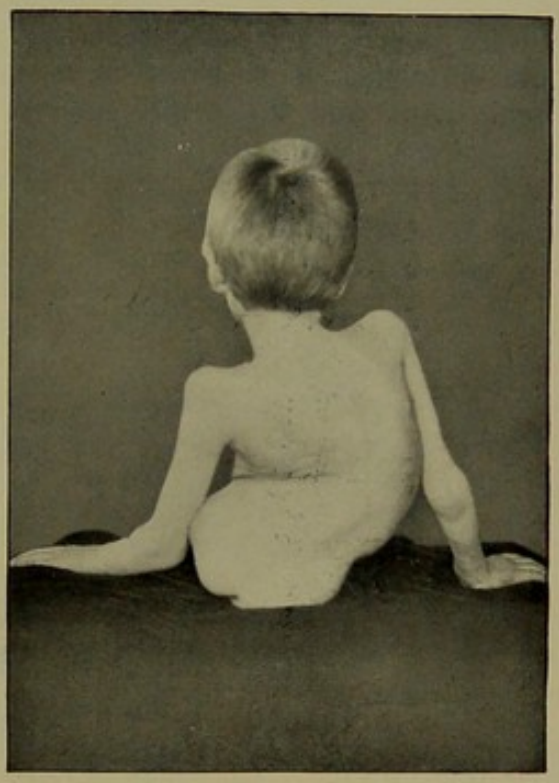


FIG 3.

The spinal form of Heine-Medin disease with extensive paralysis and deformity. (After Johannessen.)

of the limbs and rapidly progressed to a fatal issue by involving the medullary centres. The history of this disease furnishes a good example of the way in which an arbitrary and narrow classification may prevent the recognition of wide and important relationships between diseases. Observers overlooked the fact, which was clear from the identity of the anatomical findings, that Landry's paralysis was only "infantile paralysis" with a fatal issue; further, that fatal cases of infantile paralysis ran the same clinical course as cases of Landry's paralysis. As Wickman said, they

appear to have made the death of the patient the essential feature of the diagnosis. During the Swedish epidemic, Wickman was able to convert the probability of the identity of the two diseases into a certainty. The basis of this type is a "poliomyelitis acutissima," beginning in the centres for the lower limbs, spreading rapidly to those for the upper limbs and leading to a fatal issue in a few days by involving the centres in the medulla. In a few cases the arms are affected first, the paralysis being simultaneously ascending and descending.

(*d*) *Bulbar and Pontine Types.*—Medin was the first to call attention to the frequency with which the cranial nerves were attacked. It is rare to see them involved alone; usually the spinal centres are affected at the same time. The facial nerve is the one most frequently paralysed, generally on one side only and in its whole distribution. With it is associated sometimes the hypoglossal (figs. 4 and 5).

FIG 4.

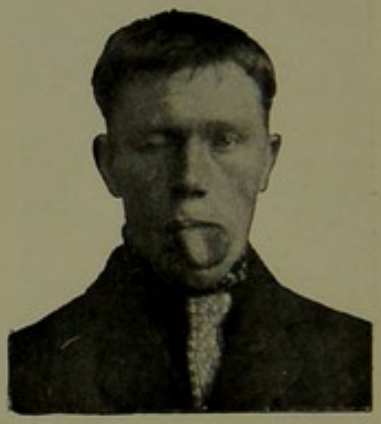


FIG. 5.

The bulbar form of Heine-Medin disease with paralysis of the left facial and hypoglossal nerves. In fig. 5 the patient is trying to close both eyes. (After Wickman.)

More rarely the abducens and the motor oculi are involved, and occasionally the trochlear nerve. Nystagmus has been observed by Medin, Müller, and Netter. The optic nerve has been affected; the trigeminal, as shown by paralysis of movements of the lower jaw, and very rarely the other cranial nerves. The clinical picture is extraordinarily variable, according to the particular nerves affected, the degree of their paralysis and the amount of involvement of the spinal cord which is present. Of course, all isolated palsies of cranial nerves are not due to Heine-Medin disease and in such cases serum diagnosis is of great importance (*vide* Chapter VI).

(*e*) *Cerebral Type.*—Strümpell maintained the identity of certain encephalitic processes with epidemic poliomyelitis. Medin

confirmed his views, but they were not generally accepted owing to the rarity of observations on cerebral cases. At the present time there can be no doubt of the existence of such cases. Pathological encephalitic lesions quite analogous to those found in the spinal cord have been seen, and during epidemics spastic and flaccid cases have been observed side by side by Möbius, Medin, Buccelli, Hoffmann, Leegaard, Eduard Müller, Zappert, Spieler, Schlesinger, Nonne, and Krause; they have been observed in the same patient by Williamson, Neurath, Calabrese, Oppenheim, Pierre Marie, and Wickman. The serum diagnosis is of value both in proving the existence of encephalitis due to Heine-Medin disease as also in differentiating that from encephalitis due to other causes.

(*f*) *Ataxic Type.*—Medin first described ataxia similar to that seen in Friedreich's disease, also Wickman, Zappert, Spieler, Lindner and Mally, Netter, Nonne, and others. Zappert does not consider it advisable to make a special ataxic group; he prefers to classify such cases in the pontine group. Wickman, on the other hand, holds that all the ataxic cases are not due to a lesion in the pons or medulla, but that some are caused by lesions of the cerebellum, the mid-brain or Clarke's column.

(*g*) *Polyneuritic Type.*—This was recognized first by Medin, and later by many other observers. It is doubtful, considering the absence of sensory signs, whether the process involved is a true neuritic one. Its existence is not definitely proved, but the amount of work which has been done in this connection is not large. This type could be explained by involvement of the central nervous system. On clinical grounds the retention of this type is justifiable, and later a simplification may be possible.

(*h*) *Meningitic Type.*—The meningitic form is that in which the symptoms due to involvement of the pia mater are the most prominent; such are vomiting, headache, pain in the neck, pain and stiffness in the spine, and a slight degree of opisthotonos. We owe it to Wickman that such cases were recognized as belonging to Heine-Medin disease. Formerly they were classed as cerebrospinal meningitis occurring with infantile paralysis, and it was even suggested that cerebrospinal meningitis and infantile paralysis were one and the same disease. Later epidemics have led to Wickman's view being upheld. Netter found that 29 per cent. of his cases belonged to the meningitic type. Lhermitte, as late as 1909, assumed a close relationship between infantile paralysis and cerebrospinal meningitis, and he also denied the connection between epidemic infantile paralysis and Landry's disease; but he is almost the only observer who holds such views.

Prognosis.—For many years Heine's dictum held good, that the prognosis *quoad vitam* was good, but the prognosis *quoad sanationem* bad. At the present time, owing to the researches of Wickman, we would rather invert Heine's prognosis.

The mortality in different epidemics and within the same

epidemic varies immensely. Wickman found the figure to vary between 10 per cent. and 42.3 per cent.

		Total number of cases with paralysis	Mortality
Wickman	Sweden, 1905 ..	868	16.7 per cent.
Leegaard	Norway, 1905 ...	577	14.56 ,,
Zappert	N. Austria, 1908 ...	266	10.8 ,,
Lindner and Mally	E. Austria, 1908 ...	71	22.5 ,,
Fürntratt	Steiermark, 1908 ...	433	13.6 ,,
Krause	Westphalia, 1909 ...	633	12.3 ,,
Ed. Müller	Hesse-Nassau, 1909	100	16 ,,
Peiper	Pomerania, 1909 ...	51	11.7 ,,
Eichelberg	Hanover, 1909 ...	34	20.58 ,,

In this table the mortality figure is in relation to the cases with paralysis only; the abortive cases are not included.

In general the fourth and fifth days are the most dangerous. There is further a marked difference between the infantile and the adult cases. Wickman found:—

In children up to 11 years—Mortality 10.5 per cent.
In patients above 11 years—Mortality 27.6 per cent.

The statistics of other authors show a similar result.

In connection with the prognosis *quoad sanationem* the relationship between the transitory abortive type and the types with paralysis has already been mentioned.

Recovery from paralysis, which was specially emphasized by Neurath in 1901, occurs in at least 20 per cent. of all cases (Wickman).

In this respect also there is a great difference between children and adults.

Wickman gives the following:—

In patients 9 to 11 years old—48.4 per cent.
In patients above 11 years old—32.2 ,,

Leegaard finds:—

In patients up to 14 years—30.4 per cent. recovery
In patients above 14 years—22.2 ,, ,,

The prognosis is from every point of view worse in adults than in children.

Sporadic Infantile Paralysis.—Finally, let us consider the so-called sporadic type. The more recent writers have not only considered the identification of these cases with epidemic infantile paralysis doubtful, but have denied this identity. They do this on the ground that the clinical picture is quite different in the two cases, the paralysis sets in suddenly without any prodromal symptoms, and the cases occur in a totally isolated way. It must

be remembered, however, that no case of sporadic poliomyelitis has been recorded to which a counterpart cannot be found among epidemic cases. Other undoubtedly infectious diseases occur in a sporadic manner, *e.g.*, meningitis and scarlet fever; further, it is doubtful whether so-called sporadic cases are ever really sporadic, owing to the fact that the associated cases, being abortive, are overlooked. It has been maintained that the prognosis is different in the two groups, that death and recovery from the paralysis never occur in sporadic cases. But this means merely that the fatal cases have been called "Landry's paralysis," and those which recover have been called "polyneuritis," that the difference depends upon an arbitrary nomenclature. However, at the present time no doubt can exist, as the identity of the disease in the sporadic and the epidemic forms is proved by means of the serum test.

CHAPTER III.

Etiology of the Disease.

I.—MICROSCOPICAL AND CULTURAL RESEARCHES WITH EXPERIMENTS ON ANIMALS.

The older Views.—The disease is even now sometimes called "paralysis during dentition" in England. The views of Marshall, Kennedy, and others appear seemingly still to have some adherents, though probably this is only apparent; they blamed difficult dentition as the cause of Heine-Medin disease. At the present time we cannot pass by this theory without some recognition, particularly as a larger clinical experience and, before all, experiments on animals have taught us that the mucous membrane of the mouth, nose, and throat is a frequent point of entrance of the virus; and, moreover, as these older physicians associated the beginning of the disease with disturbance of the intestinal canal. In the oldest observations therefore we find the same points of entrance indicated, which we still regard as the most important. It was from the English writers that Heine took his idea that difficult dentition lay at the root of the trouble; or at any rate he was supported by them in his theory. Such an assumption was in accordance with the spirit of the times; men sought rather for endogenous than for exogenous causes of disease. The disturbances which accompany dentition together with the great developmental activity occurring at the same time in the central nervous system formed, according to Heine, a sufficient cause of irritation of the delicate nervous system; an additional proof was found in the fact that inflammation of the brain and spinal cord occurred most frequently during these years. Although we cannot accept Heine's theory in its entirety to-day, we must admit that there was some justification for it; we ourselves know no reason why Heine-Medin disease attacks children specially, and occurs in certain years of childhood more than in others. In his theory as to pathogenesis Heine compels admiration for his acumen. He was strongly opposed to the theory that the disease was hereditary or due to a defect in development; this theory was certainly a convenient explanation, so convenient

that up to quite recent times it has appeared in the text-books. Taking into consideration the state of medical knowledge of his time we must admit that his reasoning was not lacking in clarity. The twenty years after Heine's monographs produced nothing of importance. One reason for this may be found in the rise of the French theory of an "essential" or "idiopathic" infantile paralysis; this tended to make inquiry into the cause of the disease appear unnecessary, even when pathological investigation had proved that such a term as "essential" was quite unjustifiable.

Strümpell's Hypothesis.—We owe it to the broad view of the subject taken by the great clinicians Strümpell, Seeligmüller, and Pierre-Marie that once more attention was drawn to the subject of the etiology of the disease. The direction in which they moved proved to be at once definite and fertile of result. They started from the clinical observation that the whole clinical picture of the disease, particularly in its early stages, showed great similarity with other diseases which were produced certainly by infection from without. Further, that cases which appeared to be sporadic could be arranged in groups, and consideration of the question whether the disease was not only infectious but even contagious became imperative. I cannot do otherwise than quote some of the more pregnant of Strümpell's dicta. In 1884, in his thesis, Strümpell discusses the etiology of some of the diseases of the nervous system. He says: "Passing in review the other nervous diseases from this point of view, one group stands out by itself, the members of which show great similarity with one another in their course and in their symptomatology. This group consists of the acute multiple neuritis, acute poliomyelitis and acute encephalitis of children. All have a sudden onset accompanied by considerable fever. The patients show mental dulness, suffer from headache, gastric disturbances, and occasionally enlargement of the spleen, swelling of the joints, and a slight albuminuria. According to our present point of view *these are all signs of infection by a pathogenic organism.*"*

In another place Strümpell says: "The peculiar clinical appearances of spinal infantile paralysis have frequently given rise to the opinion that in this disease we have to deal with an acute infective process. As in the case of so many undoubtedly infectious diseases, we cannot prove this to be so by direct demonstration of the causative agent. At present we can rely only upon the following facts: The peculiarity of the clinical course; the sudden onset for which no obvious cause is present; the moderately high temperature; the severity of the general symptoms; finally, the nature of the changes found in the spinal cord, which point unmistakably to a truly inflammatory process."

Seeligmüller and Pierre Marie bring forward similar arguments to prove that the disease is due to a specific infection. How little

* In the original not italicized.

general acceptance was given to these arguments is proved by the rejection of the theory of infection by so important an authority as Dejerine even as late as the year 1888; he maintained that clinically and pathologically the disease belonged to the group of system diseases.

Nevertheless, when on the report of an epidemic (about 1881) there followed more and more announcements of epidemics of infantile paralysis, the probability of an infective basis of the disease became greater, and from that time dates the era of active etiological investigation along bacteriological lines, particularly after the publication of Medin's famous investigations in 1890.

Microscopical and Cultural Investigation.—Attention had already been directed to the spinal cord as possibly harbouring bacteria. Goldscheider in 1893 had stained the cord of an acute case with methylene blue and by Gram's method, and failed to find any bacteria. Siemerling and Dauber obtained similar negative results; their negative findings were confirmed repeatedly by other observers. These results, obtained by using well-recognized bacterial stains, made observers chary of accepting later positive findings obtained by means of cultural methods. By some the difficulty was overcome by assuming that bacteria were destroyed very rapidly in the grey substance of the cord.

The Era of Cocci.—Schultze, by describing a case which clinically gave evidence of considerable involvement of the meninges, began this era which I have called the era of cocci, because of the nature of the organism which was found. He found, on examination of the lumbar puncture fluid, "many diplococci, arranged in rows, similar to gonococci but having the appearances of the meningococcus of Weichselbaum and Jäger." It was remarkable that all attempts to culture these organisms failed, although they were numerous, and although cultures were made from other samples of the lumbar puncture fluid. Upon these facts Schültze constructed a theory of the identity of meningitis and poliomyelitis; he regarded the two diseases as due to different localization of the same morbid agent.

Following on this, many positive results were obtained by bacteriological examination, and it appears as though the discovery of Schültze had exercised a certain influence upon later observers. Bülow-Hansen and Harbitz (in 1898) also found a Gram-positive diplococcus in the cerebrospinal fluid, but do not lay much stress upon their discovery on account of the very numerous negative results which they obtained. Courmont and Bonne (1899), Concetti (1900), Dercum (1900), Looft and Dethloff (1901), Gossage (1902), Engel (1900), Spiller (1903), Batten (1904), Barnes and Miller (1907) all found micro-organisms which were considered to be meningococci in some cases, pneumococci or staphylococci in others. These results served to strengthen the theory of the microbial origin of the disease. Giersvold's observations during the first great Norwegian epidemic in 1905 and 1906 caused a considerable sensation;

he found Gram-positive cocci shaped like beans and forming short chains, which he believed to be identical with the Jäger meningococcus. These organisms grew on the ordinary culture media. Harbitz and Scheel were obviously influenced by these results; they also found cocci in the cerebrospinal fluid, but reserved judgment as to their exact etiological significance.

A study of the literature shows that in no case has any clear proof of the causal significance of the cocci observed been brought forward; further, the bacteria seen have been of the most various kinds, they have been observed only in isolated cases, and no inoculation experiments have been made with any of them.

The Accumulation of Negative Results.—Doubts as to the importance of the few positive results become much greater when we compare them with the vast number of negative results obtained. Guinon and Rist in 1903 found the cerebrospinal fluid of an epidemic case to be sterile, and with the advent of the larger epidemics in Scandinavia (1905-1907), North America (1907-1908), Austria (1908-1909), Germany (1909), and France (1909) the negative evidence has become overwhelming. In Sweden Wickman and Jundell not only found eight perfectly fresh specimens of lumbar puncture from different cases sterile, but also all material obtained from autopsies on cases of epidemic Heine-Medin disease. Ellermann also obtained only negative results, but fell into the error of proclaiming certain rhizopods to be the cause of poliomyelitis; his statements did not hold good in the face of criticism. In America the results obtained by many experimenters were all negative—Purkins and Dudgeon, Sherman and Spiller, Greene, Wilson and Rothrock, Thomas, Taylor, Hoch, Wollstein, Starr, and Stephens. For example, out of 226 cases Stephens obtained a culture in only seven cases, and these he recognized definitely as contaminations. There were no positive results in France. The first observers had found cocci which were in no way difficult of demonstration or of culture, and this gave further importance to the consistently negative results obtained from a far greater material, and led to the opinion that the original discoveries were due to errors in technique. One such error was explained by Leiner and v. Wiesner, who found that if only the first portion of the lumbar puncture fluid was used a growth of cocci could be obtained fairly frequently, but never from the rest of the fluid; they carried out the same experiment in the case of diseases other than infantile paralysis, and obtained the same result, thus proving that the positive results were due to mere contamination, probably from the skin of the patient. They also pointed out the danger of using broth cultures in this connection, because bacteria will flourish in the broth without giving any indication of the number originally present. Koch's axiom is still more or less justified, namely, that for proof of the etiological significance of any organism it must be shown to be present in a quantity proportionate to the severity of the clinical signs.

So far, therefore, the history of the search for the cause of

Heine-Medin disease is a succession of mistakes. A short historical retrospect is not without its advantages if we learn from it the great danger of accepting any results in a scientific inquiry with undue haste. I have alluded above to my own impression, that it was the expressed or unexpressed underlying conviction that epidemic infantile paralysis was only a form, differently localized, of epidemic cerebrospinal meningitis which led observers to consider bacteria as the cause of a disease which we know now has nothing to do with them. The experiments carried out under these conditions only confirmed them in their view. At this point I would draw attention particularly to Wickman's conclusions; at a time when nothing was known for certain of a non-bacterial cause of the disease, and when there were many adherents of the theory of the identity of meningitis and poliomyelitis, he stated definitely, on the basis of thorough pathological, clinical, and epidemiological investigation, that if cocci were really the cause of both diseases they must be fundamentally biologically different in the two cases.

Personal Bacteriological Research.—I cannot deny that when I began to study this disease at a time when my clinical, pathological and epidemiological experience was limited, I was under the influence of the hypothesis that meningitis and infantile paralysis might be identical, or, at any rate, related diseases; as a result, in my first bacteriological experiments I devoted my energies to the finding of cocci. Owing to the fact that in our Hessian epidemic the respiratory tract was the site of the prodromal symptoms, whereas in the Westphalian epidemic studied by Krause it was the alimentary tract which suffered first, I was led to make cultures from the pharynx and tonsils. The results disclosed the ordinary organisms; in the first experiments I found pneumococci to be somewhat in excess of normal, and in the later cases the staphylococcus albus; under the influence of the above-mentioned hypothesis I spent considerable time in investigating the latter organisms. On turning my attention to the cerebrospinal fluid the problem became clearer; specimens were obtained from chronic, very acute, severe, and slight cases, and always the result was negative. The specimens were quite clear; vigorous centrifugalization gave not a trace of deposit; with the microscope a few lymphocytes were seen; an organic virus was not seen either in stained or in unstained specimens. The stains used were of the most various kinds, the usual aniline dyes, Gram's stain, Ziehl's stain for *Bacillus tuberculosis*, Giemsa's stain. Many culture media were used: Bouillon, gelatine, agar, glycerine-agar, grape-sugar-agar, ascites-agar, agar with the addition of the sera of different animals, coagulated serum, &c. Equal parts of lumbar puncture fluid and bouillon were mixed and incubated at a temperature of 37° C. The result of the tests was that the tubes remained sterile except in a few instances. The growth in these cases could be identified always as a common contamination. Examination of the blood in a severe case led to the same result.

It must be admitted that these experiments, together with the results obtained by others, did not furnish proof that the disease was not caused by a micro-organism; it was not known for certain whether the virus existed in the blood or in the cerebrospinal fluid; indeed, later experiments on animals have shown that the virus exists at most in extremely small quantities in either of these fluids. Certainty could be attained only after examination of the central nervous system, in which a living virus, if present at all, would be found.

The material I used for this investigation was obtained from children who had died from the effects of a typical attack of Heine-Medin disease. The details of the cases I will give later when describing the experiments on animals. Cultures were made from the brain, the pons, and the spinal cord, which were placed at my disposal by Professor Beneke. The tubes remained sterile except in a few instances of contamination. Careful search in stained sections revealed no bacteria although the pathological appearances were typical of poliomyelitis. Inasmuch as the later experiments on animals proved that the virus was present in large amount in the affected portions of the nervous system I was able to state with confidence that *it was impossible that a microbe which could be stained and cultivated easily could be the active agent in the causation of epidemic infantile paralysis.*

I have mentioned already the researches of Wickman which had led to the same result; there followed the work of Landsteiner, and particularly the wide researches of Krause and Meinicke, who throughout the whole Westphalian epidemic never found any bacteria which could be regarded as playing a part in the etiology of the disease.

All these researches, of great importance but all negative, brought about unanimity of opinion in 1909 that a bacterial cause of Heine-Medin disease does not exist; it was like a voice from the past when Pottpeschnigg in October, 1909, announced the discovery of a coccus with some claims to be considered pathogenic, but he very soon acknowledged that the coccus was merely a contamination.

Important Microscopical Findings.—Although ordinary bacteriological methods were thus proved unavailing it was not thereby made certain that the microscope and culture tubes would not ultimately yield results. As will be demonstrated later, the virus belongs to the variety which is capable of passing through the filters of Berkefeld, Chamberland, and Pukall, which keep back ordinary bacteria. Starting from this fact it was necessary to seek the virus in filtrates which were free from the normal cellular constituents of brain and spinal cord. With Joseph and Siebert I examined such filtrates by means of the ultramicroscope. We found very small, oval, slightly illuminated bodies which were motionless or showed only Brownian movements; they attracted our attention because we did not find them in filtrates of normal brain.

From experience gained in previous ultramicroscopic investigations of proteins we were able to exclude the theory that these bodies were due to coagulation of albumin. On the other hand, the appearance of these bodies was not constant enough to enable us to state that they were connected with the disease, or that they were the actual causative agent. The observation is, however, of importance, because Flexner observed similar bodies at a later date, and his description corresponds very closely with our own observations. Flexner says also that he was able to render these bodies visible by means of Löffler's stain. Levaditi had previously obtained the same result; by means of a "culture" which we shall describe later, he had obtained small rounded bodies which he succeeded in staining by Löffler's method, and also with weak solutions of fuchsin; he expressed himself with regard to the interpretation of his results in the same guarded way as we had done with ours. Leiner and v. Wiesner assert that they have seen "very small oscillating bodies" in a hanging-drop preparation made from virus-containing filtrate. They also state that they are not convinced that the bodies represent the virus itself.

Specific Intracellular Bodies.—In yet another direction the use of microscopic methods seems to give some promise of success. Wickman has drawn the analogy between poliomyelitis and rabies as a result of his excellent pathological investigations. This analogy becomes only more striking the more the nature of the active agent is considered. Negri has called attention to certain intracellular bodies, which are found only in the ganglion cells in hydrophobia, and are characteristic of this disease. There is still much discussion as to whether these bodies are to be considered the cause of the disease, cellular degeneration products, or merely the capsules of the pathogenic agent which is as yet unknown. Wickman looked for similar intracellular appearances in cases of epidemic infantile paralysis, but failed to find them. However, a recent discovery makes it probable that renewed search is justifiable. Joest has shown that Borna's disease in horses, which occurs in epidemics, is a disseminated, infiltrative myelo-encephalitis; this disease is so similar to Heine-Medin disease in its histological appearances—due allowance being made for difference in localization, Borna's disease attacking the olfactory lobe, and Heine-Medin disease the grey matter of the anterior horns—that one might almost regard the two diseases as being identical. Joest with Degen, using Mann's method of staining, demonstrated the presence of intranuclear bodies in the ganglion cells in cases of Borna's disease; the nature of these bodies is not understood as yet, but they appear to be specific to the disease. At a meeting of the Medical Society of Marburg (November 3, 1909) I stated my belief that, in view of Joest's and Degen's results, it would be of value to investigate cases of poliomyelitis using the same methods. In spite of most energetic search, however, Joseph and myself have been unable to find any constant intracellular bodies either in

sections or in smear preparations made from human material, or from the brain and cord of infected apes. Leiner and v. Wiesner, Landsteiner and Levaditi have carried out similar researches, and have arrived at the same negative result.

On the other hand, Bonhoff found bodies included in the nuclei of the glia cells, particularly of the lumbar enlargement, of a case of undoubted poliomyelitis, which bodies he considers specific; they were demonstrated only by using Lentz's modification of Mann's stain applied to sections. The size varied from a very small, red dot to an oval with a diameter of 3 to 4 μ; the average size had a diameter of 2 μ. Occasionally as many as five bodies were found in one nucleus; they were surrounded by a clear zone, and the largest of them showed one or two minute granules which stained clearly with the Mann-Lentz method. Similar bodies were found in the nuclei of cells forming the adventitia of the blood-vessels, of the ependymal cells, and in some nuclei of the round-celled infiltration. In specimens made from the spinal cord in normal cases and in other diseases these bodies were not found. Without going into the question whether these bodies represent one form of the cause of the disease, Bonhoff claims that they are abnormal and characteristic of Heine-Medin disease.

"Cultures" of the Virus.—I said above that attempts to cultivate the virus of Heine-Medin disease might not be without value, even though one might be of the opinion that the cause of the disease was not a bacterium. It is well known that certain trypanosomes, which are classed usually among the animal organisms, can be grown on specially prepared media. I will at once confess that none of my own attempts have yielded the smallest result, even with the media which Flexner and Lewis described later. These authors at first stated that they had obtained no cultures of what could be considered to be a virus of poliomyelitis; later they reported certain "cultures" which they claimed to have obtained. They made an emulsion of an infected spinal cord, filtered this through a Berkefeld filter, and added the filtrate to equal parts of ordinary bouillon and of human serum (in some cases the serum of rabbits was used). After a few days they found some opacity in the tubes; when injected into apes these "cultures" produced the typical picture of experimental poliomyelitis. Levaditi confirmed this experiment, but it proves only that after being kept for a certain time (for fifteen days in Levaditi's case) at a temperature of 37° C. the fluid still contained the active virus of poliomyelitis. The mere fact of virulence does not prove growth of the virus; it may be that the degree of dilution with serum-bouillon was not enough to prevent the activity of the virus, and Flexner and Lewis themselves have proved that it is possible to cause disease and death in apes with much more dilute virus. Flexner and Levaditi state that they obtained a cloudiness in a second series of tubes inoculated from the first, but that from these secondary tubes they were unable to produce the disease in monkeys, so that they themselves are

cautious in their interpretation of the remarkable appearances observed by them. As we ourselves have never been able to see any clear evidences of growth of the virus in any media, and as Leiner and v. Weisner have had the same experience, it may well be wise to doubt whether the cloudiness observed by Flexner and Lewis can be considered as a culture at all, specially as these authors themselves are exceedingly cautious in so describing it. It may be mentioned that the attempts to intensify the virus in collodion capsules *in vivo* by Leiner and v. Wiesner have failed also.

All investigation into the etiology of the disease has shown that the active agent cannot be a bacterium, nor can it be any micro-organism capable of being cultivated easily. We have no evidence which will bear the test of criticism as to the morphological characteristics of the virus.

Experiments on Animals.—The earlier experiments on animals were few, but caused less confusion than the supposedly positive bacteriological results. At a time when it was still doubtful whether the disease was infectious the aim of all experiments on animals was to find out if any materials would produce myelitic lesions in animals comparable to those of Heine-Medin disease in man. The first experiments were carried out on rabbits, a point on which I would lay particular stress. Roger infected fourteen rabbits intravenously with streptococci, and found that in two to three weeks the animals wasted, and showed marked atrophy in the muscles of the hind limbs almost exclusively, but without any definite paralysis. Histologically changes were found in the anterior horn cells; the number of cells was diminished, they were irregular in shape, and showed vacuolation with degeneration of the nuclei in some cases. The vessels were full and enlarged, and in places there were small hæmorrhages. Roger concluded that a more or less systematized myelitis could be caused by an infective agent. In the same year Gilbert and Lion made similar experiments on rabbits, using *B. coli*. In those animals which did not die very shortly paralysis occurred on about the twelfth day and at the same time diarrhœa. In these cases also degeneration of the anterior horn cells and hyperæmia were found. Vincent obtained similar results in a rabbit infected with a mixture of bacteria. Thoinot and Masselin in 1894 carried out the most complete experiments (Hoche gives a complete bibliography). Out of forty-three rabbits infected with *B. coli* four died rapidly. The thirty-nine survivors all suffered from paralysis, generally of the hind limbs, with muscular atrophy and general wasting. Rabbits infected with staphylococci were affected in the same way. Vacuolation of the anterior horn cells was found but *no interstitial change, while the vessels were normal.*

Hoche succeeded in producing changes in the spinal cord by direct arterial infection with pneumococci, staphylococci, and *B. coli* only when at the same time he injected starch or lycopodium

granules or some other powdery material which would produce embolic lesions in the cord. In his case the changes were all of a parenchymatous type affecting only the cells and nerve fibres, the blood vessels being affected only very slightly and the interstitial tissues not at all. Homén also failed to obtain any results; he made very numerous experiments with streptococci, injecting them specially into the lymph spaces and intraneurally. Wickman used strains of bacteria which had been passed repeatedly through animals, but he was forced to admit that no definite palsy occurred in any of his animals, although they wasted considerably; his cases on section also did not show the appearances of true poliomyelitis. We must confess that all these experiments produced very little of value in giving an answer to the question whether the changes of poliomyelitis were due to an infective agent. Judging from the descriptions and illustrations given by the various authors, the microscopical changes observed had very little similarity with those presented by the lesions of true poliomyelitis, in spite of the occasional changes seen in the ganglion cells. The characteristic adventitious and perivascular cell infiltration is absent, as also the increase in the number of nuclei, which is so typical in the sections in cases of Heine-Medin disease. If any comparison with a spontaneous disease is permissible it is with progressive muscular atrophy; this disease, however, is certainly totally different in its etiology to Heine-Medin disease.

Although we cannot lay so much stress on the results of these earlier experiments on animals as was claimed for them at the time, yet they prove one fact very clearly: Bacteria of very different kinds, by whatever route they enter the body, do not tend to produce lesions typical of poliomyelitis. If further proof that bacteria do not cause the disease were needed, the numerous negative results recorded above might be interpreted in that sense.

A further point is that rabbits are peculiarly liable to suffer from paralyses when any molecular substance is injected into the blood-stream. As we shall see later, this observation is of importance when considering the rabbit as an animal for experimental research in poliomyelitis.

The attempts to produce poliomyelitis in animals by injecting material from the organs of cases of Heine-Medin disease will be further considered below.

II.—EXPERIMENTAL RESEARCH ON POLIOMYELITIS IN MONKEYS—CLINICAL HISTORY OF EXPERIMENTAL POLIOMYELITIS.

Landsteiner's Original Experiment.—In the case of successful research with animals there is a definite point where this branch of the subject begins. Landsteiner, with the aid of Popper, has the credit of having for the first time succeeded in transmitting

the disease to monkeys. Landsteiner published his results in full in the *Zeitschrift für Immunitätsforschung* on April 5, 1909.

I give a full abstract of his results owing to their great importance:—

> The material used was the spinal cord of a child of 9 years, who died on the fifth day of an attack of typical Heine-Medin disease. An emulsion was made and this was injected into the peritoneum of two monkeys. The first, a young *Cynocephalus hamadryas*, became seriously ill on the sixth day and died on the eighth. At the autopsy the internal organs were found to be normal with the exception of the spinal cord which was seriously affected. The conditions found were: Infiltration of the pia mater of the cord with cells, perivascular infiltration in the grey matter, diffuse infiltration in the grey matter which was disorganized by œdema; the anterior horns were much more affected than the posterior ones. Similar inflammatory infiltrations were found in the medulla, pons, mid-brain and cortex. The cells of the infiltration were mostly lymphocytes. Where inflammation was present the ganglion cells were much altered, and chiefly in the anterior horns (outline blurred, granular disintegration, vacuolization, nuclei staining poorly, invasion by round cells).
>
> In the second monkey, a young *Macacus rhesus*, between the twelfth and seventeenth day paralysis appeared, which became complete in both lower limbs. The changes found were similar but less marked to those obtaining in the first monkey. The animal was killed on the nineteenth day. Two more monkeys were injected with emulsion of the spinal cord of this monkey, but the experiment was without result.

The description given of the illness of the second monkey and of the histological appearances in both cases, also the illustrations of the histological changes, leave no doubt that Landsteiner and Popper succeeded in producing poliomyelitis in monkeys, which ran a course similar to the disease in man and caused lesions identical from the histological point of view.

The probability that the disease was caused by a living virus was increased by these experiments and would have become a certainty if the attempt to transmit the disease to a further series of monkeys had been successful. As this failed entirely the possibility was not excluded, that the disease might be transmitted by a non-living agent (*e.g.*, a toxin). Landsteiner and Popper reject this theory on the ground that the histological changes had all the characters of an inflammatory process. They explain the failure of the attempt to transmit the disease further by suggesting that the potency of the virus was diminished by its passage through one animal. We may say at once that another and better explanation may be brought forward, namely, that the intraperitoneal route of infection is unsatisfactory and cannot be depended upon to give results. Experiments made by Knöpfelmacher and by Strauss and Huntoon can be explained in the same way; in these instances also monkeys were infected with human virus, but the attempt to inoculate further monkeys failed.

Personal Experiments with Monkeys.—The repeated failures

to transmit the disease from ape to ape indicated that there was some factor in the question which was as yet unknown.

When I began to perform experiments myself, I had, of course, Landsteiner's experience before me; but I took advantage also of Pasteur's work on "Hydrophobia." I have already drawn attention to the analogy which exists between poliomyelitis and rabies. Wickman had shown the close similarity of the histological changes in the two diseases. My own researches had convinced me that poliomyelitis was not caused by bacteria and that the virus, like that of rabies, showed a selective preference for the central nervous system. One of the first points in Pasteur's work was the discovery of a practically certain method of transmitting the disease from animal to animal. Anyone who knows the history of his work knows what a definite advance was made by the discovery of a new and certain technique for infecting the animals. Pasteur used subdural or intracerebral injection of the virus. I chose intracerebral injection into monkeys.

The technique is extremely simple. The monkey is enveloped in a towel; an assistant holds the head; the head is shaved over an area the size of a crown; the operation is performed over the central gyri on one side or the other, and in skilled hands does not require an anæsthetic. An incision not more than 3 mm. long is made through the scalp down to the bone; the skull is perforated with a small bore in a few seconds; a little practice enables one to go through the skull without piercing the dura. The needle of a small syringe filled with the virus is then passed into the hole made by the bore, through the dura and into the brain to a depth of about 1½ cm.; not more than .5 to .6 c.cm. of the emulsion is injected slowly. The needle is rapidly withdrawn, a small plug of gauze is pressed firmly on the wound for a short time and the wound then closed with collodion. The whole operation must be carried out with carefully sterilized instruments.

By means of this intracerebral method I was able at once to produce a disease in monkeys which was clinically and pathologically identical with poliomyelitis in man; I was able also to transmit the disease from one monkey to another. *This proved that the virus which caused the changes in the brain and spinal cord was living and not merely a toxin.* Considering that we and others had proved that it was impossible to cultivate the virus on artificial media, it was of the greatest importance that a means of cultivating it *in vivo* had been discovered. In order that virus and disease could be investigated experimentally, it was essential that some method of cultivating the virus by means of transmission from one animal to another should be available.

I reported my experiments in November, 1909, to the Medical Society of Marburg and published them shortly afterwards in the *Münchener med. Wochenschrift.* I believed at the time that I was the first to succeed in transmitting the disease from one animal to another. However, at the same time, and partly before me, but all during the month of November, 1909, other results

proving the same point were published—Flexner and Lewis, on November 13; Leiner and v. Wiesner, on November 18; and finally Landsteiner and Levaditi, on November 27, 1909.

(a) SOURCE OF THE VIRUS USED IN MY EXPERIMENTS.

The original material was obtained from the brains and spinal cords of patients who died from poliomyelitis during the epidemic of the autumn of 1909 in Hesse-Nassau. To remove all doubt as to the fact that the cause of death was poliomyelitis I append the full clinical and *post-mortem* records of the cases. The clinical notes were written by Professor Dr. Müller, the pathological reports by Professor Dr. Beneke, who have kindly allowed me to make use of them here. They have already appeared in a monograph by Professor Müller.

I.—Julie M., aged 6 years, from Frankfort. History given by Dr. Veupel in Frankfort.

The patient attended school up to the date of her illness. No other source of infection known. On November 3 she became suddenly ill with a high temperature (39·6° C.), listlessness, anorexia, furred tongue, vomiting, and constipation. She had pain in the neck, was restless at first, later drowsy; marked sweats, but no particular tenderness. She complained only of pain in the neck and throat, and when she sat up she asked that her head might be supported. No sphincter trouble.

When examined on the third day the child could not cry (there is no record of other bulbar symptoms), arms normal, marked meteorism, flaccid paralysis of both legs, deep reflexes absent. A short time before death she rolled her eyes and was unable to cry or speak. Death occurred during the evening.

Autopsy on November 6, 1909:—

Development normal; rigor mortis present; moderate cyanosis; marked *post-mortem* staining; fat well developed; muscles dry; muscles of the thigh soft and of a light grey-red colour; calf-muscles dry, dark red-grey colour, firm.

Thorax.—A few drops of fluid in pericardium. Heart-muscle firm, light grey-red colour, no marked degeneration. Lungs engorged; no pleurisy, no local lesions.

Trachea.—Markedly red along whole length; no exudate; marked bronchitis, with much mucus in the larger branches.

Larynx.—Normal.

Tonsils.—On both sides double the normal size, not projecting, light-grey in colour, covered with slight grey inflammatory exudate.

Œsophagus.—*Nil.* Thyroid.—*Nil.*

Abdomen.—Spleen slightly enlarged, soft, friable, dark red-grey, follicles numerous.

Kidneys and suprarenals.—*Nil*, the former are slightly more red than normal.

Genital organs.—*Nil.*

Liver.—Large, soft, dull, red-grey in colour, with many ischæmic subcapsular areas.

Stomach.—Contains partially digested food and some mucus. Mucous membrane rather dull, soft and red.

Intestine.—Normal colour and contents; the follicles in both small and large intestine are increased in size; Peyer's patches are prominent and certainly enlarged.

Cerebrospinal fluid obtained by lumbar puncture was copious, slightly cloudy and colourless. A few drops of fluid in the ventricles of the brain.

Brain and spinal cord.—Moist, soft; the grey matter looks somewhat red. No œdema of the pia; no hæmorrhages; no extradural œdema; no gross local lesion in the anterior horns of the spinal cord grey matter.

Microscopical examination :—

(1) Dorsal spinal cord.—Moderate infiltration of the pia; vessels much engorged. Marked infiltration of the ventral median fissure. Considerable infiltration of anterior horns; posterior horns affected to a less degree. Ganglion cells seen only in Clarke's column. In all sections the white matter shows perivascular infiltration; a similar condition found in the cervical cord. In many places the limits of the infiltration mark off the grey from the white matter in a very striking way.

(2) Medulla oblongata.—Slight infiltration of the pia; marked perivascular infiltration around the larger vessels; much scattered infiltration, here and there clearly affecting the region of ganglion cells. Olives practically unaffected. Marked enlargement of perivascular lymphatics.

(3) (*a*) Brain.—In the neighbourhood of the great ganglia some perivascular infiltration; here and there some subependymal infiltration, in places almost forming abscesses, which is not connected with ganglion cells.

(*b*) Cortex.—Pia not affected; slight œdema of the vessel sheaths; no infiltration.

Pathological diagnosis.—Poliomyelitis spin. cerebral; tonsillitis; rhinitis post.; tumour lien.; hypertroph. follicul. intest.

From Professor Beneke I received portions of the pons and of the lumbar cord; of each of these a piece the size of a pea was emulsified in 8 c.cm. of the cerebrospinal fluid of the case. A monkey weighing 1,970 gm. (mangabey monkey, No. 1) was given an intracerebral injection of this emulsion. The monkey died on the eighth day after showing signs of paralysis (for details *vide infra*). An emulsion of the spinal cord was injected into a second monkey intracerebrally (mangabey, No. 2). This animal became ill on the tenth day, and died on the eleventh.

The virus thus obtained will be called p.m. virus No. 6.

II.—Karl Schn., aged 2¾ years, from Marburg. No family history of nervous disease. Parents and brothers and sisters remained well during the patient's illness. The child had suffered from a club-foot, which had been operated upon previously, and from furunculosis following vaccination, otherwise well. He attended an infant school where he came in contact with children from the suburb Weidenhausen, which was an affected area. A few weeks ago the mother met a woman with her child who had suffered from an attack of poliomyelitis some months previously. The father is a shoemaker with an open shop, says that recently he has not worked for families in which there was any poliomyelitis, that he has not had any visits from or paid visits in any infected area.

The child became ill on November 22 with a high temperature and rigor; much wandering and restlessness; sleepless, occasional jerking of the limbs and starting up in bed.

The mother reports that sweating was profuse. The child complained that he "could not move" when he was lifted up, cried a great deal when put on the chamber. On November 23 very little urine was passed, and the child was unable to stand or walk alone, fell when he was put on his feet, and "was quite slack like an idiot."

Examination on November 24.—Very pale, apathetic. Cranial nerves not affected. Slight bronchitis, pulse-rate increased. The body is remarkably flaccid; the child cannot sit up; epigastric reflexes only just obtained. Movements of the upper limbs are good; marked fine tremor of the hands even when at rest. Child cannot stand or walk; falls down when put on his feet. On the right side club-foot which has been operated upon. Deep reflexes are still present on both sides; plantar reflex present. All movement or touching of the legs causes pain. Leucopenia is present.

November 25.—High temperature (39·5° C.). Great restlessness and general collapse. Very pale; apathetic; alæ nasi move with respiration; no herpes; no membrane on the throat; no marked swelling of the glands of the neck. Resonance diminished at the left base with bronchial breathing, vocal resonance present; marked general bronchitis with dyspnœa, although intercostals do not act and respiration seems to be entirely diaphragmatic. Abdomen soft; some tympanites; abdominal reflexes absent. The muscles of the limbs are generally hypotonic; there is no definite localized paralysis; the deep reflexes are present but diminished. Lumbar puncture: copious clear sterile fluid, showing a few lymphocytes on centrifugalization. Death occurred in the evening; the child was conscious, but unable to cry up to the last.

Autopsy on November 29:—

Well-built child, aged 2¾ years; pale; moderate degree of club-foot; slight rickets; muscles soft.

Thorax (opened from behind).—Heart strong and not obviously degenerate. Upper lobe of left lung slight emphysema; lower lobe grey-red in colour, pneumonic; bronchi contain some pus and mucus; right lung normal.

Spleen normal in size, moist. Kidneys normal in size and shape, microscopic examination normal. Blood taken from the left pulmonary vein contains *Diplococcus lanceolatus*, but in addition a considerable number of organisms of the nature of spirochætes, staining feebly with Löffler and showing feeble movements; some have granules like streptococci; also a few grey oval bodies showing extremely active karyokinesis. The leucocytes do not show karyokinesis; it is confined to these large cells which, on the other hand, contain no fat globules. Red blood-cells normal. In the bronchial secretion exclusively Fränkel's diplococcus was found. Blood from spleen, heart and spinal cord contained no bodies like spirochætes or like the oval bodies described above.

The capillaries of the lung where it is not inflamed contain many polymorphonuclear leucocytes. In the inflamed parts there is rather an absence of leucocytes. In the larger arteries and veins of the lungs the blood contains mainly lymphocytes, leucocytes being rare. The pneumonic infiltration contains many leucocytes, the exudate being serous rather than suppurative.

Heart.—The musculature shows no abnormality; there is no infiltration.

Spleen.—Follicles markedly enlarged; the central portion is large with many degenerate nuclei; the periphery is comparatively free from degeneration. Many follicles are composed almost completely of germinal areas with practically no peripheral portion. Spleen pulp hyperæmic, generally disintegrated and poor in cells.

Kidneys.—Slight signs of irritation in the convoluted tubules; no other pathological appearances.

The dura contains a small amount of fluid. Spinal cord firm, white matter normal, grey matter everywhere red.

Dorsal region of the cord.—Slight infiltration of the pia; infiltration more marked around the vessels in the anterior longitudinal bundle, most marked in the vessels of the anterior horns and in the anterior portion of the lateral tracts. Central canal normal. Diffuse infiltration of both anterior horns, they are small and show only traces of the ganglion cells. Definite œdema. Clarke's column quite unaffected, ganglion cells normal. In the white matter some local lesions. Ganglion cells are found practically not at all throughout the anterior horns. Occasionally a normal ganglion cell is seen.

Pathological diagnosis.—Poliomyelitis acuta; pneum. lob. inf. pulm. sin.; bronchitis purulenta.

From the lumbar cord a 5 per cent. emulsion was made in normal saline and injected on the same day into the brain of a *Macacus rhesus* (No. 4). The amount used was ·3 c.cm. The monkey remained well; on December 2 and 3 it seemed to us that he did not care about using his right fore limb, but this weakness gradually disappeared. It is possible that this was one of the abortive cases which are seen in man frequently.

Thus it was not possible to transmit the disease from this case of undoubted poliomyelitis to a monkey in a manner which was devoid of doubt. The question whether we should have succeeded if we had used more monkeys cannot be discussed. The fault did not lie with the animal (No. 4), because at a later date, and with a different virus, it died rapidly with paralysis. One point may be mentioned: that the lumbar cord was not examined microscopically as the dorsal cord had been.

III.—Karl D., aged 2¾ years, from Arfurt. Report from Dr. Hartmann, of Villmar a. d. Lahn. Nothing known of method of infection. No illness in the family or neighbourhood; no mortality among animals. The family had not left their premises during the last few weeks, nor had they had visitors. The nearest place where cases of poliomyelitis have occurred recently is two kilometres distant.

The child became ill on November 29. Fever, lassitude, one attack of vomiting. Cough and restlessness; no sweats or hyperæsthesia. On the fourth day palsy of the neck and left arm; no affection of the bulb or cranial nerves. On the next day the right arm and leg were attacked. The muscles of both legs were flaccid and the deep reflexes absent. Death on the sixth day (December 2).

Autopsy on December 4, 1909:—

Well-developed child; cyanosis slight; fat well developed; muscles soft, rather pale.

Heart and lungs.—Normal.

Spleen very large, tense, dark black red in colour, firm and dry.

Kidneys and liver dull, engorged, otherwise normal.

Intestines.—Marked hypertrophy of the follicles.

Mucous membrane of the stomach smooth, fairly thick, very red, covered with thick layer of pus and mucus.

Organs of the throat normal.

Tonsils and glands in the neck small, pale.

Pancreas.—Normal.

Peridural fat normal. Spinal cord soft. Sections show definite red discoloration of the grey matter, which is shrunk and softened. White matter is bulky and moist.

Dura is tense. Pia not œdematous, markedly red, the whole brain is of a diffuse red colour.

Microscopical examination :—

(1) Dorsal region.—No infiltration of the pia. Little infiltration in the anterior longitudinal fissure; rather more in the anterior horns and adjacent white matter. Central canal in places infiltrated with small round cells; anterior horns small, cells almost absent; a diffuse patchy infiltration with mononuclear and polymorphonuclear cells. Clarke's column unaffected; no other infiltration.

(2) Cervical region.—Widespread, well-marked infiltration of the anterior horns; in places a few ganglion cells remain. Moderate hyperæmia, slight œdema, marked infiltration of the vessel sheaths. In the rest of the cord only a slight diffuse cell infiltration.

(3) Medulla oblongata.—Ependyma raised slightly by œdema; marked perivascular infiltration in the subependymal region and round the larger vessels. A diffuse fairly well-marked cell infiltration not directly related to any particular cell group. Olives and ventral part of sections unaffected.

(4) Pons.—Slight infiltration round larger vessels; a few local lesions found in pons and in cerebellar peduncles. Cerebellar convolutions normal. The large cell nuclei of the pons are remarkably free from disease, which is most marked around the aqueduct and the larger vessels in this region. Ventral portion unaffected.

(5) Thalamic region.—Marked linear infiltration round the vessels. Ganglion cells in the neighbourhood of the infiltration are destroyed; other areas of ganglion cells unaffected.

(6) Cerebral cortex.—Only a few scattered cells in the pia; perivascular lymph spaces much enlarged; no definite infiltration.

(7) Hippocampus.—Relatively large, in places marked, vascular infiltration, also general diffuse infiltration.

Pathological diagnosis.—Poliomyelitis acuta; enlargement of the spleen; acute gastritis; renal and hepatic degeneration.

A 5 per cent. emulsion was made from the lumbar cord and injected as follows :—

The monkey No. 8 (*Cercopithecus ruber*) received an intracerebral injection of ·4 c.cm.; it remained well until December 15, 1909; on the 16th it became weak in the hind-limbs, there was tremor of the head, and the monkey was depressed. On the 17th general condition improved, but the paresis of the hind-limbs was more marked. The paresis began to improve on the 18th and disappeared by the 21st (? abortive poliomyelitis).

Monkey No. 9 (*Cercopithecus fuliginosus*) was given 1 c.cm. subcutaneously, and remained healthy. It was observed until February 15, 1910.

Monkey No. 10 (*Cercopithecus fuliginosus*) had ·2 c.cm. injected direct into the left sciatic nerve, and remained entirely healthy up to January 15, 1910.

Monkey No. 6 (*Macacus rhesus*) received ·8 c.c. of a 2·5 per cent. solution which had passed through a Berkefeld filter, injected into the brain. It remained quite well (observed until January 5, 1910).

No success therefore attended the attempts to transfer the disease to monkeys by means of the virus of Case III.

IV.—Wilhelm P., of Weifenbach, near Biedenkopf, aged 9 months. Admitted to hospital on December 6, 1909. The first case of the disease in that village. Parents and three brothers and sisters quite well both before and during patient's illness. On November 27 the child had a boil on the neck, which disappeared without medical treatment. The child is still being suckled and has had no illness. The father is a telegraph official, and has to go about all over the district. No other possible source of infection is known.

Onset of the disease occurred on December 2; high fever, vomiting, anorexia, somnolent during the day and wakeful at night. Diarrhœa. On the following night convulsions, the eyes being rolled and the face drawn to the right side. No stiffness of the neck. General tenderness: the child objects when it is touched, though it is unable to cry. Marked sweating, particularly of the head. Incontinence of urine.

Examination on December 5.—Eyes normal; mouth drawn over to the right; swallowing difficult; bronchitis; other organs normal; abdomen soft; abdominal reflexes absent; cremasteric reflexes absent.

Hypotonia of all extremities; both arms and legs paralysed. Deep reflexes all absent.

Lumbar puncture.—12 c.c. of clear, sterile fluid under considerable pressure. Centrifugalized showed a few lymphocytes.

December 6.—No improvement; passing much mucus; much dyspnœa; during the night suffocative attacks requiring artificial respiration.

December 7.—Pulse fair; respiration diaphragmatic. Heart improved after a second lumbar puncture. During the evening collapse and death from respiratory failure.

Autopsy on December 7.

Well-developed child; marked *post-mortem* staining. Rigor mortis fairly well marked; scars of punctures in the back. Muscles of the back dry and soft.

Extradural connective tissue œdematous.

Abdominal organs normal.

Spleen small, rather shrivelled, but full of blood. Thymus large; clear fluid in pericardium; heart full of clots, firm and dark-red musculature. No demonstrable degeneration. Left lung very hyperæmic, more so in lower lobe, soft, contains air. Some mucus in bronchi; mucous membrane pale. Right lung almost entirely collapsed; bronchi do not contain much mucus; the mucous membrane is pale.

Parotid gland normal. Glands in neck normal. Tonsils small; no sign of inflammation; base of tongue and mouth the same.

Larynx and trachea normal. Thyroid normal. Upper portion of pharynx somewhat swollen; nasal mucous membrane slightly red and covered with pus. Inferior turbinate much swollen with mucopurulent catarrh above. The upper portion of the nasal cavity, together with the septum, show only slight redness of the mucous membrane.

Intestines are distended with gas; in the lower part a *post-mortem*

invagination. Lymph nodules remarkably enlarged, containing many malformed nuclei. The larger lymphatics in many places distended with lymphocytes.

Appendix.—Shows condition similar to that of ileum; much lymphoid tissue; lymphatics distended with lymphocytes; many wander cells in the lymph nodules.

Adrenals are small and pale; kidneys deep red-grey in colour, full of blood, no obvious degeneration.

Liver small; on section rather dull and dry; microscopical interstitial infiltration; some apparent increase in wander cells, which here also tend to form rows of cells; no abscess formation.

Microscopical examination :—

Lymphatic glands.—Germ centres much developed, with extraordinary number of malformed and degenerate nuclei of wander cells. Lymph channels packed with lymphocytes.

Thymus.—Hyperæmic, but not otherwise abnormal.

Spleen.—The germ centres of the follicles are large, and contain many malformed nuclei. Many follicles contain only germ centres. Pulp relatively poor in cells.

Testis.—Normal; no infiltration. Epididymis the same. Blood-vessels normal.

Bone-marrow (from vertebræ).—Structure very dense, full of cells; hypertrophied. Fairly numerous leucocytes; a few giant cells.

The middle part of the spinal cord removed for bacteriological purposes. The rest shows marked redness and softness of the grey matter, the white matter being of a relatively firm consistency. Considerable subdural hæmorrhages in the form of flat, soft coagula. Pia very hyperæmic in the region of the right anterior vein. The ventricles appear empty. Œdema of the extradural connective tissue. The brain firm and moist. Cerebral cortex rose-coloured; marked venous hyperæmia in cortex, white matter and large ganglia; no œdema of the pia. The base of the brain, particularly the medulla, is very red. Sections through the pons and cerebellar peduncles show moderate hyperæmia. Consistency of the medulla practically normal; the colour of the grey matter is normal.

Cerebrum.—In the region of the uncinate gyrus, both in the cortex and the white matter, many separate wander cells of various shapes. The pial vessels are filled in places with leucocytes, which almost constitute a thrombus. No abscess.

Convexity.—Moderate infiltration of the pia; slight œdema of the perivascular lymph spaces; everywhere degenerate wander cell nuclei; no well-defined lesion or marked infiltration.

Pes hippocampi.—Everywhere wander cells and small infiltrations, chiefly subependymal; vessels hyperæmic; many leucocytes sometimes causing a thrombus; a similar condition in a few instances in the veins of the choroid plexus.

Microscopical examination of the cord and brain stem :—

Lumbar region.—Marked infiltration of the vessel sheaths. Considerable cell infiltration in the anterior longitudinal fissure. Anterior horns on both sides show great infiltration and œdema of the vessel sheaths, with wander cells of various shapes. A few ganglion cells are present; these do not appear changed. In the rest of the section only a slight perivascular infiltration. Nerve roots normal.

Dorsal region.—Infiltration is less in degree, but similar in distribution. Anterior horn cells are in many cases atrophic, but are not invaded by leucocytes.

Cervical region.—Similar to lumbar region. Hyperæmia well marked; much œdema and infiltration of the anterior horns. The wander cells have nuclei of a remarkably long, thread-like shape.

Medulla oblongata.—Much perivascular infiltration in the region of the ependyma; also some diffuse infiltration in that region. A few wander cells present all over the section, also in the olives, of an elongated shape and fairly numerous.

Pons.—Considerable pial infiltration at the base where the vessels contain a large number of leucocytes. A fair number of long-shaped wander cells. Near the aqueduct both infiltrations and wander cells are more numerous; the infiltration is in the form of local collections of cells, the ganglion cells in the neighbourhood being quite well preserved.

Pathological diagnosis.—Acute poliomyelitis; collapse of the lung; follicular catarrh of the intestines.

Five per cent. emulsions were made from the lumbar cord, the dorsal cord and the brain in the region of the basal ganglia. They were used for inoculation in the following manner:—

Monkeys (*a*) and (*b*) (both *Cercopithecus fuliginosus*) received an intracerebral injection of ·5 c.c. on December 7, 1909. Monkey (*a*) became ill on the 14th and died on the 15th. Monkey (*b*) sickened on the 15th and died, typically paralysed, on the 16th.

·5 c.c. of a 1 in 10 dilution of the original emulsion was injected intracerebrally into monkey No. 11 (*Macacus rhesus*). Paralysis set in on December 20, 1909, and death occurred on January 11, 1910.

The virus obtained from Case IV is referred to as virus No. 11, and was made the basis of many further injections into monkeys.

V.—Heinrich R., aged 3, from Schweinsberg. Parents and other children well both before and during illness of patient. Child at school up to date of illness. No other possible source of infection known.

December 11.—Fever, headache, anorexia, vomiting. Sleep restless, much crying out and tossing in bed. Head retracted; spine held stiff. When taken hold of child complained much of pain. No respiratory or intestinal trouble; no sweats.

December 12.—Examination at the medical clinic. Remarkable dermographia over the whole body. Eyes and cranial nerves normal. Difficulty in swallowing; mouth clear. Head and spine held rigid; abdomen soft. Possibly some paresis of the right shoulder muscles; left upper and both lower limbs normal. Deep reflexes and plantar reflexes present. Kernig's sign positive.

December 13.—Much headache; rigidity of head and spine more marked. At noon, sudden attack of dyspnœa, with failure of pulse and cyanosis. The head fell limply to the right side. Towards evening tracheal râles. Paralysis of muscles of respiration. X-ray examination showed that only the left half of the diaphragm was still acting. Oxygen improved the pulse. Later respiration became more embarrassed. Deep reflexes abolished in all limbs. Epigastric reflexes present. Death from respiratory paralysis. Lumbar puncture and brain puncture had proved useless.

December 14.—Autopsy.

Well-developed child; fat abundant; muscles well-developed; skin pale. No degeneration in the muscles.

Lungs.—Pleura clear. Many large areas of collapse in both lungs. Much frothy, yellow-brown mucus in the bronchi. Very slight redness of mucous membrane. Pharynx, larynx, and trachea normal. Spleen moderate in size, tense, firm, dark red. Liver small, soft, contains fair amount of blood, rather dull. Adrenals small, elongated, and soft. Kidneys engorged, otherwise normal. Stomach contains much thick yellow-brown mucus, with many black thread-like clots. Many small hæmorrhages in the mucosa, which is red. All lymphatic tissue in the intestinal tract is swollen; mucous membrane red in places. Pancreas and urogenital tract normal. The spinal cord was removed whole.

On section the grey matter was distinctly more red than normal. The white matter moist and swollen. Over the brain the dura was tense. Over the right parietal region a superficial hæmorrhage about the size of a five-shilling piece. The whole brain engorged; the white matter universally rose-coloured. Ventricles empty; not enlarged. The pons definitely hyperæmic.

Microscopical examination :—

Medulla.—Slight, definite perivascular infiltration of the subependymal vessels. In the substance of the medulla many disseminated infiltrations with elongated and degenerate cell nuclei. Some of these infiltrations are of considerable size.

Ganglion cells which are implicated in these infiltrations show degeneration, and are attacked by leucocytes. In the region of the olives, and generally in the deepest parts of the sections, no infiltration.

Pons.—The basal pia shows cell proliferation; no perivascular infiltration in the pia, but much in the region of the iter and fourth ventricle, both perivascular and diffuse. Wander cells are few except in the infiltrated parts.

Cerebellum.—Pia almost unaffected; here and there small infiltrations; cortex and medulla free of inflammation.

Ganglia of mid-brain.—Some slight subependymal œdema; some indications of perivascular infiltration; in places a suggestion of local infiltration.

Spleen.—Well-developed follicles with large germ centres. In these markedly malformed, elongated, and degenerate nuclei, but no definite necrosis. Here and there slight hyaline degeneration.

Pathological diagnosis.—Acute poliomyelitis; collapsed lung; acute gastritis; follicular catarrh of the intestines.

A 20 per cent. emulsion was made from about equal portions of the brain stem, the medulla oblongata, and the dorsal region of the cord. Monkeys Nos. 13 and 14 received ·5 c.c. intracerebrally, and at the same time 3 c.c. into the peritoneum. No. 13 became paralysed on December 26, and died on January 5; No. 4 was paralysed by December 23, and died on December 24. On histological examination typical poliomyelitis was found in both cases. The virus obtained from Case V will be called Virus No. 12; it was passed through many animals.

The Susceptibility of Monkeys to the Virus of Poliomyelitis.—We succeeded in transmitting the disease to monkeys in three out of five human cases; we were able to transmit the disease to other monkeys in these cases. In two cases the disease could not be transmitted. I can give no satisfactory reason why this was the case. I consider

that the possibility has not been excluded, that the parts of the cord selected were affected but slightly by the disease, and consequently contained only a small amount of virus. One result of the experiments is that in any single case of poliomyelitis it is advisable to inoculate several monkeys either intracerebrally only or together with an intraperitoneal injection. It is not justifiable to draw the conclusion that it is possible to infect only three-fifths of all monkeys. For such a purpose a much larger number of animals would have to be used. In that case I believe that a much larger percentage of animals would be found to be susceptible to the disease, considering that at the time we made our experiments our knowledge of the technique of inoculation was in its infancy. At the same time Leiner and v. Wiesner have reported lately that out of six cases they were able to infect monkeys in only three.

The figures of re-inoculation from monkey to monkey are quite different. Taking all the experiments together, in which sufficient doses of virus were given to unaffected monkeys by cerebral injection, the results are as follows: Out of forty-two monkeys thirty-eight became paralysed, of which the greater number died; in two animals the symptoms were doubtful, and two remained quite well. If the doubtful cases are added to those which remained well the resulting figure is 9.8 per cent. of failures; in 90.2 per cent. therefore, infection followed at once. I may mention that in the cases in which the virus was injected into both brain and peritoneum, the number of successes was 100 per cent. My figures correspond very closely with those obtained by Flexner and Lewis: Eighty-three monkeys received an intracerebral inoculation; of these seventy-seven became markedly paralysed, two slightly paralysed, while four remained well, *i.e.*, 95 per cent. of successes. Landsteiner and Levaditi had 95 per cent., Leiner and v. Wiesner 85 per cent. of positive results. The latter authors found intraneural injection to be as successful as intracerebral.

I used *Cercopithecus fuliginosus*, *C. ruber*, *Macacus rhesus*, *M. cynomolgus*, and in one instance a Tota monkey. Flexner and Lewis found that *M. nemestrinus*, *C. callitrichus*, and *Papio babium* were susceptible; Landsteiner and Levaditi the chimpanzee, *M. sinicus*, and the mandrill. Flexner and Lewis found that the monkeys of the New World were not so susceptible as those of the Old. It is of interest to note that phylogenetically the monkeys of the New World are less closely related to man. Liener and v. Wiesner found that young monkeys were more susceptible to the disease than old ones.

(b) THE CLINICAL HISTORY OF POLIOMYELITIS IN MONKEYS.

Period of Incubation.—I have personal experience only of cases which were caused by intracerebral inoculation or simultaneous intracerebral and intraperitoneal inoculation. The duration of the incubation period varied from three and a half days to fifteen days,

an average of nine and a half days. Other authors record a similar average figure. The shortest period observed by Landsteiner and Levaditi was four days, the longest twenty. Flexner and Lewis state that out of eighty-one monkeys eighteen were paralysed before the eighth day, and sixteen after the twelfth day; the longest period which they observed was thirty-three days; the majority of the animals became ill between the eighth and twelfth days. Leiner and v. Weisner even record a period of forty-six days in one case, in which the virus had been passed through a Riechel filter.

The amount of virus used seems to have some effect upon the length of the incubation period. All the above writers report that whenever the virus was passed though a filter capable of holding back all bacteria the incubation period was longer. It is probable that the filter keeps back some of the virus, and that, in effect, a smaller dose of virus is administered. Leiner and v. Wiesner report a case in which the spinal cord emulsion was first centrifugalized, then repeatedly passed through filters of paper and wadding; the period of incubation with the filtered virus was twenty-seven days, while in a control in which unfiltered virus was used the period as only seven days. Flexner and Lewis have observed that when the virus is administered by any other way than by intracerebral injection (*e.g.*, subcutaneously or into the peritoneum) the period is longer; likewise when other organs than the brain and spinal cord are used for making the emulsion. Leiner and v. Wiesner record an incubation period of twenty-three days in a monkey which had been given the virus by mouth. I myself gave intracerebral injections of the concentrated emulsion to two monkeys, one-tenth of the dose to a third, and one-hundredth of the dose to a fourth; the first two became ill on the seventh day and died on the eighth, the third sickened on the twelfth and died on the thirtieth day, while the fourth monkey remained well. Leiner and v. Wiesner showed that it is true only up to a certain point that an increased dose shortens the period of incubation and increases the severity of the attack; when a certain point had been reached they found that increasing the dose made the incubation longer and the attack less severe. They believe that the central nervous system contains a substance antagonistic to the virus (as is known to be the case in rabies), although they have not succeeded in demonstrating its presence in monkeys.

Prodromal Symptoms.—Sometimes, but not constantly, certain indefinite symptoms precede the paralysis. The monkeys are less merry; they are tired, do not climb about so much; their expression becomes discontented and surly; sometimes they seem to age, their eyes become dull. Occasionally there is a tremor of the whole body, particularly of the head. Fairly frequently gastro-intestinal symptoms appear, anorexia, diarrhœa, and sometimes vomiting. I have observed, however, that the gastro-intestinal symptoms occur more commonly later when paralysis is beginning. The temperature did not show any characteristic changes; in most cases our animals

were wild, and the chase necessary to capture them caused a considerable rise in temperature. In the case of three tame animals a reliable record could be obtained; all these suffered from typical poliomyelitis ending in death, and I give the temperature charts in figs. 6 to 8. Monkey No. 4 shows a considerable rise of temperature two days before any paralysis was apparent; on the first day of paralysis the temperature remained raised, and only became subnormal on the second day shortly before death. In monkeys Nos. 13 and 14 the temperature was apparently not affected by the disease. The shaded areas in the figures represent the degree of paralysis. Leiner and v. Wiesner, also Flexner and Lewis, could

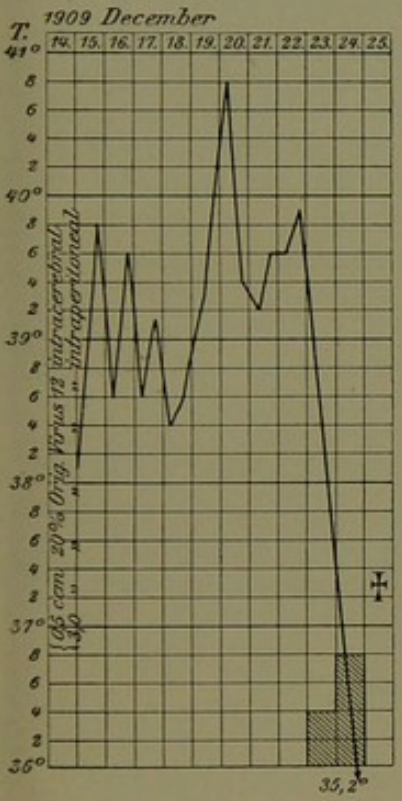


FIG. 6.
Monkey No. 4.

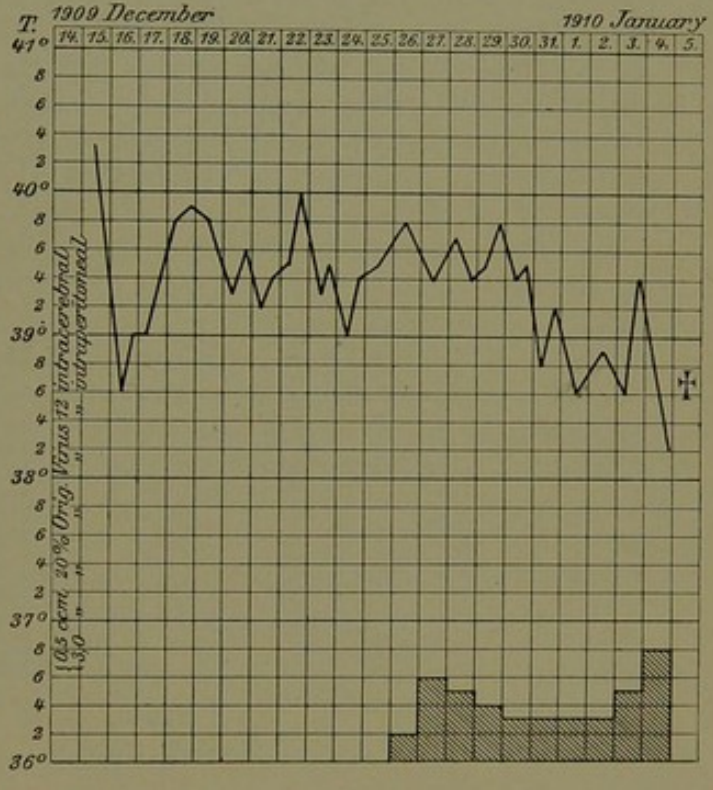


FIG. 7.
Monkey No. 13.

not find any typical change in temperature during the prodromal stage.

Stage of Paralysis.—This stage frequently begins suddenly without any warning symptoms. Monkeys which in the evening were seen to be quite lively were found paralysed in one or more limbs on the following morning; even during the day in the course of a single hour a monkey became severely paralysed. The clinical course varied very much in different animals. The several types of paralysis, together with the examples on which they are based, will be described below. Of great interest and importance from the point of view of the pathogenesis of the disease is the fact that, although

the monkeys were infected in the brain, the paralysis is in almost all cases of the spinal type, flaccid and with consequent atrophy, while the paralysis affects the limbs first of all; further, the lower limbs are affected more often and more severely than the upper. The type of paralysis which is most common in man is most common in monkeys. There is therefore a close analogy between the disease artificially produced in monkeys and that occurring naturally in man, although the point of entrance of the virus is undoubtedly different in the two cases.

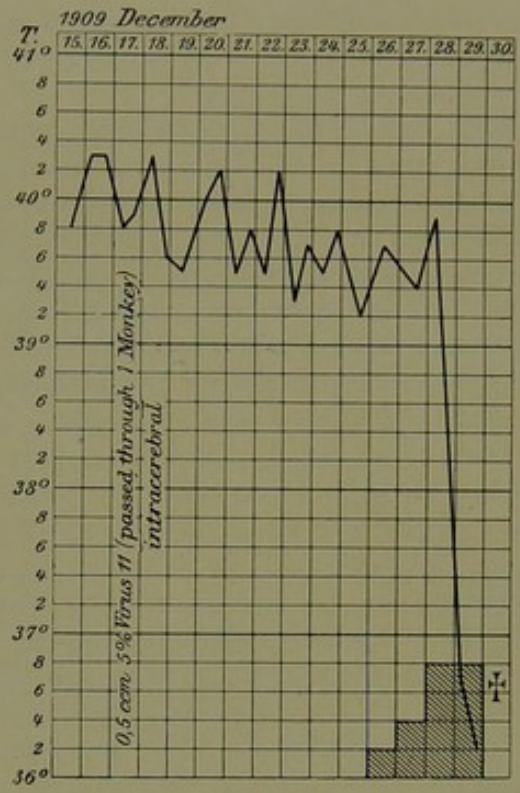


FIG 8.
Monkey No. 14.

(a) Poliomyelitis acutissima.—After intracerebral infection the course of the disease may be so rapid that one can hardly speak of a paralytic stage. The following are two such cases:—

Monkey No. 45 (*Macacus rhesus*) was injected on April 7, 1910, with ·5 c.c. of emulsion of virus No. 6, and at the same time with 4 c.c. of the same intraperitoneally.

At 10 o'clock on the evening of the 13th eyes dim; climbs about in a tired way, but with complete control of all limbs.

At 7 a.m. on the 14th found dead in the cage.

On histological examination, typical changes in cord and medulla.

Monkey No. 1 (*Cercopithecus fuliginosus*), intracerebral injection with ·5 c.c. of virus No. 6 on September 6, 1909.

September 7-12.—No change.

September 13.—Languid and sad; no paresis visible. At 11 p.m. I

happened to be at the laboratory, and observed a slight paresis of the left fore limb; the animal still used the limb, but it gave way under him, and there was less resistance to passive movements. The tone of the muscles appeared diminished.

September 14.—The monkey lies on the floor apparently completely paralysed in all limbs. The mind is clear; with the eyes he follows movements of objects. The neck muscles appear unaffected. On trying to place him on his feet he collapses at once. Death occurred in the evening. The *post mortem* revealed very typical poliomyelitis.

In both these animals (Nos. 45 and 1) the form of the disease was so acute and atypical that it would have been difficult to be certain that death was due to infection with poliomyelitis if it were not for the microscopical examination and the results of inoculating the virus into fresh animals. In the most severe cases, where all four limbs are affected together and suddenly, it is difficult to determine whether the animal is suffering merely from extreme general weakness due to a severe infectious disease or from an actual paralysis due to a lesion in the spinal cord. Leiner and v. Wiesner also record a case in which death occurred without any preliminary paralysis on the sixth day after infection; in this case the cause of death was proved to be true poliomyelitis by means of microscopical examination. Flexner and Lewis also report a case of experimental poliomyelitis in a monkey in which death occurred a few hours after the onset of paralysis. Such cases remind one of Landry's disease in man; Wickman finds that the great majority of cases of Landry's disease are merely examples of a particular type of Heine-Medin disease.

(b) Poliomyelitis acuta.—In other cases death does not occur so rapidly, but still more quickly than in the majority of human cases. An example is the following:—

Monkey No. 2 (*Cercopithecus fuliginosus*).—On November 17, 1909, received an intracerebral injection of ·4 c.c. of an emulsion made from virus No. 6.

November 17-26.—Remained well.

November 27.—Depressed; remains huddled on the floor of his cage. No apparent paralysis.

November 28.—Marked flaccid palsy of both hind limbs; moderate degree of flaccid palsy of fore limbs; the hind limbs can still be moved with the help of the fore limbs; movements of the tail still powerful; the muscles of the back seem to be affected. No cranial nerve lesions. Death during the night of November 28.

The histological findings were very typical.

(c) Typical Spinal Paralysis.—Other cases are quite comparable to those in man, which develop gradually, show wide spread of the paralysis, and end in death within a few days. Examples are:—

Monkey No. 29 (*Macacus rhesus*) received an intracerebral injection on February 7, 1910, ·35 c.c. of virus No. 12, filtered through paper and mixed with ·35 c.c. of the serum of a healthy monkey.

February 8-14.—Remained well.

February 15.—When walking in the evening spares the right hind limb.

February 16.—Both hind limbs almost entirely paralysed; upper limbs appear quite unaffected. The monkey moves forwards by means of the arms and drags the flaccid hind limbs.

February 17.—Total flaccid palsy of the hind limbs.

February 18, a.m., *in statu quo ante;* p.m., the resistance of the right fore limb is less on passive movement; the limb frequently gives way under the animal. Much diarrhœa.

February 19.—Condition unchanged.

February 20.—*In statu quo.* Diarrhœa has ceased.

February 21.—The fore limbs are now completely paralysed; the monkey lies quite flaccid on the ground; apparently the muscles of the neck are paralysed, as the chin also lies on the ground; there is no resistance to passive movement of the head, and it drops on to the ground when one lets go of it. No lesion of the cerebral nerves.

February 22.—Death.

Histological examination shows typical poliomyelitis, mainly in the lumbar cord and the medulla.

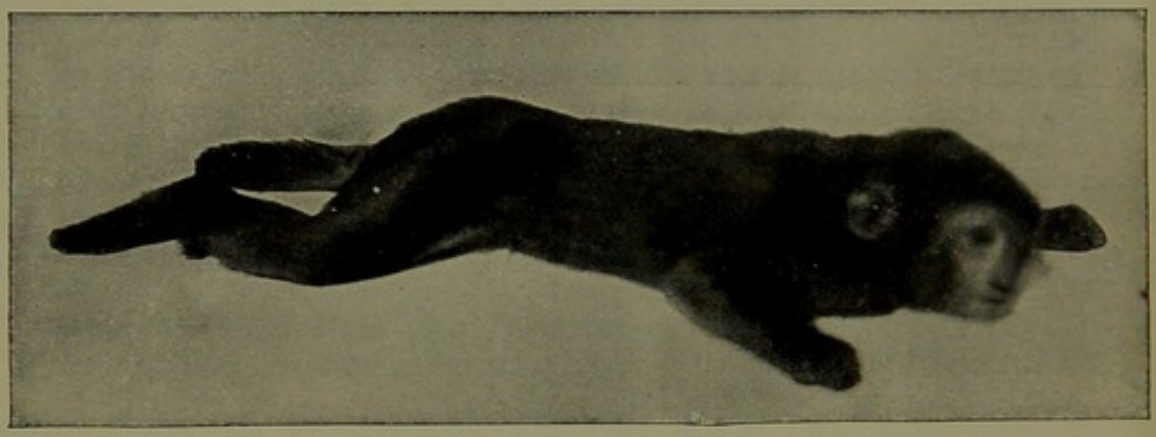


FIG. 9.
Monkey No. 14.

Monkey No. 14 (*Macacus rhesus*), intracerebral injection of ·5 c.c. of virus No. 11 emulsion on December 17, 1909.

December 18-25.—No signs of illness.

December 26.—Slight weakness of the hind limbs, which often give way under the animal and cause it to fall to one side. Otherwise they can be used quite well. The resistance of the hind limbs seems less than normal.

December 27.—Almost total flaccid palsy of the hind limbs.

December 28.—Fore limbs now markedly paralysed. Resistance to passive movements still quite good in the fore limbs.

December 29.—Total flaccid palsy of all limbs. Cranial nerves not affected; compare the photograph above, which was taken on this day.

December 30.—Death at 2 p.m.

Microscopic appearances in the cord are typical.

Monkey No. 46 (*Macacus rhesus*), intracerebral injection of ·5 c.c. and intraperitoneal injection of 4 c.c. of an emulsion of virus No. 11 on April 7, 1910.

April 8-16.—No apparent disturbance.

April 17.—Marked flaccid palsy of the right hind limb. Much diarrhœa. In the afternoon total paralysis of the right and possibly a slight palsy of the left hind limb.

April 18.—In the morning total paralysis of both hind limbs. The monkey can move only by means of the fore limbs. On attempting to climb he pulls himself up by his fore limbs, but is unable to use his hind limbs. In the evening found crouching on the floor of his cage. Marked palsy of the right upper limb. Can no longer climb at all; the animal cannot even climb over the threshold of the cage, which is only 15 cm. high. He can still seize and grasp an apple with the left hand.

April 19.—Condition *in statu quo*. Slight palsy of left arm.

April 20.—Total flaccid palsy of all extremities.

April 21.—Moribund. Death during the afternoon.

Histological examination.—Very typical changes of poliomyelitis in the spinal cord.

(d) Bulbar and Cerebral Forms.—The preceding types are the most common in monkeys; they are spinal only in so far as clinical observation is concerned, as the microscopical appearances always show more widespread disease than one would expect from the clinical signs. In most of my cases the paralysis was of the ascending type, beginning in the legs, next attacking the arms, and finally causing death by involvement of the medulla. I lay particular stress on this point because the path of infection was in all cases by the brain and in most cases exclusively. I shall return to this later. Occasionally the cerebral nerves were affected, and in most of such cases it was possible to demonstrate that the nerve nuclei were affected by the disease. These cases constitute therefore a bulbar type quite similar to that observed in man.

Monkey No. 48 (*Macacus rhesus*), on April 7, 1910, received an intracerebral injection of ·5 c.c. and an intraperitoneal injection of 4 c.c. of an emulsion of virus No. 11.

April 8-16.—No signs of disease.

April 17.—Slight palsy of the left fore limb and the right hind limb just perceptible. When climbing about his cage the monkey falls frequently. In the afternoon the left arm quite paralysed; the palsy of the right leg more marked.

April 18.—Besides the paralysis of the left arm there is some paralysis of both hind limbs. In the evening weakness of the right arm. The animal falls to one side while walking.

April 19.—The monkey sits crouching on the floor of the cage. Total palsy of the left arm, definite weakness of the right arm. The animal is still able to hold a small apple in the right hand for some minutes. Marked palsy of both hind limbs. While walking the monkey falls sometimes to one side and sometimes forward. The head hangs forward owing to paralysis of the muscles of the neck. Movements of the tail are strong. There is also a marked palsy of the lower part of the left facial nerve, which is very obvious when the monkey is made to express pain. The left angle of the mouth is not moved, nor does the lower part of the left cheek show any trace of the wrinkling which is seen on the right side. In the evening the monkey became moribund and was killed.

Unfortunately it was not possible to obtain a photograph of the facial paralysis, because the animal was so ill that the expression of pain was only momentary. Professor Müller succeeded in the case of another monkey in photographing a facial palsy, and with his permission I have reproduced his photograph of a total right-sided paralysis.

Leiner and v. Wiesner have also observed facial palsy. Levaditi and Stanesco have described a very beautiful case of which they obtained a characteristic photograph (*cf.* fig. 11). The paralysis of the whole of the left facial nerve set in on the ninth day after an intracerebral injection; the muscles of the eye were

FIG. 10.
Monkey No. 102.
Right-sided facial paralysis.

likewise affected. The case is remarkable in that the facial palsy was the first sign of the disease noticed, the paralysis of the limbs following later.

Levaditi and Stanesco found marked changes in the ganglion cells of the facial nerve.

Netter, as well as Flexner and Lewis, observed facial paralysis. Flexner and Lewis give one illustration of the condition; the photograph also shows a definite paralysis of the hypoglossal nerve, the tongue deviates to the left, on which side the facial nerve was paralysed (fig. 12).

FIG. 11.
Left-sided facial paralysis. (After Levaditi and Stanesco.)

FIG. 12.
Paralysis of the facial and hypoglossal nerves on the left side. (After Flexner and Lewis.)

Monkey No 61 (*Macacus rhesus*) received on June 3, 1910, an intra-cerebral injection of '6 c.c. of a 5 per cent. emulsion of virus No. 11 (mixed with normal human serum).

June 14-17.—No signs.

June 18.—Slight paresis of the right fore limb. During the afternoon this became more marked and was definitely flaccid in type. The hind limbs were, on the other hand, very markedly spastic; the animal frequently fell down when the hind limbs showed a strong tremor. In addition there was a marked ptosis on the right side, the eyeball was deviated outwards and downwards and could not be made parallel to the left eyeball. No changes were observed in the pupils (fig. 13).

FIG. 13.
Monkey No. 61.
Paralysis of the right oculomotor nerve.

June 19.—Found dead.

On microscopical examination considerable lesions were found in the cerebral cortex and in the basal ganglia. The changes in the cord were less marked.

In this case the oculomotor nerve was affected, and at the same time the limbs were involved owing both to cerebral and spinal lesions.

Other cases were observed in which the disease was even more definitely cerebral in type; cases analogous to the cerebral type of Heine-Medin disease in man.

Monkey No. 27 (Mangabey) received on March 3, 1910, an intracerebral injection of ·6 c.c. of an emulsion of virus No. 12.

March 3-10.—Remained well.

March 11.—Depressed.

March 12.—Clearly ill, breathing heavily.

March 13.—Frequent tremor of the whole body. Walks stiffly and with difficulty, but is not definitely paralysed.

March 14.—Lies on the floor; extremities show violent tremors and are stiff. Died at 4 p.m.

On microscopical examination typical poliomyelitis. The changes affect the pia mater in the region of the central gyri; much perivascular infiltration in the cerebral cortex and in the basal ganglia. Very slight, apparently only beginning, changes in the spinal cord.

Relatively seldom therefore a purely cerebral form of experimental poliomyelitis occurs in monkeys. Flexner and Lewis record similar cases in which, however, convulsions occurred, a thing I never observed. Flexner found in eight out of eighty-one cases that the disease began with cerebral or bulbar symptoms, although these cases became later spinal in type. In one monkey in which the paralysis was due chiefly to the cerebral lesions they observed distinct nystagmus; this is the only time that nystagmus has been observed in a monkey so far as I know.

The symptom-complex due to cerebral localization of the lesion of poliomyelitis in monkeys is by no means characteristic; in any case caution is necessary in making the diagnosis of a purely cerebral lesion from the symptomatology alone in experimental poliomyelitis; unless the diagnosis is controlled by microscopical examination mistakes may easily occur. The following cases illustrate this point:—

Monkey No. 7 (*Macacus rhesus*) inoculated on December 17, 1909, with ·5 c.c. of an emulsion of virus No. 11.

December 19.—Marked spastic paresis of the right hind limb and moderate spastic paresis of the right fore limb.

December 20.—Condition the same.

December 21.—Paresis apparently less marked.

December 22.—Paralysis increased, the degree varies during the day.

December 23.—Found dead.

On examination none of the lesions typical of Heine-Medin disease were found in the cerebral cortex or elsewhere. The paralysis was due to an abscess, the size of a hazel-nut, in the region of the central gyri on the left side at the site of the injection. From this abscess streptococci were cultivated.

Monkey No. 60 (*Macacus rhesus*) inoculated on July 13, 1910, with ·5 c.c. of emulsion of virus No. 11.

July 15.—Unsteady while jumping.

July 16.—Definite weakness of both left limbs.

July 17-25.—Very marked paresis of the left fore limb, of a spastic kind.

July 26-28.—Paralysis increasing.

July 29.—Found dead.

Microscopically no lesions indicative of poliomyelitis were found. In the right central gyri at the point of inoculation an abscess the size of a bean.

(e) Gastro-intestinal Symptoms.—Diarrhœa coincident with the paralysis has already been mentioned above, and in some of the cases reported. It is difficult to decide whether the poliomyelitis is the cause of the diarrhœa because so many monkeys, when bought recently, suffer from gastro-intestinal disturbance owing to change of surroundings or of food. At the same time, the number of cases in which diarrhœa occurred at the same time as paralysis is so large, even in monkeys which had been kept in the institution for a considerable time, that I have no doubt that the gastro-intestinal symptoms are a part of the poliomyelitic infection. The following are examples:—

Monkey No. 23 (*Macacus rhesus*) inoculated on January 20, 1910; ·5 c.c. into the brain and 5 c.c. into the peritoneum.

January 21-26.—No symptoms.

January 26.—In the evening the monkey seems more tired than usual.

January 27.—Sudden violent diarrhœa; at the same time total flaccid paralysis of the hind limbs with slight paresis of the fore limbs.

January 28.—Diarrhœa has ceased. Paralysis of the hind limbs the same, of the fore limbs more marked. Paralysis of the bladder.

January 29.—Complete paralysis of all limbs. Death during the afternoon.

Microscopic appearances in the cord are typical.

Monkey No. 38 (*Macacus rhesus*).—Intracerebral inoculation on March 2, 1910, with ·35 c.c. of an emulsion of virus No. 12 (mixed with serum from a normal monkey).

March 3-9.—No symptoms.

March 10.—Ill; takes food badly; *severe diarrhœa*; no paralysis.

March 11.—General condition the same. Unsteady gait. Resistance to passive movement is diminished in all limbs. No definite paralysis observed when walking.

March 12.—Monkey lies apparently completely paralysed on the floor of the cage. Death 12 noon.

At the *post-mortem* there was found severe gastro-enteritis with redness and swelling of the follicles of the small intestine and of Peyer's patches; the mesenteric glands were increased in size, being as large as beans. Typical, but not intense, changes in the brain and spinal cord. Cultures made from the blood and from the glands remain sterile. (Intracerebral injection of material from the mesenteric glands into another monkey produced typical poliomyelitis, *cf.* p. 98).

(f) Abortive Forms.—Wickman did great service in calling attention to cases of Heine-Medin disease in man in which there are no definite symptoms of paralysis; he named this the abortive

type. In monkeys it is possible to produce a slight as well as a severe form of the disease. It is difficult to decide whether true abortive forms without paralysis occur in monkeys, because we have no criteria by which we can determine the causal connection between the general malaise and the injection of the virus. It may be possible later to furnish proof by means of serum diagnostic tests (*vide infra*). Personally I have no doubt at the present time that such cases occur, because of the very slight and transient palsies which I have observed. The following two examples may be considered within certain limits to be cases of "abortive" experimental poliomyelitis.

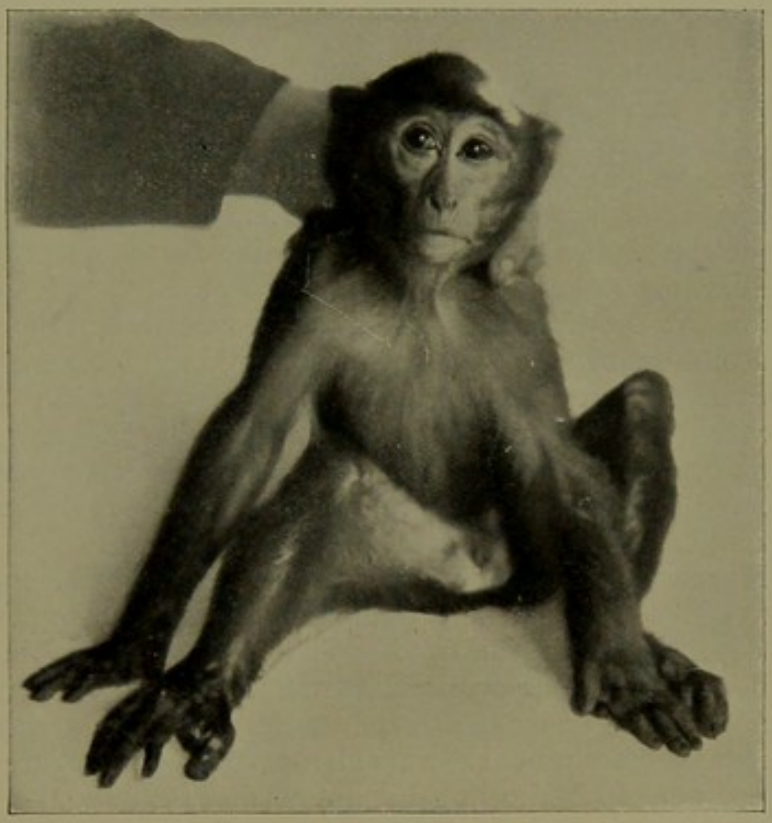


FIG. 14.
Monkey No. 44.
A trace of paralysis of the right hind limb.

Monkey No. 44 (*Macacus rhesus*), on March 23, 1910, intracerebral injection of ·6 c.c. of an emulsion of virus, also 3 c.c. into the peritoneum.

March 23-28.—No symptoms.

March 29.—The monkey appears more tired than usual.

March 30.—Severe diarrhœa. Weakness of the right hind limb, scarcely noticeable on walking, but obvious when the animal is sitting; the right leg cannot be adducted as strongly as the left. Wherever one places the monkey it always assumes this peculiar attitude, which is shown well in the photograph (fig. 14).

March 31.—Diarrhœa less. Paralysis almost disappeared.

April 1 and subsequently.—Quite normal.

Monkey No. 59 (*Macacus rhesus*).—Intracerebral injection on June 13, 1910, with ·3 c.c. of emulsion of virus No. 11 (mixed with normal human serum).

June 15-21.—No symptoms.

June 22.—Severe diarrhœa.

June 23.—Condition the same.

June 24.—Similar condition; in addition, slight paresis of the right fore-limb.

June 25.—Unchanged.

June 26.—Paresis almost absent; diarrhœa less.

June 27.—Complete recovery.

That in this case the virus was responsible for the condition was proved later. On reinoculation this animal remained well while the control died (*cf.* p. 153).

Such abortive cases appear to be rare in monkeys. This may be owing to the slighter symptoms being missed; even paralysis can be observed with certainty only when it is fairly well marked. In the last cases quoted above the paralysis was noticed because we had already considerable clinical experience. Flexner and Lewis have no doubt of the existence of abortive forms of experimental poliomyelitis in monkeys.

In some cases I observed general weakness, the monkeys looked ill and suffered from gastro-intestinal symptoms, but as no paralysis occurred it was not possible to associate the symptoms directly with the infection. I intended to test the immunity of these animals by repeating the injection, but they died shortly afterwards from tuberculosis of the lungs. In my statistics I have included them among the unsuccessful inoculations.

(g) Marasmic Forms.—Leiner and v. Wiesner described this form, but I have not had any opportunity of observing it. These authors describe it as follows: "After inoculation the animals remained for some time well; towards the end of the incubation period they became depressed, tired, suffered from diarrhœa (which cleared up under treatment), wasted rapidly, did not care to move about, were able to climb but did not wish to do so, the muscular power was generally diminished; in one word, they became marasmic. Some of them died between the sixth and thirteenth day after inoculation without showing any signs of paralysis, others lingered on for a longer time. Microscopical examination showed beyond the possibility of doubt that these animals were suffering from an atypical form of poliomyelitis. Besides hyperæmia and hæmorrhages there was marked degeneration of the ganglion cells with a certain amount of cell infiltration. We are convinced that these animals succumbed to an atypical form of poliomyelitis without paralysis. The striking feature of this form is the wasting of the animals, and we have called it therefore the 'marasmic' type." Leiner and v. Wiesner have produced confirmatory evidence of their contention by inoculating other monkeys with the spinal cord of these, and finding that the new monkeys died of typical polio-

myelitis. Eduard Müller reports a human case in which he observed marked general wasting although ample nourishment was taken. He compares his case with those reported by the Austrian observers.

(h) Recovery from the Acute Stage.—The foregoing types are all characterized by the fact that almost all the monkeys succumbed to the disease. In man it is more usual for life to be preserved, even though the extent of the paralysis is considerable. In monkeys such cases are rare; in my small amount of material I saw one such case:—

Monkey No. 37 (*Macacus rhesus*).—Intracerebral injection on March 2, 1910, with ·3 c.c. of an emulsion of virus No. 12 (mixed with the serum of a normal monkey).

March 3-8.—Healthy.

March 9.—Marked weakness of the right hind limb; left somewhat weak.

March 10.—Flaccid paralysis of both hind limbs; severe diarrhœa.

March 11.—Complete paraplegia.

March 12 and the weeks following.—The condition remained the same; there was total flaccid paralysis of the hind limbs, while the rest of the muscles acted well. On walking the hind limbs are dragged. Climbing must be carried out by the arms alone and the monkey therefore soon becomes tired. The monkey was cinematographed in this condition, and the film was shown at the Congress for Internal Medicine at Wiesbaden in April, 1910. Occasionally œdema of the legs was observed. This can be explained by the position assumed by the monkey when sitting on its board, the hind limbs hung down over the edge and the consequent compression of the vessels caused the œdema. At the same time one must bear in mind the possibility of vasomotor paralysis as a factor. The monkey died on April 14 in a marasmic condition.

(i) Recovery from the Paralysis.—In other cases, as is so common in man, we observed considerable improvement in the paralysis.

Monkey No. 47 (*Macacus rhesus*).—On April 7, 1910, intracerebral injection of ·5 c.c. of emulsion of virus No. 11, also 4 c.c. into the peritoneum.

April 8-16.—No change.

April 17.—Slight weakness of left hind limb. Falls frequently while climbing. In the afternoon paresis of both hind limbs.

April 18.—Marked flaccid paralysis of both hind limbs. The monkey uses the arms only while climbing.

April 19-21.—Practically the same. The monkey walks with the arms only, dragging the legs, which are completely flaccid.

April 22.—Condition the same; incontinence of urine.

April 26.—The left hind limb is used slightly; the right hind limb appears œdematous at times.

May 2.—The paralysis of the left hind limb is much less and can be observed only by testing the resistance of the limb to passive movements.

May 21.—No paralysis of the left hind limb; the right hind limb is still completely paralysed. The photograph represents the monkey at this stage;

the total paralysis of the right leg can be seen clearly on comparing the attitude of the limb with that of the left leg which is normal (fig. 15).

Complete recovery from severe and extensive paralysis was seen in the following cases:—

Monkey No. 32 (*Macacus rhesus*) on February 7, 1910, received an intracerebral injection of ·5 c.c. of an emulsion of virus No. 12 which had been warmed for half an hour at a temperature of 45° C.

February 8-14.—Quite well.

February 15.—Slight palsy of both hind limbs.

February 16.—Paralysis more marked.

February 17-20.—Condition unchanged.

February 21.—The paralysis is less; improvement more marked in the right than in the left limb.

February 26.—Only a trace of weakness remains in the left hind limb.

March 12 onwards.—The monkey remained quite well.

FIG. 15.
Monkey No. 47.
Paralysis of the left hind limb.

Monkey No. 40 (*Macacus rhesus*).—On March 4, 1910, intracerebral injection of ·6 c.c. of an emulsion of virus No. 12, also 4 c.c. into the peritoneum.

March 5-10.—No symptoms.

March 12.—Slight paralysis of both hind limbs.

March 14.—Paralysis of both limbs well marked.

March 15-23.—Condition unchanged.

March 24.—Definite improvement in paralysis.

March 25 onwards.—The improvement is rapid.

April 3.—Paralysis entirely disappeared.

Monkey No. 41 (*Macacus cynomolgus*).—Intracerebral injection of ·6 c.c. of virus No. 11 on March 15, 1910.

March 16-25.—No change.

March 26.—Slight paresis of hind limbs.

March 27.—Unchanged.

March 28.—Paresis of hind limbs more marked; definite slight paresis of the right fore limb.

April 1.—Condition of hind limbs improved; the right fore limb now total flaccid paralysis.

April 5 onwards.—Steady improvement in all the affected limbs.

May 5.—No paralysis in any limb.

Monkey No. 49 (*Macacus rhesus*) received an intracerebral injection of ·6 c.c. of an emulsion of virus No. 12 on April 27, 1910.

April 28 to May 9.—No symptoms.

May 10.—Paresis of hind limbs, right more than left.

May 11-12.—No change.

May 13.—Paresis less, barely perceptible on left side.

May 14-15.—No change.

May 16.—Monkey climbs well; there is still a slight weakness of the left limb.

May 21.—No paralysis at all.

(k) Relapses.—One case may be quoted as a curiosity in which there was a definite relapse; the monkey appeared undoubtedly to be recovering. Such a sequence of events is sometimes found in human poliomyelitis.

Monkey No. 11 (*Macacus rhesus*).—Intracerebral injection of ·5 c.c. of an emulsion of virus No. 11 on December 8, 1909.

December 9-19.—No symptoms.

December 20.—Severe paralysis of right hind limb; perhaps also a slight paresis of the arms.

December 21.—Marked paralysis of both hind limbs; slight paresis of the arms.

December 22-25.—No change.

December 28 onwards.—Much improvement in all limbs; paresis in the arms scarcely noticeable. The hind limbs are used occasionally. The improvement is considerable.

January 9.—Monkey becomes suddenly weaker.

January 10.—Hind limbs almost completely paralysed; the animal drags them after it. In the evening the fore limbs appear completely paralysed and the monkey lies flat on the floor of the cage.

January 11.—Found dead.

Microscopical exmination shows typical acute changes in the spinal cord.

Levaditi and Stanesco report a similar case. In a monkey which became paralysed on the eleventh day after injection and died on the twenty-ninth day in a condition of chronic paralysis, they found both acute and chronic lesions in the spinal cord.

It is extremely difficult to say whether any disturbance of sensation occurs in monkeys. Absolute and relative anæsthesia

cannot be tested for with any certainty. It appears to me, however, that shortly before the paralysis appears there is a stage of hyperæsthesia similar to that observed in man on which Eduard Müller lays so much diagnostic stress. Monkeys, which previously had been quiet and friendly, uttered loud cries when they were touched or when the attempt to capture them made them move about.

It is quite certain, from our purely clinical observations, that in monkeys the spinal symptoms of the disease are the most marked, whether the monkeys are infected *viâ* the brain or the brain and peritoneum at the same time. According to other authors it does not matter whether the injection is made into the subcutaneous tissue, the nerves, or the eyeball; the picture is always essentially one of spinal paralysis. Usually the paralysis is of the ascending type and causes death by involvement of the medulla with consequent respiratory paralysis. Occasionally bulbar signs (facial palsy, &c.) are observed; the combination of bulbar and spinal symptoms produces a clinical picture similar to that of Landry's disease in man. Finally, there can be no doubt that monkeys are subject to a purely cerebral form of the disease, analogous to the rare human cases of cerebral Heine-Medin disease. Marasmic, abortive and relapsing forms of the disease have been observed. In short, clinical investigation of cases of experimental poliomyelitis in monkeys reveals types similar to the manifold forms of Heine-Medin disease in man, and the point of entry of the virus does not influence the result.

Prognosis.—One important point of difference between human poliomyelitis and the experimental disease in monkeys is the mortality. The figure varies in human beings, as has been shown above. It lies between 10 and 20 per cent., when only those cases are counted in which paralysis has occurred. Similar statistics in monkeys show a much less favourable figure. In my own monkeys, counting only those in which paralysis appeared, I find that 76·4 per cent. died of the paralysis, 6 per cent. survived paralysed and 17·6 per cent. recovered completely. These figures are very similar to those obtained by Flexner and Lewis. They found that 75 per cent. of all cases with paralysis died. This figure, however, is only an estimate, because they killed many of their animals for purposes of investigation. I myself waited in almost every case until the animal was moribund before killing it. My figures are consequently quite reliable. Flexner and Lewis state that by passing a virus through many animals they obtained finally a mortality of 100 per cent. The prognosis in experimental poliomyelitis of monkeys is therefore much less favourable than that of natural poliomyelitis in man. This is of importance in judging of the value of any therapeutic measures when applied to the experimental disease.

Fig. 16 shows clearly the relations between duration of incubation and duration (*i.e.*, severity) of paralysis; it illustrates the question of recovery and duration of paralysis.

According to this table a short incubation period corresponds to a short violent course of the disease. In the case of monkey No. 37, however, a short incubation period did not mean a subsequently fatal attack. Further consideration of the table shows that there is no fixed correspondence between the length of the incubation period and the severity of the attack. Monkeys Nos. 13, 11, and 35, with incubation periods of 10½, 11½, and 15 days respectively, suffered from a long paralytic stage, which ended fatally; but, on the other hand, the monkeys Nos. 2 and 36 had an equally long incubation period and yet died very rapidly. We find also that in some cases (monkeys Nos. 32 and 40), in spite of a relatively short incubation period, the disease ended in complete recovery.

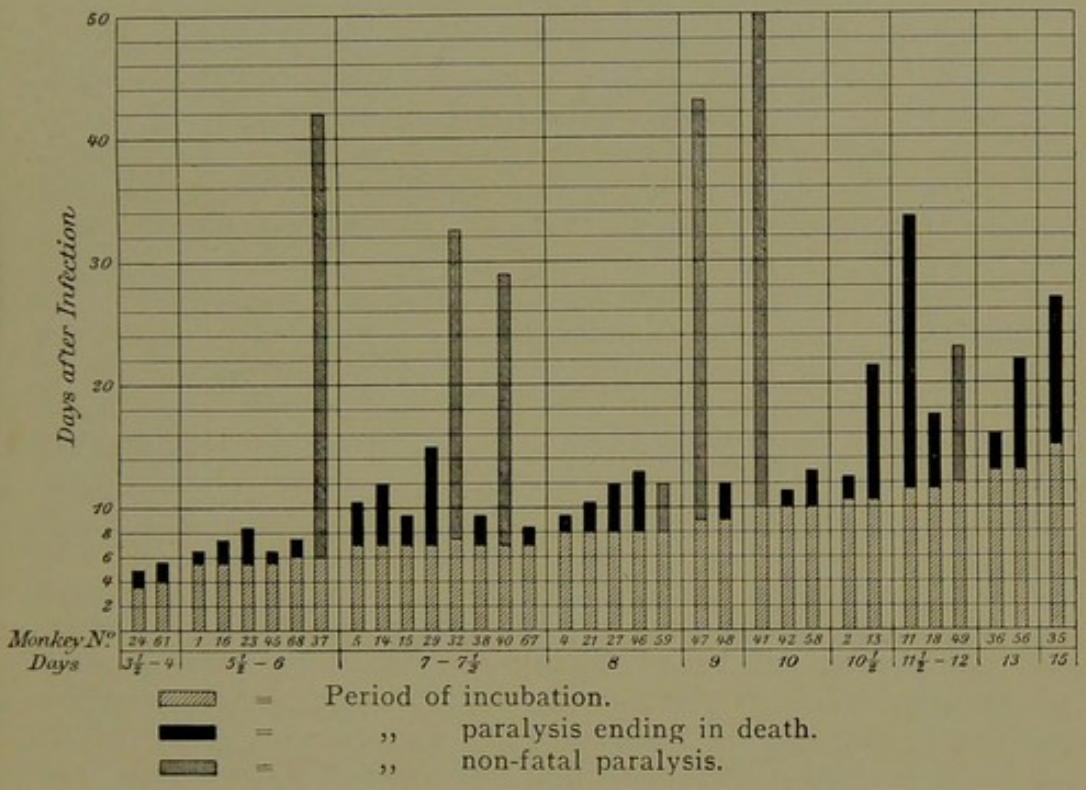


FIG. 16.

The conclusion to be drawn from these experiments is that *no rules for prognosis can be formulated which are based upon the length of the period of incubation.*

III.—THE NATURE OF THE VIRUS.

The results of my first experiments convinced me that the virus of poliomyelitis must be fairly stable. I was successful in the case of monkey No. 1 in inoculating a virus which had been kept for forty-eight hours after the autopsy, and with monkey No. 2 in inoculating one kept for sixty-four hours. Flexner and

Lewis came to the same conclusion; they used a virus which was thirty-eight hours old. Landsteiner and Levaditi used a virus four days after the death of the child in their original experiment. In his fundamental work Landsteiner, together with Popper, made the suggestion that the cause of Heine-Medin disease belonged to the group of viruses capable of filtration. The following experiments prove the correctness of his suggestion.

Filtration of the Virus.—Flexner and Lewis demonstrated simultaneously with and independently of Landsteiner and Levaditi that the virus would pass through various filters which were fine enough to hold back bacteria. I give below the tabulated results of Landsteiner and Levaditi's experiments; from them can be seen the difference in virulence between the filtered and unfiltered virus.

	Name of filter	Monkey	Incubation period	Course
a	Berkefeld	*Macacus cynomolgus* No. 18	8 days	+ in 5 days
	,, ...	,, ,, ,, 19	10 ,,	Survived
	Control	,, ,, ,, 100	5 ,,	+ in 2 days
b	Berkefeld	*Callitrichus* No. 26	12 ,,	Survived
	Chamberland ...	,, ,, 27	16 ,,	+ in 1 day
	Control	,, ,, 25	8 ,,	+ in 2 days
c	Berkefeld I ...	*Macacus sinicus* No. 32 ...	12 ,,	+ in 15 days
	,, II ...	,, ,, ,, 28 ...	15 ,,	+ in 2 ,,
	Control	,, *rhesus* ,, 31 ...	6 ,,	+ in 7 ,,
d	Reichel A	*Macacus rhesus* No. 23 ...	11 ,,	+ in 5 days
	,, B	*Macacus cynomolgus* No. 24 ...	8 ,,	Killed
	Control	Mandrill No. 25	4 ,,	+ in 1 day

Landsteiner and Levaditi and also Flexner and Lewis proved that a living virus was present in the filtrate and not merely a toxin contained in the spinal cord, by injecting the spinal cord substance of monkeys infected with the filtrate into other monkeys with a positive result.

Leiner and v. Wiesner at first obtained negative results when using Reichel filters; later they obtained positive results with virus passed through Pukall filters. Their results show the influence of filtration upon the length of the incubation period.

Inoculation with filtrate		Inoculation with unfiltered emulsion	
Monkey No.	Incubation period	Monkey No.	Incubation period
22	10 days	21	8 days
23	15 ,,	21	8 ,,
36	12 ,,	37	7 ,,
41	11 ,,	40	6 ,,

The period of incubation is longer when the filtered virus is used, as can be seen from both tables. Flexner and Lewis state further that when they used virus which had been intensified by being passed through many animals, a very small dose of the filtrate produced severe paralysis after an incubation period of the *usual* length; they conclude that the virus must be extraordinarily fine.

Personally, I had but little success with emulsions filtered through a Berkefeld filter; I was able only indirectly to prove that the filtrate contained the virus by showing that a monkey which had been inoculated with it without result was immune to a lethal dose of the emulsion.

These experiments prove that the virus is capable of passing through filters like the Berkefeld, Chamberland, Reichel, and Pukall filters, through all of which bacteria cannot pass.

Resistance to Glycerine.—In its behaviour towards filters the poliomyelitis virus shows again its similarity to the virus of rabies; on the whole it seems to pass through filters more easily than the latter virus. This led to further experiments being made to discover further similarities. One of the most important of these is the resistance shown towards glycerine. Landsteiner and Levaditi made the first experiment; in their first experiment they used with success a virus which had been preserved in 33 per cent. glycerine for four days, in order that it might be sent from Vienna to Paris. We ourselves, usually against our inclination and only because our modest means did not always allow us to inoculate direct from one monkey to another, had ample opportunity of studying the resistance to glycerine of our virus. In the following table I have put together all the injections in which virus preserved with glycerine was used; each original virus is placed in a separate table.

It is clear that the virus remains potent for at least ninety-one days when kept in 50 per cent. glycerine, but this does not represent the limit of time that it can be kept (*cf.* monkeys Nos. 46, 59, and 61). Although the inoculation of monkey No. 44 with virus which had been kept for 95 days resulted only in a doubtful illness, the reason of this is to be found rather in a peculiar resistance of this particular animal than in the virus itself. The experiments with virus No. 6 shows that 142 days in pure glycerine is not enough to cause any diminution of potency. There is some slight difference in behaviour towards glycerine between the virus obtained direct from man and that obtained from inoculated animals. Yet experiments with virus Nos. 11 and 12 show that after passing through five and six animals the virus resists glycerine as well as the original virus (*cf.* monkeys Nos. 59 and 61).

These results correspond with those obtained by Landsteiner and Levaditi; these authors supplement my figures in so far as they used 33 per cent. glycerine in their experiments. They proved that the virulence was not affected after seven, nine, and twenty-

two days in 33 per cent. glycerine. Flexner and Lewis also have proved the resistance of the virus to glycerine.

The discovery of this fact is of great practical importance; experimental work is rendered easier by the knowledge that direct inoculation from monkey to monkey is not necessary. Glycerine

Virus No. 11.

PRESERVED IN 50% GLYCERINE.

No. of monkeys passed through	No. of monkey	Method of infection	Length of time in glycerine	Length of incubation period	Duration of the fatal illness
Original virus	44	i-c. and i-p.	95 days	12 days	Abortive p.m.?
III	23	,,	14 ,,	5½ ,,	3 days
III	46	,,	91 ,,	8 ,,	5 ,,
V	47	,,	24 ,,	9 ,,	Survived
V	48	,,	24 ,,	9 ,,	2 days
V	58	i-c.	78 ,,	10 ,,	2 ,,
V	59	,,	91 ,,	10 ,,	Survived
V	61	,,	91 ,,	4 ,,	1½ days
VI	56	i-c. and i-p.	30 ,,	13 ,,	9 ,,

Virus No. 12.

PRESERVED IN 50% GLYCERINE.

No. of monkeys passed through	No. of monkey	Method of infection	Length of time in glycerine	Length of incubation period	Duration of fatal illness
Original virus	21	i-c. and i-p.	31 days	9 days	2½ days
II	29	i-c.	8 ,,	8 ,,	7 ,,
II	27	,,	31 ,,	8 ,,	4 ,,
II	37	,,	31 ,,	6 ,,	Survived
II	38	,,	31 ,,	8 ,,	2½ days
II	40	i-c. and i-p.	33 ,,	7 ,,	Survived
III	43	,,	8 ,,	9 ,,	Abortive p.m.
III	42	i-c.	10 ,,	10 ,,	1½ days
III	35	i-c. and i-p.	20 ,,	15 ,,	11 ,,
V	49	i-c.	24 ,,	12 ,,	Survived

Virus No. 6.

PRESERVED IN CONCENTRATED GLYCERINE.

No. of monkeys passed through	No of monkey	Method of infection	Length of time in glycerine	Length of incubation period	Duration of fatal illness
I	19	i-c. and i-p.	59 days	10 days	5 days
I	45	,,	142 ,,	5½ ,,	1 day

can be used as a preservative when the virus has to be sent from place to place. Especially is it important in cases of suspected Heine-Medin disease, when the virus may be kept in 50 per cent. glycerine until a monkey can be procured. Preservation in glycerine may be used for material that has become contaminated with bacteria; in 50 per cent. glycerine the bacteria are slowly destroyed.

The Effect of Low and High Temperatures.—The behaviour of the virus towards different temperatures presents various points of interest. The above figures relating to the resistance to glycerine provide some data owing to the fact that all the preparations were kept in the dark in an ice-chest. It follows that a temperature of + 4° C. is not inimical to a virus preserved in glycerine. Flexner and Lewis found that keeping the virus itself at the temperature of an ice-chest for fifty days had no effect upon its virulence; even complete mouldiness of the pieces of spinal cord containing virus did not influence the activity of the virus. They kept virus at a temperature of between —2° and —4° for forty days and still found it virulent. Leiner and v. Wiesner used a virus which had been kept for four hours in a freezing mixture; an intracerebral injection produced slight paralysis after an incubation period of twelve days. Landsteiner and Levaditi quote one case in which the virus was kept for eleven days in the frozen state and then caused paralysis of the hind limbs after an incubation period of six days; the animal survived.

These experiments prove that the virus of Heine-Medin disease is but little affected by low temperatures. As will be seen later, this has some bearing on the question of epidemiology.

There is some accidental evidence showing the behaviour of the virus towards moderate temperatures. Landsteiner and Levaditi, in the course of their attempts to obtain an attenuated virus by methods similar to that employed by Pasteur in the case of rabies, found the virus fully virulent after nine days, at a temperature of 22° C. In his experimental "cultures," quoted on page 29, Levaditi showed that the virus resisted a temperature of 37° for at least fifteen days.

The virus appears to be much affected by temperatures higher than these. We have made systematic experiments to elucidate this point.

Experiment 1.—Monkey No. 32 received an intracerebral injection on February 7, 1910, of ·5 c.c. of a 5 per cent. emulsion of brain and spinal cord heated for half an hour to a temperature of 45°. The material was obtained from monkey 24 (virus No. 12 passed through two animals). On February 15 paresis of the hind limbs, increasing for a few days, diminishing from February 22 onwards until March 12. No paralysis is present. The control, monkey 29, received ·35 c.c. of the same virus unheated, became paralysed on the 13th and died on the 15th (*vide* p. 47).

Experiment 2.—Monkey 51, on April 25, 1910, received an intracerebral injection of ·5 c.c. of 5 per cent. emulsion from monkey 36 (virus No. 11 passed through five animals). The emulsion was heated for half an hour at temperature of 50°. The animal remained well. The same virus, injected unheated on May 31, 1910, into monkey 58, proved highly virulent (*vide* p. 77).

Experiment 3.—Monkey 26, on January 25, 1910, received ·5 c.c. of 10 per cent. emulsion of brain and cord of monkey 21 (virus No. 12 passed

through one animal). The emulsion was heated for half an hour at 55°. The animal remained well. Monkey 24 injected on the same day with the same amount of virus unheated became paralysed in both legs on the fourth day and died on the fifth. Microscopical appearances typical.

When heated for half an hour at 45° the virus is still virulent, although somewhat attenuated; heating for half an hour at 50° or 55° was sufficient to destroy its virulence.

Leiner and v. Wiesner obtained similar results. They found the virus no longer virulent after being heated to 50° for one hour and to 60° for fifteen to twenty minutes. It was due probably to some peculiarity in the animal used that they found in one instance that heating for two hours at a temperature of 35° destroyed the activity of the virus; Levaditi's experiment, quoted above, with virus at 37°, and my own experience with virus kept at 45°, confirm this view. Flexner and Lewis report that warming at 45° to 50° for half an hour destroys the potency of the virus; this corresponds more or less with our own results.

Resistance to Drying.—The evidence on this point is somewhat conflicting. The following is my own experiment:—

Monkey 36 (*Macacus rhesus*) was injected with virus No. 11 on February 26, 1910. The virus was obtained from the cord of a monkey which had been dried *in vacuo* for twenty-eight days at room temperature and guarded from light. After an incubation period of thirteen days paralysis of the right fore limb and of both limbs appeared; on March 13, total paralysis of the hind limbs; on March 14, paralysis of all limbs; death on March 15. Histological appearances typical.

Spinal cord dried for twenty-eight days *in vacuo* was found therefore to be virulent. The experience of other authors has been similar. Flexner and Lewis dried the virus for seven days over caustic potash and found it virulent; Landsteiner and Levaditi, following Pasteur's method, dried a cord over caustic potash in one case for nine days, in another for twenty-four days, at a temperature of 22°. In both experiments the cord was found to be virulent. *They emphasize the difference in this respect of the virus of Heine-Medin disease and the virus of rabies.* In another experiment they dried a thick layer of emulsion of virulent spinal cord *in vacuo* at room temperature and found it fully virulent at the end of fifteen days.

On the other hand, Leiner and v. Wiesner obtained a different result. They dried a thin layer of emulsion in an incubator at 37° for four hours and found it non-virulent. In another instance they allowed a thin layer of emulsion of spinal cord to dry for twenty-four hours at the temperature of the room; the dried emulsion was washed off and injected with a negative result (unfortunately, they do not give any report of a control experiment). In this experiment they were attempting to reproduce the natural conditions and it is possible that in a very thin layer the emulsion withstands

drying less well. From this point of view it would be worth while to corroborate and amplify their results.

Behaviour towards Disinfectants.—I have not been in a position to make extended experiments on the behaviour of the virus of poliomyelitis towards disinfectant chemicals, although the subject is of the greatest importance for many reasons, particularly from the point of view of prophylaxis. I made experiments with formalin. The chemical was not mixed directly with the virus, but an active emulsion was exposed to the vapour in the course of a test disinfection of a room which will be described later. The virulence of the emulsion was found to have been destroyed. The most complete investigations into the effect of chemicals upon the virus have been made by Landsteiner and Levaditi. Their first experiments were made with menthol oil and with a powder composed of menthol, salol, and boric acid. Two cubic centimetres of an emulsion of virulent virus was shaken with ·5 c.c. of a 1 per cent. solution of menthol oil and allowed to stand for two hours at room temperature. A monkey which received an intracerebral injection of ·5 c.c. of this mixture showed only slight transient symptoms; the control animal became paralysed on the fourth day and died on the sixth. In a second experiment 2 c.c. of the same emulsion was mixed with ·05 grm. of the powder (·2 grm. menthol, 5 grm. salol, 20 grm. boric acid), well shaken and kept at room temperature for two hours. The monkey injected with this also suffered from transient symptoms.

A 1 in 1,000 watery solution of thymol mixed with an equal quantity of emulsion for one hour at 37° did not diminish the virulence. The activity of the virus was destroyed after mixture with a 2 per 1,000 solution of potassium permanganate for one hour at 37°. A 1 in 5 (6 per cent.) dilution of perhydrol (Merck) mixed with an equal part of emulsion for forty-five minutes at 37° killed the virus. Flexner and Lewis found a 1 per cent. solution of H_2O_2 was effective, but do not give the length of contact necessary.

Of some importance with regard to personal prophylaxis is the discovery by Landsteiner and Levaditi of the efficacy of potassium permanganate and peroxide of hydrogen.

Kraus investigated the influence of carbolic acid on the virus. He found that the filtered emulsion is more easily killed than the unfiltered; this is due to the presence in the latter of coarser particles of the spinal cord, which enclose the virus and prevent the carbolic from acting on it. Contact with a ·5 per cent. solution of carbolic acid for five days lessened the virulence and in some cases destroyed it. A 1 per cent. solution did not kill the virus in one to three days, but it was efficacious in four to five days.

The Durability of the Virus in Animals.—My own material bearing on this point is small. In general I used only the emulsions obtained from the brain and cord of animals which had died acutely for further injections. The spinal cord of monkeys

which had died on the fourth day after infection proved fully virulent. That the virus can remain virulent for a long time within the body of the animal is proved by the case reported above (*vide* p. 59); monkey 11 received an intracerebral injection on December 8, 1909; paralysis set in on the 26th and then improved for a time; on January 9 a definite relapse occurred and the animal died on January 11. The typical appearances of acute poliomyelitis found in the spinal cord, together with the results of further injections into other animals, proved that the virus was still fully virulent after thirty-three days. Leiner and v. Wiesner found potent virus in the cord of an animal which had been ill for twenty-four days. It is probable, however, that these results do not represent the normal condition of affairs; relapses are very rare in monkeys and I have only seen one case. In another case Leiner and v. Wiesner found that the spinal cord of a monkey, which had suffered from paralysis for only six days, was no longer virulent; the monkey which was injected with this cord showed no signs of paralysis up to the twenty-fourth day. Landsteiner and Levaditi found virulent spinal cord on the fourth day after injection, but thirty-nine to forty-five days later they found no virulence.

No rule as to the viability of the virus in monkeys can be formulated from the small amount of material available. There is a wide field for further investigation in this direction. Landsteiner and Levaditi suppose that the virus usually disappears at the end of the acute stage, but that in isolated instances this does not take place.

The virus appears to remain longer in regions other than the central nervous system. Flexner reports that Osgood and Lukas, two American investigators, found the mucous membrane of the pharynx virulent six months after the monkey had received an intracerebral injection, and at a time when the virus had completely disappeared from the central nervous system. In another case the brain, spinal cord, and mucous membrane of the nose and throat were all virulent eight weeks after the intracerebral injection.

The Effect of passing the Virus through Animals.—The question whether the biological characteristics of the virus become altered when it is passed through animals is of great interest. The material available is not large. According to my own experience the behaviour towards glycerine is the same in the original virus and in virus which has been passed through animals; I have found no constant difference in virulence (pathogenic energy) towards monkeys between them. Leiner and v. Wiesner found no diminution of virulence after a "long" series of reinoculations. Flexner and Lewis, who have passed virus through longer series of animals than anyone else, have come to the conclusion that the virus becomes more powerful, or, at any rate, loses none of its potency and becomes more constant in its effect. This increase in constancy is shown in three ways: (1) The higher proportion of fatal cases; (2) the higher percentage of successful intracerebral

inoculations (100 per cent. instead of 75 per cent. with the original virus); and (3) a greater uniformity in the duration of the incubation period. These experiences remind one of the results obtained by Pasteur in hydrophobia; he found that the virulence towards rabbits was increased by passing the virus through a large number of rabbits; intracerebral inoculation acted more certainly and with a shorter incubation period. We know now, however, that the term exaltation of the virus must be used *cum grano*, because the "exalted" virus is less potent than the ordinary kind, when administered subcutaneously. At any rate, some peculiar biological change does take place in the virus, and we are inclined to regard it as the essential factor underlying protective inoculation against hydrophobia. The observations of Flexner and Lewis make it not improbable that continued passage through monkeys causes some biological change in the pm. virus, turning it into a kind of "virus fixe," as shown by the greater constancy of the incubation period, of the morbidity and of the mortality. Further investigations must be made to find out if the changes produced in this manner can be demonstrated by other means.

Flexner and Lewis have called attention to a point which is of importance in this connection. They assume that the sudden change from man to monkey ("change of host") must have a considerable effect upon the virus because it is so often destroyed in the process. My own experience confirms this in some measure; of the five original examples of virus I succeeded in transmitting only three to monkeys. We must regard it as a possibility that the transference of the virus to monkeys causes some biological change in the virus. The present state of our knowledge does not admit of any more definite statement. A wide field is left open in this direction also to future experimenters.

IV.—THE USE OF OTHER ANIMALS FOR EXPERIMENT.

The Susceptibility of Different Animals.—It would be a great advantage if some other animal, more easy to obtain and keep and less costly, could be submitted for the monkey. I have experimented with white mice, guinea-pigs, sheep, goats, and dogs; using the method of intracerebral injection, which proved the best in the case of monkeys, I nevertheless was unable to produce any symptoms of poliomyelitis in these animals. In all the experiments the brain and spinal cord emulsions proved entirely non-virulent, although the same emulsion injected into monkeys produced typical lesions of poliomyelitis. Other observers (Leiner and v. Wiesner, Landsteiner and Levaditi, Krause and Meinicke, Flexner and Lewis) obtained the same negative results. Flexner and Lewis even used pigs, horses, cows, and cats; they observed the animals for weeks after the injection but they never saw any paralysis.

Leiner and v. Wiesner, and also Landsteiner and Levaditi, used young dogs and injected the virus both into the brain and the peritoneum, but they obtained no single positive reaction. The same authors and Krause and Meinicke have proved that fowls and pigeons are not susceptible. It is quite certain therefore that all the animals mentioned are not susceptible to the virus of poliomyelitis. This negative finding is of importance in judging the assumption which is made frequently, that the occurrence of paralysis in animals, particularly fowls and dogs, can be connected with epidemics of Heine-Medin disease.

Earlier Experiments with Rabbits.—There has been much controversy about the susceptibility of rabbits. The rabbit was the first animal used for experimental injection of material obtained from children who had died of paralysis. The first attempt was made in 1899 by Bülow-Hansen and Harbitz. They injected emulsion of the spinal cord and cerebro-spinal fluid into rabbits and mice, using the intracerebral method among others. The results were all negative. The experiments of Guinon and Rist (1903), in which cerebrospinal fluid from cases of poliomyelitis was injected into rabbits, led to no positive results. In 1908, Pasteur, Foulerton, and MacCormac reported positive results with rabbits for the first time. They injected cerebrospinal fluid, obtained eleven days and four weeks after the commencement of the disease, into rabbits; in some the injection was subcutaneous, in others intraperitoneal, and finally intracerebral. Many of these animals became paralysed some time after the injection; the authors report that in a few cases they were able to infect other rabbits with the cerebrospinal fluid of these first rabbits, but that it was not possible to transmit the disease to a third generation. Histological examination of the spinal cord of one of the paralysed rabbits showed *no changes characteristic of poliomyelitis.*

Krause and Meinicke's Experiments with Rabbits.—The experiments of the English authors raised hopes that poliomyelitis might be produced experimentally in rabbits and their experiments were repeated by Krause and Meinicke in the summer of 1909 at the time of the great Westphalian epidemic. These authors used "large doses" of cerebrospinal fluid obtained from autopsies or by lumbar puncture; the injections were intraperitoneal, intravenous or subdural. Very many of the animals became ill after the injection, and Krause and Meinicke observed "a certain regularity in the period of time elapsing before the illness began, in the character of the symptoms and in the total duration of the illness. Death was ushered in by symptoms which pointed to a lesion of the spinal cord." In their first paper Krause and Meinicke do not record any microscopical examinations. They found that spleen pulp, blood, and cerebrospinal fluid of rabbits dying of poliomyelitis were suitable for further transmission of the disease as well as the brain and spinal cord. It is to be noted that the disease consisted of the above peculiar symptoms.

Results of Personal Experiments.—In my first experiments I used rabbits bred in the laboratory. The animals were full grown and weighed from 2,000 to 3,000 grm. I chose adult rabbits which were already acclimatized to the laboratory, because young rabbits are known to succumb readily to secondary infections. The first experiments with their results are as follows:—

Experiment 1.—Cerebrospinal fluid was obtained by lumbar puncture from a 3-year-old child who had suffered from paralysis for three weeks and was in the chronic stage of the disease. The fluid was kept in an incubator at temperature 37° for ten days in order to "exalt" the virus. An intracerebral injection of ·2 c.c. was made into two rabbits. Both animals remained quite well.

Experiment 2.—Fluid was obtained by lumbar puncture from a very acute and extensive case which died twenty-four hours later and showed typical microscopial changes in the cord. The virus was "exalted" for seven days, as in Experiment 1, and ·2 c.c. was injected into two rabbits. Both remained well.

Experiment 3.—·2 c.c. of the fluid from the case used in Experiment 1, but obtained fourteen days later, was injected into two rabbits. The one died of suppuration from a bite on the abdomen; on microscopical examination the brain and spinal cord were normal. The other animal remained well. Two other animals received an intracerebral injection of ·2 c.c. of the same virus passed through a Berkefeld filter; they remained well. Finally ·2 c.c. of the blood of this case was injected into a rabbit, which remained unaffected.

Experiment 4.—Fluid was obtained from a baby, 9 months old, suffering from paralysis of moderate degree for seven days. Two rabbits each received an intracerebral injection of ·1 c.c. and both remained well.

These results contradict the experience of Krause and Meinicke, who found cerebrospinal fluid suitable for the transmission of the disease. It should be noted further that in some of my experiments the fluid was obtained from acute and severe cases. The attempt to "exalt" the virus in the incubator cannot have affected its virulence. The entirely negative character of the results made me sceptical about those reported by Krause and Meinicke. On the other hand, this fact proved nothing against the possibility that rabbits might be susceptible to the disease and so of use in research. On the one hand, it was doubtful if the cerebrospinal fluid contained virus at all, and, on the other hand, whether it contained a sufficient quantity of the virus.

In my subsequent experiments I always used material which I was certain contained virus, *i.e.*, emulsion of the brain and spinal cord of human beings and monkeys known to have died of the disease.

Experiment 5.—An emulsion of virus No. 6 was injected into six rabbits, two by intravenous injection (·5 c.c.), two intraperitoneal (·5 c.c.), and two intracerebral (·2 c.c.). All remained well, although a monkey

injected with the same material died of acute, severe poliomyelitis, and material from this monkey proved fully virulent.

In consequence of these results I felt bound to advise caution in judging of the value of reports of positive results obtained with rabbits. The rabbit is known to be a very sensitive animal and this has several times led to much confusion in etiological investigations; the French have even called it an "animal capricieux."

Subsequent investigations confirmed my previous conclusions. Each original virus, which I described on pp. 34-42, was injected into rabbits as well as into monkeys. I shall not describe the results obtained with virus 2 and 3, because no definitely positive result was obtained with these in monkeys. Injection of these strains into rabbits remained without any effect. The following description relates only to those strains with which a positive result was obtained in monkeys.

Experiment 6.—Original virus No. 11 injected into six rabbits, three intraperitoneal and three intracerebral. A 5 per cent. emulsion, which had been allowed to stand for a time in order to separate the larger particles, was used; the dose was ·2 c.c. for intracerebral, and 3 c.c. for intraperitoneal injection. All the rabbits remained well, while monkeys (*a*), (*b*) and No. 11 died with typical paralysis (*cf.* p. 41).

Experiment 7.—A 20 per cent. emulsion of original virus No. 12 was used. Six rabbits received injections: two intracerebral (·2 c.c.), two intraperitoneal (3·5 c.c.), and two intravenous (2 c.c. of emulsion filtered through paper). One rabbit which received an intracerebral injection died of pleuropneumonia on the twenty-third day; one of the intravenous cases died on the sixteenth day of some unknown cause; the brain and spinal cord of this animal showed no pathological changes (another rabbit which had received no injection happened to die on the same day, and in this animal also we failed to find any cause of death). The rest of the rabbits remained well. Monkeys Nos. 4 and 13, infected with this emulsion, died with typical poliomyelitis.

No injection, therefore, was successful in which virus obtained direct from human beings was used. In the following cases virus was used which had been passed through monkeys.

Experiment 8.—With an emulsion of virus No. 11, passed through one monkey, injections were made into eight rabbits on December 17; four intraperitoneal (4 c.c.), four intracerebral (·2 c.c.). One of the latter died on the twenty-first day from pleuropneumonia. All the rest remained well. Monkeys Nos. 14 and 5 became ill on the ninth and seventh day, and died with typical paralysis on the third and fourth day later. Typical *post-mortem* changes (*cf.* pp. 48 and 155).

Experiment 9.—On December 24 six rabbits were injected with an emulsion of virus No. 11, passed through two monkeys; three injections were intravenous (2 c.c. of emulsion filtered through paper), and three intracerebral (·2 c.c.). All remained well. Monkey No. 15, injected on the same day, became ill on the eighth day, and died of paralysis two days later. Typical changes *post-mortem*.

Experiment 10.—On December 28, 1909, five rabbits received an intracerebral injection (·2 c.c.) of a 5 per cent. emulsion of virus No. 11, passed through two monkeys. The animals remained well. Monkey No. 16 was injected with the same emulsion; it became paralysed on the sixth day, and died on January 5, 1910. *Post-mortem* appearances typical.

It is necessary for me to discuss these results more fully than I have done so far, because Krause and Meinicke have stated, in the *Deutsche med. Wochenschr.*, 1910, 14/15, that they are justified in not considering my experiments to be unobjectionable repetitions of their own; in another place these authors say their results cannot be interpreted otherwise than in their own sense unless "unobjectionable repetitions" of the experiments lead to different results. In my opinion no objection can be brought against my own experiments. Krause and Meinicke seem to imagine that the experiments on rabbits reported in my first paper formed the basis of my statement that "the Krause-Meinicke experiments allow of an interpretation other than that given by the authors." But in my second paper, the one attacked by Krause and Meinicke, it will be seen that I injected the virus of three cases of human poliomyelitis and of five cases of experimental poliomyelitis in monkeys into rabbits without any positive result; the virus from all these cases, injected into monkeys, immediately caused disease and death. These are the experiments I have described in full above; in my second paper, owing to the entirely negative character of the results, I did not feel justified in burdening the reader with the full details. In their first paper Krause and Meinicke made the general statement that rabbits are susceptible to the virus of poliomyelitis, without specifying any conditions as to age or variety of the rabbits used. If they object to my experiments on this score it can be only because they overlook the fact that they set up such standards at a later date. There is only one point to which perhaps I have not given sufficient attention and which might make the criticism of Krause and Meinicke justifiable. In their first paper they state that "very large doses were used." Unfortunately, no indication is given as to what doses they regard as being "very large." Later they rejected the intracerebral method of injection because it did not allow of large doses being administered; but the reports in their first paper contradict the necessity for this course, because in them they state that they succeeded in infecting rabbits by just this method.

Results obtained by other Observers.—Very competent observers, such as Flexner and Lewis, Leiner and v. Wiesner, Landsteiner and Levaditi, have obtained entirely negative results with virus which promptly produced paralysis in monkeys. At a later date Eichelberg, Selter, and Potpeschnigg all failed to produce the disease by injection of lumbar puncture fluid. However, Krause and Meinicke make the further accusation against me, that I have not paid enough attention to the reports of positive results; they quote in this connection the experiments of Bonhoff, Beneke, and Dahm.

Bonhoff reported that three rabbits died twenty-two days after inoculation with material from a case of human poliomyelitis, but that none of them showed any microscopical lesions characteristic of poliomyelitis, nor did material obtained from the brain, spinal cord, and spleen of these animals affect other rabbits in any way. He concludes: "I cannot trace

the cause of death in these animals. They were well nourished, and suffered from no injuries. I agree with my colleague, Römer, that no symptoms such as those described by Krause and Meinicke appeared in our animals; in particular, no paralysis occurred." I do not think that this statement by Bonhoff contained anything which could justly cause me to change my opinion of the results obtained by Krause and Meinicke. The experiments of Beneke would have been more likely to do so. He injected three rabbits with material containing the virus of poliomyelitis, and observed peculiar symptoms ending in the death of the animals; but the spinal cords were found to be free from any demonstrable pathological change. Considering that I used the same material as Bonhoff and Beneke for an extensive series of experiments on monkeys and rabbits, and that I did not observe the death of one single rabbit in circumstances which were in any way suspicious, I was unable to accept the observations of Beneke and Bonhoff as in any way proving that rabbits were susceptible to the virus of poliomyelitis. I may add that these authors themselves do not agree that their results can be considered to constitute a proof of the transmissibility of the disease to rabbits, as Krause and Meinicke have tried to make out.

The observations of Dahm are of but little value, as they do not include any microscopical examination of the material.

In the same papers Krause and Meinicke quote Kraus and Levaditi in support of their argument. They state that the experiments of the latter constitute a "confirmation and completion" of their own.

Kraus at first was unable to obtain any positive result with intracerebral injection of pm. virus into rabbits; later, he saw *one* animal die with symptoms like those of rabies; the medulla and brain of this rabbit injected into other *young* rabbits produced symptoms of disease. He draws the conclusion that "these experiments, which will be carried further, show that transmission of the disease to *young* rabbits is possible." Krause accentuates the fact that "the lesions characteristic of poliomyelitis were not found in these animals." Later, Krause again became very sceptical about the value to be attached to experiments with rabbits. At the meeting of the Freien Vereinigung für Mikrobiologie, held in Berlin in 1910, he stated that all attempts to transmit the disease from the "infected" rabbits to monkeys had failed. He again called attention to the fact that the result of microscopical examination was entirely negative, and said that the whole question of the transmission of the disease to rabbits was not proven, and that all apparently successful inoculations should be received with scepticism.

The experiments of Landsteiner and Levaditi can be accepted still less as constituting a "confirmation and completion" of those of Krause and Meinicke. The former report that in all attempts save one they failed to obtain any result; this particular rabbit received an intracerebral injection on December 29, 1909, of virus which had been passed through a monkey; twenty-four days later the animal died without showing any signs of paralysis. On microscopical examination appearances were seen which were similar to those observed in human poliomyelitis. The perivascular infiltration, so typical in human and monkey poliomyelitis, was but little marked. Landsteiner and Levaditi give it as their opinion that in this one case there was an affection of the central nervous system, similar to that observed in poliomyelitis in man and the monkey. How far removed they

were from admitting that rabbits are suitable subjects for the investigation of poliomyelitis, or that the experiments of Krause and Meinicke are of any value in proving this, is shown by the exhaustive criticism to which they subject this theory in their latest work (November, 1910). We shall return to this matter later. Landsteiner and Levaditi say cautiously that the transmission *appears* to have been successful in this case. But the proof is by no means complete, as no successful inoculations into other animals, specially monkeys, were made from this case. I suggest further, in view of the fact that this case of Landsteiner and Levaditi is the only one in which lesions in any way resembling poliomyelitis have been seen, that it is not impossible that they were due to a spontaneous disease in the rabbit and not to the experimental inoculation. Joest and Degen have proved the existence of the epidemic Borna's disease in horses, and it is quite possible that a similar disease occurs in rabbits.

So far, none of the results obtained by other authors can be regarded as confirming those recorded by Krause and Meinicke. The experiments made by Lentz and Huntemüller at the Institute for Infectious Diseases in Berlin are more to the point.

Lentz and Huntemüller received from Krause and Meinicke in Hagen rabbits and monkeys which had been inoculated with the cerebrospinal fluid, brain and spinal cord, spleen and blood of patients who had died of infantile paralysis. They report that most of the rabbits died after a shorter or longer period, generally seven to eleven days, but sometimes two months (!) afterwards; rabbits and monkeys were inoculated successfully with various organs from these animals. Lentz and Huntemüller believe that the symptoms were due to the poliomyelitis virus received in Hagen. Krause and Meinicke, in their most recent paper, formulate the conditions under which a successful result with rabbits may be expected. These are:—

(1) Only particular varieties of rabbits must be used; Krause and Meinicke describe these more closely.

(2) Only young rabbits of not excessive body weight are susceptible.

(3) Only rabbits which have received "large doses" show signs of the disease. (Unfortunately, in this their latest paper these authors omit to state what they mean by "large doses." If this point is really of so much importance, it is essential in our opinion that some data should be given respecting the weight of fluid, blood, or emulsion used.)

Renewed Repetition of the Experiments.—In view of the new conditions laid down by Krause and Meinicke, and of the results obtained by Lentz and Huntemüller, I felt that a new situation had arisen. In collaboration with Joseph I carried out a new series of experiments in order to settle the question of the utility of rabbits in this field of research.

As the criticism of Krause and Meinicke was directed solely against myself, I asked Dr. Joseph to form his judgment as to the suitability of the rabbit for experiment quite independently; in this way I hoped to obtain an unbiased opinion. Dr. Joseph made the following experiments independently of me; we also observed the animals apart from one another. The conditions under which the experiments were carried out were those described as the most favourable by Krause and Meinicke: Belgian giant-rabbits of unobjectionable, well-attested pedigree, chosen by an experienced breeder of rabbits, were used exclusively; only young animals were

employed which we had watched growing up ourselves; the weight of the animals used varied from 400 gm. to 710 gm., an average of 600 gm.; the method of inoculation was that recommended by Krause and Meinicke as the most certain, viz.: simultaneous intraperitoneal and intravenous injection. Contrary to Krause and Meinicke, we made an attempt to measure the dose given; it was weighed in the moist state before injection. The material used was an emulsion of the brain and spinal cord of a monkey which had died of typical poliomyelitis.

Experiment 11, April 27, 1910.—The virus used was an emulsion of the brain and spinal cord of monkey 42 (virus No. 12 passed through four monkeys). Four Belgian giant-rabbits (946, 947, 948, and 949) weighing from 460 gm. to 630 gm. each received 2 c.c. of 5 per cent. emulsion filtered through paper intravenously, and 3 c.c. of the same emulsion unfiltered into the peritoneum. On the same day monkey 49 (*Macacus rhesus*) received an intracerebral injection of ·6 c.c. of the same virus.

Result: Monkey 49 well until May 9. On the 10th paresis of the hind limbs, right more than left; this became worse during the next days. Improvement began on the 13th, but there was well-marked paralysis for a long time. Later the animal got quite well.

Rabbits 946, 947 and 948 remained well for four months, during which time they were observed daily. Rabbit 949 became paralysed in the left fore limb and left hind limb on May 14; the paralysis varied in degree and was permanent. It affected only the limbs of the left side, and was definitely spastic in character, *e.g.*, the left hind limb can scarcely be bent at all. The animal was killed on June 21 for purposes of diagnosis. Macroscopic investigation was negative.

Dr. Joseph took the trouble to make serial sections of the spinal cord and of pieces of the medulla and brain. No lesions characteristic of poliomyelitis could be found in this animal. Unfortunately, he did not succeed in finding any cause for the paralysis. We have never observed a spastic hemiplegia in monkeys, nor has Wickman throughout his wide experience in man, and it is probably not incorrect to assume that the paralysis in this rabbit was not due to the injection, or, at any rate, was not the result of infection with poliomyelitis. I may mention here that paralysis is observed very frequently in rabbits kept in hutches in the laboratory, and that the cause cannot be found always.

Experiment 12, May 19, 1910.—An emulsion of the brain and spinal cord of monkey 48 (virus No. 11, passed through six monkeys) was used. Rabbits 943, 944, 945, 950, 951, and 952 received an intravenous injection of 2 c.c. of a 5 per cent. emulsion filtered through paper, also an intraperitoneal injection of 3 c.c. of the same virus unfiltered. Monkey 56 received ·8 c.c. of the emulsion into the brain and 3 c.c. into the peritoneum.

All the rabbits remained perfectly well, without a trace of paralysis, during four months under daily observation.

Monkey 56 remained well until June 1. On June 2 in the morning paresis of the fore limbs; in the afternoon definite paresis of the hind limbs; June 3 paresis more marked; June 4 total paralysis of the left hind limb and of the right fore limb, marked paresis of the other limbs; June 5-7, condition unchanged; June 8, marked general paralysis. Found dead on the 10th. Typical microscopical appearances.

Experiment 13, May 31, 1910.—An emulsion of the brain and spinal cord of monkey 36 (virus No. 11 passed through five monkeys) was used.

Inoculation was carried out with rabbits 953, 954, 956, 957, 958, 959, 960, 961, 962, 963, and with monkey 58. The rabbits received an intraperitoneal injection of 2 c.c. of a 5 per cent. filtered emulsion and an intravenous injection of 3 c.c. unfiltered emulsion. Monkey 58 received ·5 c.c. of filtered virus into the brain.

All the rabbits remained well for four months under daily observation.

Monkey 58 remained well until June 10. On the 11th total paralysis of the left hind limb and paresis of the right hind limb. On the 12th total paralysis of both hind limbs and paresis of both fore limbs. On the 13th general paralysis and death. Microscopical appearances very typical and very intense in the lumbar region.

Experiment 14, July 13, 1910.—The virus used was an emulsion of the brain and cord of monkey 48 (Virus No. 11 passed through six monkeys). Rabbits 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, and monkey 102 were inoculated. The rabbits received an intravenous injection of 2 c.c. of a 5 per cent. emulsion filtered through paper, and an intraperitoneal injection of 3 c.c. of the 5 per cent. emulsion unfiltered.

All the rabbits remained well for four months under daily observation.

Monkey 102 received an intracerebral injection of ·6 c.c. of 5 per cent. emulsion, unfiltered. Well until the 24th. On the 25th typical flaccid paresis of the hind limbs and weakness of the back muscles. In the evening paralysis of the hind limbs and of the left fore limb, facial palsy on the right side. Death on the 25th. Microscopical appearances typical.

Thirty-one rabbits in four series received large doses of material containing the virus of poliomyelitis by simultaneous intravenous and intraperitoneal injection. The virulence of the material used was proved by the fate of *the four control monkeys, which all died of typical poliomyelitis*. Of the thirty-one rabbits, thirty remained well for four months under daily observation; one single animal suffered from an atypical form of paralysis for which no lesion of the nature of poliomyelitis could be made responsible.

This closes the series of our experiments with rabbits. In all, including the earlier experiments, there were eighty-one animals; of these, one died from suppuration following a bite, two died of pleuropneumonia, one of a cause unknown, and one of a form of paralysis not due to poliomyelitis, but the cause of which could not be elucidated. All the rest remained well.

Even when we conformed to all the conditions laid down by Krause and Meinicke, we were unable to corroborate their results. Our observations form a complete contrast to those obtained by Krause and Meinicke, as also by Lentz and Huntemüller. As I do not believe that the matter can be carried any further by means of experiment, I will attempt to do so by a critical discussion of the facts.

Criticism of the Arguments in Favour of using Rabbits.—Krause and Meinicke base their view, that the rabbit is a suitable

animal for experiments with poliomyelitis and that their results prove this, upon the following arguments: They emphasize the facts (1) that rabbits inoculated at the same time become ill at the same time and some time after the infection; (2) that, consequently, the symptoms observed cannot be due directly to injury received at the time of injection, owing to material from another animal being introduced into the blood; (3) that the symptoms observed were certainly "nervous in character." This argument is not quite sound; I refer the reader to the full description of my earlier experiments (pp. 30-31); there he will find that the introduction of morbid material of various kinds (streptococci, *B. coli*) in fact of any foreign substance in a molecular state directly into the blood-stream, will cause paralysis or symptoms similar to paralysis at a time considerably later than the date of injection.

Lately Selter has again found that infection of rabbits with streptococci causes paralysis. In this connection the researches of Potpeschnigg are even more instructive. He obtained a diplococcus from the cerebrospinal fluid of a case of poliomyelitis, and injected living and dead cultures of this organism into the peritoneum, veins, and brains of rabbits. "In a few cases widespread paralysis resulted." This author was prevented from drawing a wrong conclusion from his results by a knowledge of previous experiments with rabbits (*cf.* p. 31). In view of the present discussion I recommend the reader to refer again to these experiments.

In addition, Lentz and Huntemüller, who believe that they have confirmed the results obtained by Krause and Meinicke, have stated: "We would not lay much stress upon convulsions and paralysis occurring in rabbits; *we have observed rabbits which died of convulsions soon after being brought to the department and by inoculation from these animals we have occasionally been able to produce convulsions in others.*"*

Meinicke's further argument, that no other cause of death was ascertainable, is of very little value; how often do we not have to put a query under the heading "Cause of death," in the case of rabbits which die in the laboratory? One of the best arguments in support of their contention would have been the demonstration that the lesions produced in their rabbits were similar to the lesions of poliomyelitis in man or monkey. Indeed, in the course of a lecture before the Rheinisch-Westfälischen Gesellschaft für innere Medizin und Nervenheilkunde, on November 14, 1909, Meinicke said: "Together with Dr. Hohn, of Essen, we were able to demonstrate qualitatively the same changes in one of our rabbits, which died with characteristic symptoms, as are found in typical cases of poliomyelitis in man and in monkeys. Vascular and diffuse cell infiltrations and small hæmorrhages were found in the grey matter of the spinal cord and degenerative change in the tigroid of the ganglion cells." In another place he says: "It may be mentioned here that we found characteristic changes (thrombosis,

* No italics in the original.

næmorrhage, diffuse and perivascular cell infiltration) in the central nervous system of animals inoculated from these rabbits." Finally, he said: "Thus the final proof is provided; we were justified in interpreting our results with rabbits as a true transmission of the virus of infantile paralysis."

But the experiments of Lentz and Huntemüller, which he himself quotes in support of his argument, are not in keeping with this generalization. These authors write: "Microscopical evidence of any lesion is frequently very slight, but congestion of the vessels, hæmorrhages and cell degeneration are often to be found in the grey matter, particularly of the brain. *We were unable to find any cell infiltration round the vessels or in the substance of the central nervous system such as is found in cases of poliomyelitis in man and in monkeys.*"*

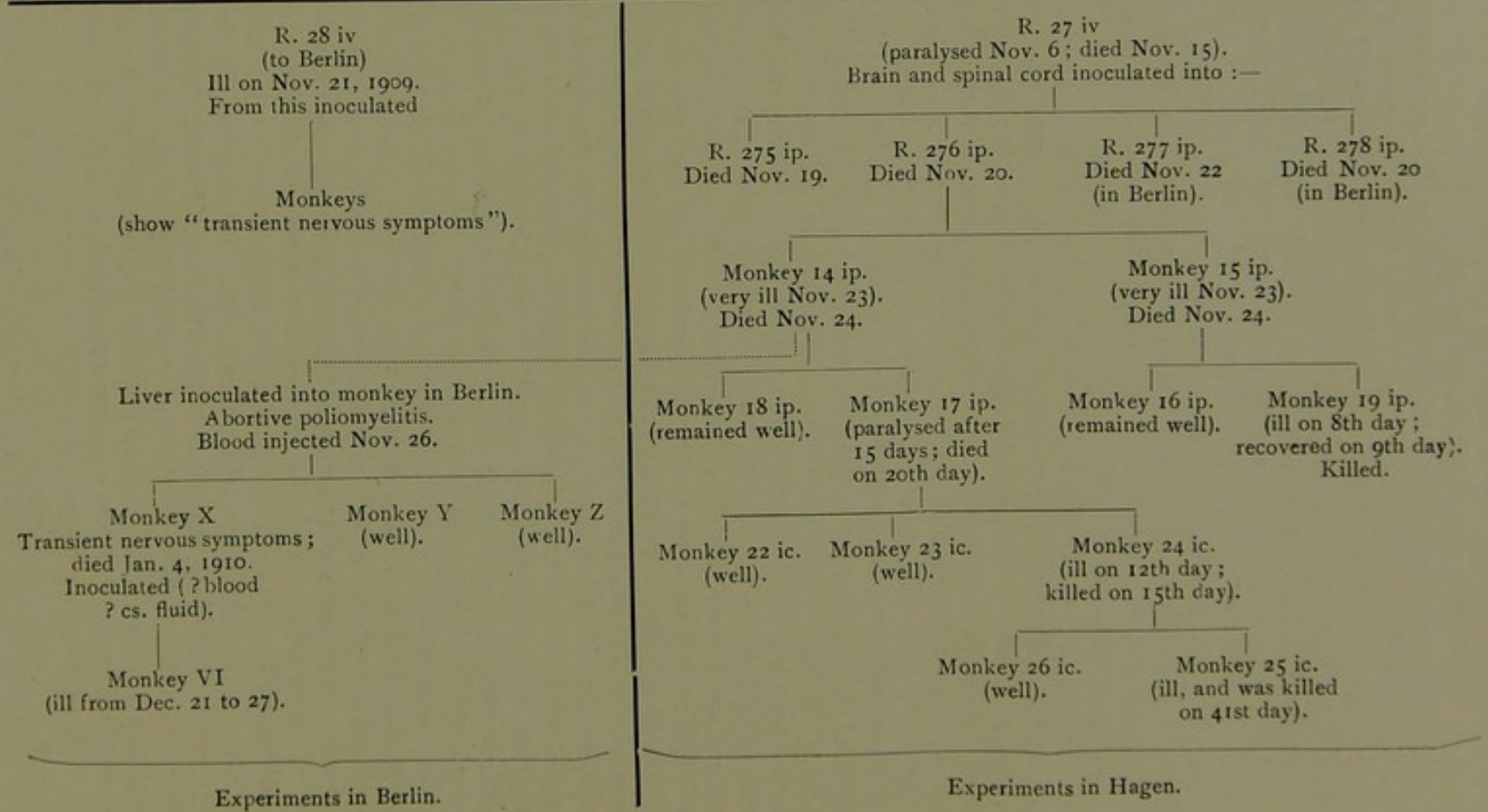
Lentz and Huntemüller make a definite statement, therefore, that they did not find perivascular infiltration as was observed by Meinicke. But we shall see later that perivascular infiltration is the most characteristic change in poliomyelitis. With regard to the findings of Lentz and Huntemüller, I must call attention again to the results of the earlier experiments in which not only bacteria of all kinds but also non-living material was used. The changes described by the former experimenters remind one forcibly of those found by Lentz and Huntemüller. Personally, I found myself unable to agree that their specimens, which were demonstrated at a meeting of the Freien Vereinigung für Mikrobiologie, showed the presence of the lesions of poliomyelitis. Landsteiner said of these specimens: "The preparations from rabbits which have been demonstrated show very slight changes; in the sections of the spinal cord of a monkey inoculated with material from a rabbit by Lentz and Huntemüller there are none of those characteristic changes which are always found in monkeys, and I do not think that a diagnosis of poliomyelitis should be made, nor do I think it a probable diagnosis. I have seen similar appearances in animals which certainly did not die of poliomyelitis."

As there can be no doubt that the monkey is susceptible to the virus of poliomyelitis, and as the disease can be reproduced in monkeys in a form both clinically and pathologically similar to the disease in man, the question whether the rabbits of Krause and Meinicke and of Lentz and Huntemüller really died of the effects of poliomyelitis virus allows of a crucial experiment. If the rabbits died of poliomyelitis, inoculation of a monkey with material obtained from them should produce the typical clinical and pathological picture of poliomyelitis in the susceptible monkey. Krause and Meinicke claim to have carried out this experiment and Lentz and Huntemüller in Berlin set up the same claim. We will consider these claims more closely.

I have collected the allegedly convincing experiments from Meinicke's papers, and arranged them in the form of a genealogy.

* No italics in the original.

ORIGINAL MATERIAL: LUMBAR PUNCTURE FLUID FROM A CASE OF POLIOMYELITIS, OCTOBER 2, 1909.



We must confess to having many doubts as to the validity of the proof put forward. In the first place, it is remarkable that lumbar puncture fluid should be the original virus-containing material, and that at a date several days after the beginning of the paralysis. As we shall see later, in no single instance has it been found possible to infect monkeys with human cerebrospinal fluid. It would be very remarkable if such material had affected a rabbit, which is at least less susceptible than a monkey. Further, the first rabbits only became ill after thirty-five days (the one which was sent to Berlin only after fifty days), while the subsequent rabbits (275-278) died in four to five days. I can hardly believe that the fact that these animals were younger can account for such a difference in incubation period. The symptoms observed in the monkeys were not in any way typical of poliomyelitis. I must refer the reader to Meinicke's original publication on this point; he says himself that he did not observe any marked paralysis in the monkeys.*

Landsteiner says of the observations made by Meinicke: "It is quite uncertain from what disease these monkeys suffered." In another place, in conjunction with Levaditi, he says: "Elles sont peu nettes et ne sauraient être idendifiées à celles que l'on relève ordinairement chez l'homme, ou les simiens infectés avec du virus de passage."

The Berlin experiments quoted by Krause and Meinicke show clearly that these authors accept a small amount of evidence as proof that poliomyelitis has been transmitted to monkeys. In these experiments the blood of a monkey alleged to be suffering from poliomyelitis was said to have caused abortive poliomyelitis. One of the monkeys inoculated showed "transient nervous symptoms" after a week had elapsed, and Krause and Meinicke actually say that "this experiment gives valuable support to our own inoculations with the blood of rabbits and human beings."

How little the symptoms observed in Meinicke's monkeys had to do with poliomyelitis is shown further by the observation made by him, that acutely and severely paralysed cases were able to overcome the paralysis occasionally, when they were stimulated to perform movements and were subjected to radiant heat. Such an observation has never been made by any other investigator of poliomyelitis. When Meinicke goes so far as to explain the atypical character of the disease produced by suggesting that the action of the virus on monkeys has been altered by its passage through rabbits he is ignoring the *petitio principii*.

* He certainly continues: "On further careful study of the results reported by Römer, I have received the impression that they more or less correspond with symptoms observed in my monkeys." But I must object strongly to the view that the symptoms observed by me bore the remotest resemblance to those described by Meinicke. I hope that the full report of the symptoms which I have given above will enable the reader to form his own judgment. Let him compare them with those described by Meinicke in the *Deutsche med. Wochenschrift*, 1910, 15, and see whether the latter bear any resemblance to the symptoms I have described, and which Meinicke himself demonstrated by means of the cinematograph at the Medical Congress at Wiesbaden in 1910.

In the Berlin experiments of Lentz and Huntemüller, which are quoted as confirmatory, monkeys inoculated with human cerebrospinal fluid died seven to eleven days after infection "without having shown any signs of paralysis." "Pathological, microscopical, and bacteriological examination proved negative." The transmission of the disease from rabbits, sent from Hagen to Berlin, to monkeys was successful. The monkeys showed "repeated short periods of paralysis at intervals of two to four weeks." Another monkey "died of marasmus following two attacks, from which it had recovered partially." Yet another was "killed during an attack." In these monkeys were found "marked engorgement of the vessels, hæmorrhages, degeneration of the ganglion cells, which were invaded by small cell infiltration," *i.e.*, no adventitial or perivascular infiltration, the characteristic lesion of the disease.

It is clear that in these experiments neither true paralysis nor characteristic microscopical lesions were observed. Lentz and Huntemüller assume that the virus was attenuated in order to explain this. The difference between my results and those of the Hagen and Berlin investigators cannot be bridged. I found that material which was fully virulent in monkeys was non-virulent in rabbits, and yet in Hagen and Berlin material which was feebly virulent or non-virulent for monkeys was virulent for rabbits The question of a biological change having taken place in the virus might have been considered if I and other writers had not obtained similar results by using virus taken direct from human beings. The fact that Lentz and Huntemüller were able to infect rabbits easily with virus sent to them by Landsteiner from Vienna and by me from Marburg, while we found the same virus entirely non-virulent for rabbits, still remains to be cleared up. I shall return to the question of how these contradictions may be explained.

So far, the results of a critical analysis prove that Krause and Meinicke are not justified in claiming that their results prove that rabbits are susceptible to the virus of poliomyelitis and, therefore, that they are suitable animals for research, nor that they had succeeded in transmitting the disease to rabbits. A number of important considerations still remain.

Further Objections to Experiments with Rabbits.—To begin with, it is remarkable that the intracerebral method should have proved less efficacious than the intraperitoneal and intravenous methods. Experiments with monkeys have proved the intracerebral method to be the most certain. Considering the selective affinity of the virus to the central nervous system, it is difficult to understand why bringing virus and the central nervous system directly together should have given such poor results. Further, it is really extraordinary that, besides the brain and spinal cord, the lumbar puncture fluid, the spleen pulp, and the blood of human beings, and the liver of a monkey should all prove to contain the virus. Even by using the very susceptible monkey, no other experimenter has succeeded in demonstrating the virus in this material. I myself had consistently negative results when using blood and cerebrospinal

fluid direct from man to monkey, and Flexner and Lewis, Leiner and v. Wiesner, Landsteiner and Levaditi have all had the same experience. Selter and Potpeschnigg injected cerebrospinal fluid without result. Only Flexner and Lewis have been able to find virus in the blood and cerebrospinal fluid of monkeys, and then only by using enormous quantities of blood and under special conditions with cerebrospinal fluid (intracerebral injection of the monkey with removal of the cerebrospinal fluid before the occurrence of paralysis).

The experience of Lentz and Huntemüller relative to the resistance of the virus to glycerine is totally different to my own. They state that preservation in 50 per cent. glycerine diminishes the virulence; that they succeeded in inoculating only one out of four monkeys with the virus which I sent to them does not alter the fact that in my experiments the glycerine virus was transmitted readily from monkey to monkey, and led to a typical illness in 90 per cent. of the cases.

Bearing in mind all the objections, the uncertainty of the clinical symptoms and the absence of any typical microscopical change, one can only be very surprised that Krause and Meinicke believe that their opinion, that the inoculation with material containing pm. virus was the cause of death in their rabbits, "has been confirmed in all directions."

To recapitulate: the following facts justify the scepticism with which numerous authors have looked upon rabbits as subjects for experimental poliomyelitis and have regarded the interpretation which Krause and Meinicke have placed upon their results. The symptoms observed in rabbits are of no value. The alleged positive results were obtained with material which was proved not to contain the virus in an infective condition, because it failed to produce poliomyelitis even in such a sensitive animal as the monkey. The *experimentum crucis* must be considered to have failed since reinfection from the rabbit back to the monkey did not produce poliomyelitis in the latter. The histological lesions found in the rabbits correspond to lesions which are easily produced whenever any foreign material is injected into rabbits, and they are quite different to the lesions of poliomyelitis. The alleged positive results obtained by Krause and Meinicke, Lentz and Huntemüller are opposed by the at least equally numerous negative results obtained by a larger number of observers, who worked with highly virulent material and in part under the optimum conditions as formulated by Krause and Meinicke. No support is given by any investigations along the lines of serum-diagnosis (*vide infra*).

An Attempt to explain the Difference.—It is naturally very difficult to elucidate the cause of death in the rabbits observed by Krause and Meinicke and Lentz and Huntemüller. The following is a possible explanation: It is possible that the animals suffered from some other disease, which was inoculable from one to the other and was carried by a non-bacterial virus. The difference

between the results obtained by Lentz and Huntemüller on the one hand, and Joseph and myself on the other, using the same virus, would seem to point to this. In Berlin the virus from Marburg produced the same results in rabbits as that from Hagen; in our hands, under the most favourable conditions and with rabbits which were said to be of the most susceptible variety, the virus proved itself innocuous to rabbits. One sentence in the paper by Lentz and Huntemüller is also significant; they say that rabbits which had not been injected and had only just arrived at the laboratory sometimes suffered from convulsions, and *that inoculations made from these animals into others caused convulsions.* We cannot say if this explanation is the true one, and I agree with the position taken up by Landsteiner and Levaditi: "que les divergences doivent dépendre de quelques circonstances encore mal définies à l'heure actuelle."

Practical Conclusions.—Krause and Meinicke, by making claims to which they have no right, make it necessary that the whole position of the rabbit should be clearly defined even at the risk of fatiguing the reader. Krause and Meinicke make no less a claim than this: "That these experiments prove for the first time that acute epidemic infantile paralysis is a communicable disease." In another place: "The proof, furnished by us for the first time, that the virus of poliomyelitis can be cultivated for a considerable time within the bodies of animals has made it possible to determine the nature of the virus more exactly, to test the efficacy of therapeutic measures by means of experiments with animals, and, above all, to study the question of immunity in animals." They claim further that they are the first to demonstrate the capacity of the virus to pass through a filter. I hope that I have proved conclusively that there is no justification for such claims.

A more important reason than this question of priority arises from the nature of the practical deductions drawn by Krause and Meinicke. In our opinion they are not justified. They recommend the rabbit for testing for the presence of poliomyelitis virus in fæces, in urine, in mucus from the throat, and in articles of food. They advise inoculation into rabbits for diagnostic purposes in doubtful cases, even in the abortive type of poliomyelitis. They hope to arrive at a diagnosis by injecting the blood of a doubtful case during life into a rabbit. A grave practical danger is present in these recommendations; the rabbit is so sensitive to all kinds of trauma and disease, and reliable criteria, by which a positive result may be judged, are so few that serious mistakes are inevitable.

One more assertion by Krause and Meinicke requires correction. They say: "A comparison of our results with rabbits and those obtained by other writers with monkeys seems to show that the rabbit is at least as susceptible as the monkey, and perhaps more so." In another place they speak of "the relatively great susceptibility of the rabbit," in which "relative" can apply only

to the monkey, the only other animal which enters into the question. The facts are the following: 90 to 95 per cent. of monkeys which receive an intracerebral injection of the virus become affected with poliomyelitis, and most of them die of the disease; in my own experience and that of most other authors not one single rabbit contracted poliomyelitis, and a critical examination of alleged positive results makes it clear, that at any rate it is very improbable that the symptoms observed can be connected with the virus in any way.

On one point one can agree with Krause and Meinicke. They point out that monkeys are not suitable for the study of conditions of immunity, because large series of these animals are not possible for obvious reasons. Unfortunately a knowledge of this fact does not render other unsuitable animals any more suitable for the purpose.

Krause and Meinicke have underestimated the importance of the experiments made with monkeys; they clearly do not realize how susceptible the monkey is and how typical are the clinical and pathological features which are produced. The number of experiments which can be carried out with monkeys by each individual investigator must remain small; but when we are in a position, as at the present time, to collect the results of experiments performed all over the world (New York, Paris, Vienna, Marburg), results may be obtained, as we have seen already and shall see later, which are of the greatest importance to science. With rabbits the most experienced investigators—Flexner and Lewis, Landsteiner and Levaditi, Leiner and v. Wiesner, and many others—have obtained only the most dubious results.

So far the rabbit has not proved to be a suitable animal for the investigation of poliomyelitis.

[Since Professor Römer thus defined the position of the rabbit as an animal for experiment, the American investigator, H. K. Marks, has carried out further experiments. Using virus obtained from the brain and spinal cord of a monkey affected with poliomyelitis he made intravenous and intraperitoneal injections into rabbits; the animals died on the eighth to fifteenth day with convulsions. *Post-mortem* examination revealed no lesions, but the disease was able to be transmitted to further rabbits by injection of the brain and spinal cord in most cases, and sometimes by using the liver and spleen. Marks was unable to carry the disease through more than six rabbits in this manner. From the second, fourth, and sixth rabbit-passages, however, he was able to produce typical lesions of poliomyelitis in three monkeys by intracerebral inoculation with the brain and spinal cord of the respective rabbits. Marks says definitely that in the rabbits "the disease cannot be recognized as poliomyelitis"; further, he claims only to have demonstrated that "the disease can survive and probably even be propagated in a domestic animal that does not show any of the peculiar symptoms

of the disease as it occurs in man." From this it is clear that his experiments do not give any support to the claims made on behalf of the rabbit by Krause and Meinicke. It is true that the results of re-inoculation from the diseased rabbits into monkeys proved the presence in them of the virus of poliomyelitis, but until the monkey was employed there was no evidence that the virus of poliomyelitis was present in the rabbits. The position of the rabbit thus remains the same as when it was defined by Professor Römer.—*Trans.*]

CHAPTER IV.

Pathology and Pathogenesis.

I.—HISTORICAL RETROSPECT—THE SALIENT FEATURES.

Heine's Views.—In my opinion a retrospect of the pathology of the disease should begin with a man whose name is not often heard in this connection. Heine in his first monograph mentioned the spinal cord as the probable seat of the lesion involved, and in his second monograph he insisted upon the spinal nature of the disease. In order to do full justice to Heine's clear and definite statement it is necessary to remember that before him no one had studied the disease in a scientific manner, and also what the condition of neuropathology was at that time. It is true that Heine did not demonstrate the lesion which he postulated, but that does not detract from the value of his discovery. He himself regretted that he could produce only hypotheses and not facts in the matter of the pathogenesis of the disease. The arguments by which he established his thesis were so exact and so comprehensive, that I feel impelled to draw attention to this portion of his services to medicine.

He first excludes the brain as the seat of the disease and, by a process of clear, logical criticism, arrives at the spinal cord as the site of the cause of the paralysis. "Although the primary irritative signs mentioned above do not exclude the possibility of a lesion of the nerve centres, and although one cannot be sure that some of the symptoms observed during the acute period are not due to an irritative lesion of the brain, yet the subsequent signs point rather to a lesion of the spinal cord as the essential factor in producing the paralysis, without more than a transient affection of the brain and its functions. The disease may consist in a sudden pressure on the cord produced by capillary extravasations or other exudates, which would lead to atrophy later, or there may be some other kind of lesion." A contemporary statement of Bardeleben's shows how much Heine's view appealed to clinicians: "Against the cerebral, and in favour of the spinal localization of the lesion, the following facts are of importance: the absence of lasting

cerebral signs; the integrity of the organs of special sense and of the intellect; finally, the rapid loss of electrical excitability in the muscles. It is well known that in paralysis due to a cerebral lesion the electrical excitability is maintained for years, while the spinal cord in this respect behaves like a nerve, and a lesion of it causes disappearance of the reaction in the muscles in two or three weeks."

Heine was undoubtedly wise in rejecting rickets, scrofula, and syphilis as being of any pathogenic importance. His firmness in adhering to his view of the spinal nature of the disease was of great value when the celebrated French clinicians, Rilliet and Barthez, published negative results from autopsies and gave the name of "essential paralysis" to the disease. And again, when Bouchut considered the disease to be a "paralysis idiopathica" caused by cold. Bardeleben criticized the negative findings of the former two authors with the words: "They are of but little value owing to the exclusively macroscopical nature of the investigation."

Heine's reasons for assuming a lesion of the cord were the following: The functions of the brain are not affected; the paralysis succeeds the general symptoms immediately, which would not be the case if the lesion were peripheral; the loss of electrical excitability, the absence of sensory symptoms, the degree of paralysis, the frequency with which the paralysis affects the lower limbs, the subsequent muscular atrophy, the incurability of the paralysis are all points against a peripheral localization. The occurrence of similar paraplegia in lesions due to other diseases affecting the spinal cord led Heine directly to a spinal localization. Finally, and this reveals the born clinician in Heine, he was convinced by the appearance of the helpless patients that he had to deal with a deep-seated lesion of the nervous system. He drew attention especially to the grey matter of the cord as "the chief channel of motor activity." With a prophetic insight into the true nature of the pathogenesis he adds: "Knowing all this, knowing that the grey matter is so well supplied with blood-vessels that accidental plethora may easily cause extravasations, while the grey matter is exceedingly liable to suffer from variations in its nutriment, knowing that the sections show atrophy of the grey matter to be the cause of the paralysis, what is to hinder us from deducing the cause of the diminution of motility from the same factors? Why should we not suppose some acute process to take place, which causes an alteration in the grey matter, impairs its conductivity, produces the paralysis in the lower limbs, and, by affecting the nutrition of the grey matter, causes secondary atrophy in it?" In another place: "Although the preceding anatomical facts and my experimental experience lead me to consider the various types of paralysis as due to spinal lesions, and being, in a way, different degrees of the same disease, I must not be understood to set apart particular portions of the cord as the invariable seat of the primary infection nor to consider any particular kind of lesion as pathognomonic; in the present state of our knowledge of the physiology and pathological anatomy of the part I cannot

make more than conjectures. Yet I cannot but give expression to my firm conviction that it is not in the brain or in the peripheral nerves, but in the spinal cord itself, speaking generally, that we must seek the cause of infantile paralysis. Even although we possessed no anatomical proof, yet the uniformity of the symptoms in 150 carefully observed cases, all pointing to this organ, is of no small importance; a theory based on observation of so large a number of cases might even venture to fill the gaps left in our knowledge of the pathology. I would ask those who are not satisfied with the results of pathological research (I myself, conscious as I am of their incompleteness, cannot regard them as being a final proof), whether they are able to bring forward other facts in support of their own different opinions or to formulate any theory which will hold as good in all the circumstances. If such people, who are only too prone to give the name 'essential infantile paralysis' to our disease, because it avoids the difficulty of specifying the nature of the illness, bring to me sections which show no lesion of the nerve centres, I would advise them to use the microscope; if this also fails to reveal a lesion I would suggest that, if at the present time changes are not evident to our eye, it is the latter which is at fault.

"Although I cannot but emphasize my conviction that it is the spinal cord which is involved, yet it remains only my humble opinion. I shall be quite satisfied if my statement has the practical result of stimulating the interest of physicians in the disease, so that the number of pathological investigations may increase and thereby a definite result be attained.

"On consideration of all the factors, and with the concurrence of many authors, I have adopted the name paralysis infantilis spinalis for this form of paralysis; with all respect to the authority of Rilliet in matters pertaining to diseases of children, I consider his term 'paralysie essentielle' which has been so widely adopted, as also that of Bouchut, 'paralysis idiopathica,' to be incorrect."

It is not going too far to say that it was Heine who showed the way for all subsequent research; he indicated the spinal cord as the seat of the disease, and in so far he was the founder of the pathogenesis of the disease.

From Heine to Charcot, Roger and Damaschino.—The *post-mortem* reports published by Heine included some cases of paralysis due to other diseases; in one case (Longet, "Anatomie et Physiologie du Système nerveux," Part I) there was paralytic club-foot, marked atrophy of the anterior roots and the corresponding lumbar and sacral nerves, but no abnormality of the spinal cord. Another case (Hutin) was certainly one of old infantile paralysis; in this there was an extraordinary atrophy of the spinal cord. This was the first positive *post-mortem*, although the findings were only macroscopic.

The Frenchman Cornil (1863) made the first thorough microscopical examination of a case (a woman, aged 49, who had suffered from the effects of infantile paralysis for forty-seven years). He

found considerable atrophy of the ventrolateral column, particularly in the dorsal and lumbar regions, amyloid bodies in the anterior horns, most numerous in the vicinity of the blood-vessels. Cornil passed by the most important change, although he not only observed it but also described and illustrated it: "On voit une cellule nerveuse, qui est du reste la seule qui montrait cette préparation; mais sur les coupes plus épaisses nous avons vu que les cellules nerveuses étaient intactes et avaient conservé leurs rapports normaux." Cornil therefore observed the absence of ganglion cells, but did not lay any stress upon it. His discovery was confirmed by Laborde in 1864, who examined two cases and found inflammatory connective tissue in the anterior and lateral tracts, but noted that the ganglion cells were "parfaitement saines."

In 1865 Prévost and Vulpian went distinctly further; they noted atrophy of the anterior horns and diminution in the number of ganglion cells, as well as atrophy of the anterior and lateral columns. Lockhart Clark confirmed this in 1868. These authors therefore observed the most important fact and described it, but did not appreciate that it was the one thing by which the occurrence of the paralysis could be explained.

This was reserved for a work which on that account may be considered as laying the true foundation of all subsequent microscopical pathology. Charcot and Joffroy, in 1870, made an examination of a woman aged 40, who had been paralysed for thirty-three years; they found similar appearances as the authors mentioned above, but they recognized the fundamental pathological importance of the loss of the ganglion cells, and formulated the brilliant hypothesis that the ganglion cells form a kind of trophic centre for the nerves and muscles belonging to them; this theory made it possible to understand the occurrence of the paralysis, and the subsequent muscular atrophy. The investigations of Charcot and Joffroy are important, not only because of this generally accepted neurophysiological theory, but because of the further conclusions which they drew. On account of the remarkable way in which certain groups of cells, markedly in the lumbar enlargement, were chiefly affected, and in view of the absence of any true inflammatory or hæmorrhagic changes, they inferred a primary affection of the ganglion cells with the production of a certain degree of secondary reaction in the neighbouring interstitial tissues.

Charcot's and Joffroy's observations were confirmed in the same year by Parrot and Joffroy, who accepted the theoretical conclusions of the former. But one further discovery was made which was to be of great importance for the further development of the subject. In a child aged 3, one year after it had been afflicted with poliomyelitis, they found blood-vessels which were more numerous, thickened, and infiltrated with small round cells in situations where the ganglion cells appeared normal. As, however, they found ganglion cells affected in other places without any particular change in the blood-vessels being present, they adhered to the theory of

Charcot. In the next year (1871) Roger and Damaschino were able to demonstrate marked changes in the vessels, with cell proliferation in the anterior horns in more recent cases (*i.e.*, after two and a half, six, and thirteen months). They raised the question, without giving any decisive answer, whether the process was primarily parenchymatous, as Charcot believed, or primarily interstitial.

In any case these investigations excluded the possibility that the process was a purely degenerative one; it was undoubtedly an inflammatory, "myelitic" process.

The Dispute over Charcot's Theory.—The discussion appears at first sight to be tiresomely academic. Wickman points out that it is not so, because the assumption of a primary interstitial inflammation at once raises the difficulty as to how the "systematic" character of the symptom-complex in most of the cases can be explained.

(a) Investigation of Chronic Cases.—Discussion was limited at first to the results obtained by examination of cases of long standing. Roth confirmed the findings of Roger and Damaschino, but came to the conclusion that the interstitial changes were primary and the degeneration of the ganglion cells secondary. Schultze in 1875 pointed out that frequently only isolated groups of cells were affected, and he considered that this would not be possible if the pathological process was primarily parenchymatous. Other opponents of Charcot's theory were Erb, Leyden (1875), Turner (1879), Taylor (1879), Eisenlohr (1880), Archambault and Damaschino (1883), who drew attention to the frequent occurrence of perivascular cell infiltration, and conceived the whole process to be one of diffuse myelitis with a tendency to greater intensity in particular regions. Eisenlohr observed further that the posterior horns and the white matter were also affected. Kawka (1889) proved the connection between the localized lesions and the changes in the vessels by means of serial sections. Jagic, Hoche, van Gehuchten, Bielschowsky, and others opposed Charcot's theory as a result of investigation of chronic cases.

On the other hand, supporters of Charcot appeared, Dejerine (1878), Stadelmann (1883), and, in particular, von Kahlden in 1893 and 1901, who examined five chronic cases, and gave it as his opinion that the interstitial changes present did not need any theory of a primary interstitial affection for their explanation. His point of view was certainly influenced, if not determined, by his theory of the nature of inflammation in general; in common with Weigert he regarded all inflammation in a parenchymatous organ as primarily parenchymatous in nature. Other authors adopted a middle view between the two extremes. Schmaus, Schwalbe, Lövegren, and Praetorius pointed out the possibility of simultaneous affection of both the parenchymatous and interstitial elements, and laid stress on the difficulty of solving the problem along morphological lines.

As a result of these studies the important conclusion was

arrived at, that the same process occurs in adults as in children; Combault in 1873 substantiated the theory of Duchenne that a spinal paralysis of adults exists, analogous to the spinal paralysis of children.

(b) Investigation of Acute Cases.—The problem had not reached solution by means of examination of chronic cases; more was to be hoped of examination of acute cases.

We owe the first comprehensive and thorough investigations to Rissler. In three acute cases he found interstitial change as well as degeneration of the ganglion cells; although the stroma was markedly affected he contended that the cells were primarily affected because: "The pathological changes in the neighbourhood of the cells were neither so constant nor sufficient to be considered to be the cause or even a contributory cause of the cell degeneration." He bases his argument largely upon one case, in which cell degeneration was very marked, while interstitial changes were but slight. Rissler admitted the possibility that the morbid agent might have an effect upon the walls of the blood-vessels as well. He was the first to prove that the pia was involved by the disease. Leegaard (1889), Gowers (1892), and Mönckeberg (1903) agreed with Rissler's view. Mönckeberg found poliomyelitis acutissima in a case of Landry's paralysis. He indicated one difficulty inherent in the theory that the localization of the disease depends upon the distribution of the blood-vessels: "How is one to understand the special liability to disease of certain regions, particularly the central portions of the cord in poliomyelitis?" He considers the theory of Goldscheider not a very happy one: "That the vessels in that region have certain peculiarities in their walls, and that the conditions of pressure of the stroma are different to those in other portions." Mönckeberg agrees with Weigert's view that there is primary damage to the ganglion cells with secondary change in the vessel walls, rendering them more permeable to leucocytes. "In poliomyelitis we find the typical picture of inflammation in a parenchymatous organ." In quite recent times (1911) Cassirer has given his adherence to the theory of primary involvement of the ganglion cells.

At the same time it is impossible not to realize that the more investigation of acute cases has been carried out the more opinion has inclined towards a primary interstitial, vascular process. Certain investigators, Dauber (1893-94—a five days' case), Redlich (1894—a ten days' case), Medin (1898), Neurath (1905—a three days' case), leave the question an open one and prefer to suppose a simultaneous affection of both parenchyma and interstitial tissue. But most investigators adopt the "interstitial" theory. Goldscheider (1893—a twelve days' case) was particularly impressed by the intensity of the vascular change, and goes so far as to state that the localization of the disease is determined by the vascular changes. He draws attention to the manner in which the central artery is affected (with reference to Kadyis's work), and holds that the cell

degeneration is secondary and due to nutritional disturbance. Siemerling (1894—an eight days' case) also regards the vascular changes as the essential feature. Similar views were expressed subsequently by Bickel and Röder (1898), Bülow-Hansen and Harbitz (1899), Matthes (1899), Placzek (1901), Marinesco (1901), and Batten (1904).

Wickman's Investigations.—The work of Wickman (1905) was of extreme importance not only because of its extent (seven acute cases, three of Rissler's cases re-examined, and two cases during convalescence) and its thoroughness and clearness of description, but also because of the expert critical analysis of all the vexed points in the pathology and pathogenesis of the disease which it contains. He raised the questions, really for the first time, of the point of entrance, the method of infection and of spread of the virus. The conclusions drawn from his exhaustive studies are extremely valuable. In 1910 he amplified them by the study of seven more acute cases.

In the following I shall not give Wickman's results in detail. I propose to compare the results I obtained by microscopical examination of cases of experimental poliomyelitis in monkeys in each case with those obtained by research in man; I shall refer mainly to the investigations of Wickman in this connection because his descriptions are so clear and his illustrations so excellent that is is easy for the layman in microscopic pathology, as I must consider myself to be, to arrive at a clear understanding of his meaning. The following is a short sketch of the more important theoretical conclusions arrived at by Wickman.

The symptoms of poliomyelitis acuta of both adults and children (the lesions are the same in both) are due to an inflammatory process in the central nervous system. This process is not limited to the spinal cord, but occurs in a disseminated form in the medulla, pons, cerebellum, cerebrum, and meninges. It is essentially therefore a disseminated meningo-myelo-encephalitis. Not only the anterior horns, nor even the grey matter in general, but also the white matter and the pia mater are affected; the process is usually most intense in the anterior horns in the cervical and lumbar enlargements. The variation in the intensity of the process is dependent upon the varying richness of blood supply to the parts. Both parenchymatous and interstitial changes are found; the latter are particularly well marked. Changes in the ganglion cells are never found in the absence of interstitial lesions, but the opposite condition is present sometimes. The process therefore is mainly interstitial and of the infiltrative, lymphocytic type. The infiltration mainly follows the distribution of the blood-vessels. Inflammatory œdema also plays some part in the pathology.

Within the nervous system the inflammation travels along the perivascular lymphatics; the perineural lymphatics probably carry the infection from the site of inoculation to the spinal cord. The alimentary tract is probably the site of infection in most cases,

because, clinically, intestinal symptoms are common, and the paralysis usually begins in the lower limbs.

As a side issue it is important to note that Wickman established the identity of Landry's paralysis and certain forms of myelitis with poliomyelitis. These investigations into the microscopic pathology of the disease formed the basis of his later clinical studies and enabled him to obtain a comprehensive view of these diseases, which differ so much in their symptomatology and yet are probably identical in their etiology. His well-deserved clinical discoveries were the ripe fruit of his careful pathological studies.

More Recent Investigators.—These have been numerous since Wickman (Forssner and Sjövall, Harbitz and Scheel, Barnes and Miller, Kadwalader, Marburg, Hoffmann, Hochhaus, Bauer, Strauss, Benecke, Pirie, Marchand). The results of Harbitz and Scheel are important both because their material was extensive (thirteen cases) and because they differ from Wickman on one point. They consider that the infection is carried to the central nervous system by the blood as well as by the lymph-stream; the vessels of the meninges are attacked first, and the infection then follows the vessels into the substance of the cord. Förssner and Sjövall lay stress on the *rôle* played by phagocytes in the destruction of the ganglion cells, and Wickman, who paid little attention to this point in his earlier works, recognizes its importance in his later ones. These two authors have the credit of being the first to describe the affection of the spinal ganglia, which discovery has been confirmed by Marburg, Strauss, Harbitz and Scheel, and Bauer. In his latest work Wickman has described round cell infiltration in the subpericardial fat.

These are the results so far of investigation by methods of microscopic pathology. Now that it is possible to produce experimentally a symptom complex in monkeys similar to that which occurs in man, we may hope that the doubtful points will be cleared up. The problems of the pathogenesis of the disease are:—

(1) Where is the most common point of entry of the virus?

(2) Along what route does the virus reach the brain and spinal cord?

(3) How does its further distribution within the central nervous system take place?

(4) What point in the central nervous system is first affected?

II.—THE DISTRIBUTION AND SPREAD OF THE VIRUS WITHIN THE ORGANISM.

The Demonstration of the Virus in Different Organs.—It is of primary importance, if the above questions are to be solved, to know where in the body the virus may be found. As the virus is so stable, we may assume that the distribution of it which is found in the cadaver holds good for the living body. In the next place

it is necessary to distinguish between the distribution found in man and that found in the monkey; in the latter the disease has been produced only experimentally by methods which we know do not correspond to the natural method of infection for the most part, or which we know to be but imperfect imitations. So far, the only way to prove the existence of the virus has been by means of experiments with monkeys, and the method of intracerebral injection has shown itself to be the most certain in its effects.

(a) In Man.—As has been shown in the chapter on the etiology, the virus was first proved to be present in the spinal cord of persons dead of Heine-Medin disease, as was to be expected *a priori*. The virus has also been found in the brain, specially in the cortex; whether it is always present in this situation, even when the clinical symptoms are purely spinal in character, cannot be stated definitely.

All attempts to demonstrate the virus in the cerebrospinal fluid have failed; this is extremely unfortunate as its presence would have been an important aid to diagnosis. I have injected fluid from two severe acute cases into monkeys; one of the cases was in the earliest paralytic stage. Flexner and Lewis have had equally negative results; in 1907 they gave intracerebral and intraperitoneal injections to monkeys without any result. The experience of Leiner and v. Wiesner, Strauss and Huntoon, Netter, Potpeschnigg and Selter has been similar. Experiments with the *blood* of persons actually ill with poliomyelitis or dead of the disease have had the same negative result.

Owing to the analogy which exists between poliomyelitis and rabies I thought of the possibility that the virus might be found in the salivary glands. I therefore gave intracerebral injections to monkeys of emulsions of the parotid gland and pancreas of a case which had died during the acute stage of the disease; the result was negative. The virus was present in the central nervous system of this case in a fully virulent form (*cf.* p. 41). In order to test the excretion of the virus I filtered the saliva of several children, after having diluted it with saline, through a Berkefeld filter; intracerebral injection of the filtrate into monkeys produced no effect.

The virus has been found in only one situation outside the central nervous system in man. Flexner and Lewis proved it to be present in the mesenteric glands of a child which had died of acute poliomyelitis; the injection of an emulsion of the glands into a monkey produced the disease after an incubation period of ten days. In no other instance has the presence of the virus anywhere in the human body been proved except in the central nervous system. Experiments in this direction have been so far few, and more extended researches are necessary. Similar experiments with monkeys are useful as supplementary studies.

(b) In Monkeys.—In these animals the central nervous system is the chief place where the virus is found, more particularly in the regions corresponding to the paralysed limbs. In order to make as sure as possible of a successful result, those segments of the

cord should be used which correspond to the limb most recently attacked. The virus is found wherever the typical lesions occur, *i.e.*, in the medulla, pons and brain.

The experience of most authors with cerebrospinal fluid has been negative (Landsteiner and Levaditi, Leiner and v. Wiesner, Römer), even with the most varied methods of inoculation. Flexner and Lewis alone obtained positive results and only when they used the fluid of monkeys which had received either intracerebral or intraspinal injections of the virus and when the fluid was removed during the pre-paralytic stage. They found also that the fluid withdrawn at this time gave evidence of a recent pial infection, being cloudy and containing more cells than normal and an increased amount of albumin. Human cerebrospinal fluid presented the same appearances and Flexner and Lewis express the hope that with the aid of monkeys the inoculation of cerebrospinal fluid may prove of use in the establishing of an early diagnosis. At the same time it must be remembered that the virus has been found only in monkeys infected by the intracerebral or intraspinal method, which certainly does not correspond to the method of infection occurring in man. Flexner and Lewis report that when paralysis has set in the cerebrospinal fluid becomes clear again, as is the case in man, and that it no longer contains virus in a virulent state.

We ourselves have been unable to find any evidence that the virus is present in the blood of infected monkeys; Flexner and Lewis, as well as Leiner and v. Wiesner, have had the same experience in the main. In one instance the Austrian observers were able to find virus in the blood; this was during the paralytic stage. They have never found it in the stage of incubation, which is important from the point of view of the theory that the virus is carried by the blood. Flexner and Lewis obtained a positive result in one case by using a very large quantity of blood (25 c.c. intravenously), withdrawn after paralysis had set in; the monkey became ill only on the seventeenth day, so that the amount of virus present in this very large amount of blood was probably small.

Experiments with spleen pulp, liver, kidney, and bone marrow were negative throughout and confirmed the previous negative results with blood (Flexner and Lewis, Leiner and v. Wiesner). In view of these results it is improbable that the virus is carried to any extent by the blood-stream.

The question of the excretion of the virus has been studied in a number of experiments. Saliva, bile, urine, and intestinal contents have been found free of virus by many authors. We ourselves obtained a negative result when using the contents of the small intestine of a monkey which had severe gastro-intestinal symptoms and in which the mesenteric glands were much swollen and contained highly virulent virus.

Monkey 50 (*Rhesus*).—On April 25, 1910, received simultaneously an intracerebral (1 c.c.) and an intraperitoneal (5 c.c.) injection of extract of the contents of the small intestine filtered through a Berkefeld filter and remained well.

At first we considered the possibility that the virus was excreted into the intestine, but in view of the experience of ourselves and others that possibility must be rejected; even the injection of the mucous membrane of the stomach and intestines has produced no result (Flexner and Lewis, Leiner and v. Wiesner). Landsteiner and Levaditi found virus once in the saliva, but they lay little stress on this case in view of the consistently negative results of their further experiments. Leiner and v. Wiesner found no virus in the salivary glands, which coincides with our own experience.

So far the injection of the organs of monkeys had produced practically no results. The following positive experiments are of more importance. Flexner and Lewis began with the idea that, considered epidemiologically, there were many points of similarity between epidemic poliomyelitis and epidemic meningitis (*cf.* Chapter V). In previous experiments they had proved that in monkeys previously infected intracerebrally with the meningococcus the organism was found in the nasal mucous membrane; conversely they had found that after infection of the nasal passages the virus wandered to the meninges. It now occurred to them to examine whether also in poliomyelitis the nasal mucous membrane acts as the point of entrance and of excretion of the virus. They succeeded in demonstrating that the mucous membrane of the nose and pharynx of monkeys after intracerebral infection contained the virus; emulsions of the mucous membrane, filtered through a Berkefeld filter, when injected into the brain of a monkey, promptly produced paralysis. The blood contained in the mucous membrane could not have contained the virus since the experiments detailed above had proved that the blood contains either no virus or at most the minutest quantity. Leiner and v. Wiesner confirmed the results obtained by the American experimenters. Osgood and Lucas found virus in the mucous membrane of the nose and pharynx eight weeks and even six months after intracerebral infection. Owing to the remarkable similarity betwen epidemic meningitis and poliomyelitis one is inclined to believe that the virus is excreted by way of the nasal mucous membrane, but the fact must not be lost sight of that there is no direct proof available that the *secretion* contains the virus; Flexner and Lewis, as well as myself, have failed to find the virus in mucus from the nose of human beings.

The discovery of the virus in the olfactory lobes after successful inoculation of the nasal mucous membrane by Landsteiner and Levaditi is of first-rate importance, as showing that the virus follows the track of the nerves.

Experiments showing the relation of the glands to the virus are of much importance. Flexner and Lewis obtained a positive result by the subcutaneous method; they found the site of inoculation free of virus, but the corresponding glands, as well as the spinal cord, contained virus. The virus had been absorbed by way of the lymphatics beyond the possibility of doubt. Still more im-

portant, it seems to me, are the results obtained by Joseph and myself. We proved that after intracerebral injection the virus passed to the mesenteric glands.

Monkey 38 received an intracerebral injection on March 2, 1910. On the 10th depressed; much diarrhœa. On the 11th, condition the same; in addition, slight paresis of all limbs; 12th, universal paralysis; died at noon. The autopsy revealed typical microscopical changes. Swelling of the mesentric glands was very marked; the coils of intestine appeared red, and the lymph follicles and Peyer's patches were swollen. The mesenteric glands were proved to contain no bacteria on microscopical examination, and were preserved in glycerine. On March 22, monkey 42 received an intracerebral injection of an emulsion of the glands. It remained well until April 1. On the 2nd, sudden severe paralysis of the hind limbs and slight paresis of the fore limbs set in; the paralysis became worse during the day, and was total in all limbs by the evening. The animal was found dead on the 3rd. The autopsy showed typical, intense changes.

I shall discuss the clinical and pathological importance of this case later. Flexner and Lewis obtained an opposite result even when the virus was injected directly into the alimentary tract. On the other hand, the more systematic research of Leiner and v. Wiesner confirmed and amplified our results. In the case of monkeys killed during the first days of illness after intracerebral injections they found virus in the submaxillary glands, glands of the neck, the mesenteric and prevertebral glands; the inguinal glands were found to be free of virus. In so far as these experiments allow of a general interpretation we may say, that after intracerebral injection in monkeys the virus passes with ease from the spinal cord to the glands in its vicinity. Leiner and v. Wiesner arrived at the conclusion that the type of disease produced by inoculation with virus from the glands was a not very severe one.

Conclusions.—The general impression produced by the foregoing recital of results obtained is perhaps rather confusing; yet, on the whole, the results make up a very uniform picture of the distribution of the virus within the bodies of human beings and monkeys. The virus has a strong affinity to the central nervous system and is found in the greatest quantity there. The other organs are practically free of the virus. The relation of the virus to the lymphatic system is exceedingly remarkable; it seems to indicate that the virus tends to spread to organs which contain much lymphoid tissue. The objection, that the experiment merely indicates the absorption of the virus from the alimentary tract, may be brought against the results of examination of the mesenteric glands in man; the same examination in monkeys, which had received an intracerebral injection, is not open to that objection. and the result shows that the virus travels by way of the lymphatics and possibly develops in them. At first I was inclined to look upon the presence of the virus in the mesenteric glands of monkeys which had received an intracerebral injection as evidence that the virus was carried by the blood. On considering the results as a whole and

particularly the fact that the blood is usually free from virus, it seems to me more probable that the virus passes by the lymphatics. That virus has been found in the mucous membrane of the nose and throat, is a further instance of the affinity of the virus for lymphatic tissue; Flexner and Lewis hold the view that the virus is most probably carried from the meninges to the mucous membrane by the lymph channels. Key and Retzius proved the existence of such channels when they found that injection of the subarachnoid space caused injection of the lymphatics of the nasal mucous membrane. The marked richness in lymphatic tissue of the nose and throat is another argument in favour of the existence of such an affinity.

The Methods of Inoculation.—From all that we know of the relation the virus bears to the central nervous system, it is clear that the intracerebral method is the most certain. Intraspinal inoculation is usually successful. Leiner and v. Wiesner observed a certain regularity in the occurrence of paralysis after intracerebral injection; they found that the limb opposite to the side where the injection was made was affected first and that it was usually the hind limb. They made the injection usually into the central convolutions as near the vertex as possible. After hearing of this observation made by the Austrian writers, we re-examined our material from this point of view, and with the following interesting result. I must mention first that, owing to the position of the operating table, we happened to make all our injections on the left side of the skull in the region of the central gyri; in the case of all the injections we entered only so far from the mid-line as to avoid wounding the longitudinal sinus. This situation corresponds with the fact that the lower limbs were affected first in most of our cases. Paralysis appeared first in the left hind limb of only one monkey out of twenty which had been injected on the left side. In eight cases one side was not affected before the other, but it must be remembered that at the time we were not paying special attention to this point. In no less than eleven experiments the limbs on the right side were paralysed first. In the majority of the cases the paralysis began in the right hind limb and then affected the left hind limb. When the fore limbs were involved first, it was the right one, with one exception, which was affected. Unfortunately, at the time when we became aware of the importance of this question we had almost finished our series of experiments. I may mention, however, that both monkeys injected *ad hoc* on the right side became paralysed first in the contralateral limbs. Should these observations be confirmed they would seem to indicate that the active agent spreads along the neuron or, at least, spreads more quickly in this direction than in any other. It is to be supposed that in doing this it passes along the lymph channels accompanying the neuron, although this would pre-suppose a considerable degree of isolation of these channels. A large number of experiments, directed towards this particular

question, are necessary; they should include as many variations in the method of injection as possible.

Direct injection into the nerves is a method which is of particular interest. The authors who have tried this method are unanimous that it is very effective and that paralysis always occurs first in the limb corresponding to the nerve injected (Flexner and Lewis, Landsteiner and Levaditi, Leiner and v. Wiesner). This is confirmatory of the views expressed by Wickman, Harbitz, and Scheel, that the virus follows the course of the nerves. Leiner and v. Wiesner designed a very beautiful experiment to illustrate the point. They first ligatured the sciatic nerve of a monkey, then injected the nerve peripheral to the ligature and finally severed the nerve at the ligature. The monkey remained well, while another monkey, in which the sciatic nerve was injected without previous ligature, quickly became paralysed in the corresponding limb. This progress of the virus along the nerve may be compared with the absorption of the virus of rabies and of tetanus. If we accept the view of Meyer and Ransom, that the axis-cylinder itself carries the virus in the latter case, it is more probable that the living virus of poliomyelitis wanders in a centripetal direction along the perineural lymphatics. The experiment confirms Wickman's theory that the virus reaches the central nervous system primarily by way of the nerves.

Other authors incline to the view that the *infection is hæmatogenous*. It is true that intravenous injection can cause the disease, but the method is an uncertain one. Landsteiner and Levaditi have shown that successful infection is produced even when the virus has to pass through the liver (injection of a mesenteric vein). This demonstration that infection is possible *viâ* the blood-stream is no proof that the virus reaches the central nervous system by that channel. We shall return to this later.

So far it has proved impossible to inoculate through the unbroken skin; on the other hand, infection by subcutaneous injection has been successful in a few instances. The virus passes, in part at least, through the lymphatic glands (*cf.* the experiment of Flexner and Lewis quoted above). Direct injection into the lymphatic glands has been successful. As in rabies, inoculation into the anterior chamber of the eye has produced the disease (Leiner and v. Wiesner, Landsteiner and Levaditi). It is doubtful whether intraperitoneal injection alone will give a positive result.

It follows from all these successful artificial methods of inoculation that, in the case of the monkey, which is as susceptible as man to the disease, a positive result can be obtained with certainty only when the virus is brought into direct contact with nervous tissue. These experiments, however, only go to prove what route the virus takes when it is once within the body. They show that the active agent is certainly capable of reaching the central nervous system by way of the perineural lymph spaces. This is not disproved by the fact that direct intravenous injection

has been successful; we know that, in the case of tetanus, intoxication by way of the blood-stream is promptly successful, but that the toxin does not pass straight from the blood to the brain and spinal cord, but is absorbed by the peripheral endings of the nerves. It is interesting to note that in successful intravenous injections the paralysis occurred first in the upper half of the body, *i.e.*, in the segments of the cord which are furnished with relatively short peripheral nerves.

Attempts to determine the Point of Entrance of the Virus.—The following experiments help to elucidate this problem. They are based upon clinical experience, which indicates the upper and lower respiratory tract (sore throat, coryza, and bronchitis) or the alimentary tract (gastro-intestinal symptoms) as the portal by which the virus enters. It is not easy to cause infection through the nasal mucous membrane; Landsteiner and Levaditi obtained no results through the undamaged mucous membrane; they were successful when the virus was injected into the mucous membrane, the infection following the nerves (the virus was found in the olfactory lobe) and causing the "type supérieur" of poliomyelitis. Flexner and Lewis succeeded by rubbing in the virus. Leiner and v. Weisner first cocainized the mucous membrane and then rubbed in the virus with a hard brush. Infection through the nasal mucous membrane is thus undoubtedly possible; it appears to be necessary, however, for the mucous membrane to be injured in some way previously.

Flexner and Lewis had no success with tracheal injections and inhalation; on the other hand, the same methods proved immediately successful in the hands of Leiner and v. Wiesner. Paralysis occurred in these cases first in the upper half of the body, in the neck and arms. In some instances the paralysis remained limited to these regions, in others it descended. The same authors have done much to clear up the problem of infection through the alimentary tract. Their experiments had no result at first. They then fed monkeys, which had been starved for twelve to twenty-four hours, and in which peristalsis had been diminished by means of opium, with the virus; this was effective. Paralysis was produced also by direct injection of virus into a loop of small intestine. In these experiments the paralysis always affected the lower half of the body first. Krause and Meinicke were not successful by the method of feeding monkeys with virus, nor were Landsteiner and Levaditi, although they used large quantities.

One is impressed, even more than in the experiments on the nasal mucous membrane, with the fact that infection is only possible under certain conditions.

These experiments, however, give some support to the clinical views mentioned above.

Finally, an observation may be recorded here which has been made by all the workers in this field. In no case has spontaneous infection of a monkey ever been observed. In the course of our

own experiments healthy monkeys were kept in quite small cages, together with monkeys which had been infected and with those which were actually suffering from the disease. Leiner and v. Wiesner purposely brought healthy monkeys into close contact with diseased monkeys, and no infection resulted. One may suppose that monkeys are not liable to infection in the natural way, although this is contradictory to the experience that they can be infected by way of the natural portals of entry of the virus and that they are very dirty among themselves. It is more probable that the artificially infected animals do not excrete the virus. It is in favour of this theory that the virus was never transmitted to anyone who was occupied with the animals, nor was it carried by them to their relatives or to any other persons, although the animals had to be kept in our laboratory itself from lack of other rooms which could be kept warm.

III.—THE PATHOLOGICAL CHANGES FOUND IN EXPERIMENTAL POLIOMYELITIS IN MONKEYS COMPARED WITH THOSE FOUND IN MAN.

It is not claimed that the statements made in this section are the result of a systematic study of the pathological picture presented by experimental poliomyelitis in monkeys, and they should not be regarded as such. Our time was too much taken up with the purely experimental side of the work (apart from other studies altogether) for us to be able to make that detailed study of the histology of the disease which is both necessary and desirable. We were obliged to use a great deal of our material for research into the nature of the virus, the means of preserving it and the question of immunity. Usually we were satisfied with the examination of small pieces from the lumbar cord, particularly the lumbar enlargement, the cervical enlargement, the medulla, the central ganglia and the cerebral cortex. We consider such an examination to be of the utmost importance, even though the clinical symptoms appear quite conclusive; otherwise serious errors may occur, as in our experience with cerebral abscesses. Histological examination is very reliable; in cases where we saw no lesions we were unable to prove the presence of virus. On the other hand, the finding of typical acute microscopical changes was followed usually by a positive result in the inoculation experiment. I will say at once that we made no microscopical examination of organs, apart from the central nervous system. As far as I know there is only one observation on record: Flexner found a round-celled infiltration close to a vessel at the site of a subcutaneous inoculation. There is a wide field for research in this direction. The lymphatic glands might repay study; they are known to contain the virus, and I think therefore that a specific lesion may be found in them.

Technique.—Directly after the death, or after the killing of the dying monkey, the portions of the nervous system mentioned above were cut out and put into 7 to 8 per cent. formalin for twenty-four hours or longer. They were then hardened in alcohol of increasing strength for at least three days. After being completely dehydrated in absolute alcohol they were transferred to xylol, where they remained until they were quite clear, usually two to three hours; the xylol was changed twice. Then they were put into a concentrated solution of pure xylol and soft paraffin for two to three hours, then into paraffin with a melting point of 42° for one hour, for five hours into paraffin with a melting point of 48°, and, finally, they were embedded.

The sections, about 15 μ thick, were cut with a microtome, and stained either with hæmatoxylin and eosin or with van Gieson. For demonstrating any bodies which might be included in the cells we used Joest's modification of Mann's stain, which he used for Negri bodies; as I have mentioned above, we found no such bodies.

Thus I am unable to give results of a systematic nature. This necessary limitation perhaps does not involve any great loss; after examining the brain and spinal cord for diagnostic purposes in about forty monkeys, I am sure that a full description of them would be monotonous. I shall confine myself to a summary description, with the aid of micro-photographs, of the changes found, and I shall compare these with the appearances in human poliomyelitis described by Wickman.

Macroscopic Changes.—In monkeys which have died of acute poliomyelitis no changes are found outside the central nervous system in most cases. Occasionally small areas of broncho-pneumonia were present, usually only in those monkeys in which the death agony was prolonged. These changes can hardly be due to the action of the virus. Redness of the intestinal mucous membrane was common, but is probably of but little significance owing to the frequency of intestinal disturbance in monkeys kept in captivity. On the other hand, we are inclined to attach importance to the swelling of the lymph follicles and of Peyer's patches, and particularly to the enlargement of the mesenteric glands, since they have been shown to contain virus. Landsteiner has observed inflammatory swellings in the neck, which were more marked than those due to the pharyngitis which is so common in these animals. Other pathological appearances have not been seen in monkeys.

In human beings the spleen is swollen sometimes; cloudy swelling and even inflammation of the kidneys has been observed, and in some cases the tonsils were swollen (Beneke). Swelling of the follicles and Peyer's patches were relatively common.

The macroscopic changes in the brain and spinal cord of monkeys dead from acute poliomyelitis may be so little characteristic, that even when one has had much experience it is not possible to say definitely whether a lesion is present or not, and certainly not to say that true poliomyelitis is present, even when the microscope reveals typical and well-marked changes. In the majority of cases, however, macroscopic changes are more obvious. On removal of

the skull-cap the pressure within the dura is found to be raised; there is an excessive flow of clear cerebrospinal fluid when the dura is turned down. The pia mater on the surface of the brain is congested, the surface itself is shiny and moist. Compared with the normal monkey's brain, which is of a yellowish white colour, the brain appears diffusely red; on section this redness is seen to be most marked in the grey matter, which has an almost violet tinge. The convolutions are often flattened. On section the brain

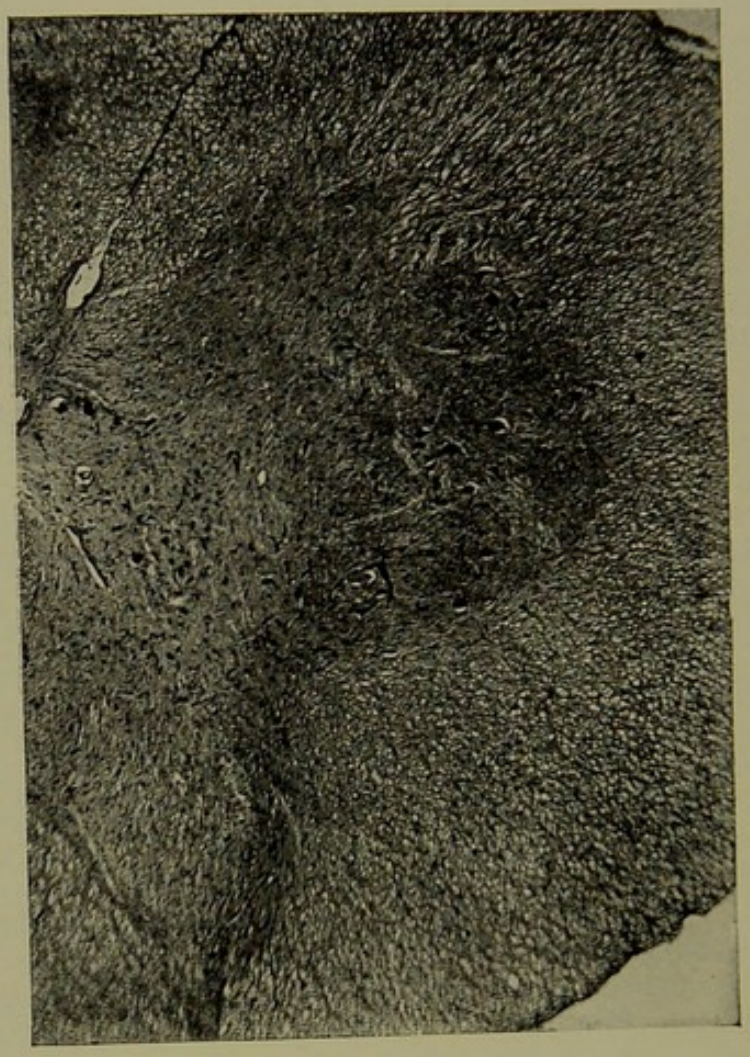


FIG. 17.

The greater part of the right half of the spinal cord of a normal monkey. Above and to the left, the anterior longitudinal fissure; above the centre, the right anterior horn. To the left, and below, the posterior horn.

is markedly œdematous. The changes in the spinal cord are more constant. The dura is more distended than usual, and an excessive amount of fluid escapes when it is opened. In quite acute cases only is there a slight opacity, with a corresponding increase in the number of cells present (lymphocytes). Generally it is quite clear.

The pia mater is congested. The cord is moist, smooth, and in places softer than normal, although without any true softening being present. The grey matter is distinctly more red than normal; this is most marked in the segments corresponding to the distribution of the paralysis. The anterior horns are most affected, but frequently the whole grey matter stands out in a red-violet colour. On looking closely minute drops of blood are seen in the grey matter; microscopical examination shows that these are almost

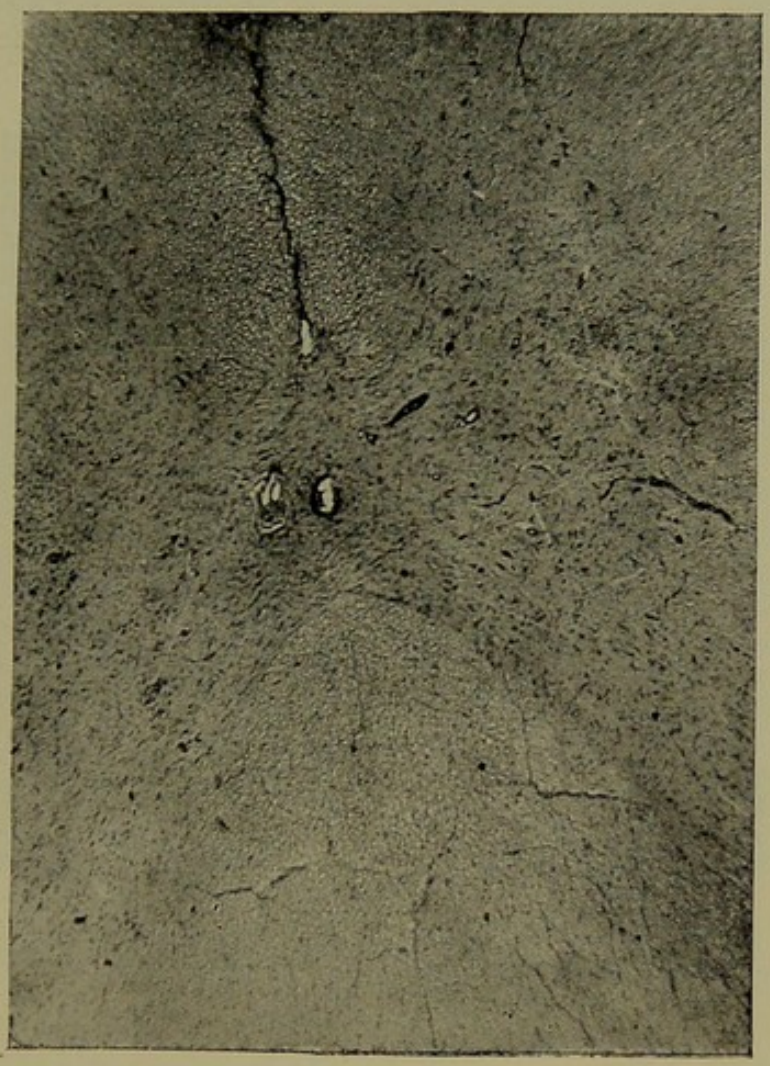


FIG. 18.

Section of the lumbar cord of monkey No. 58. To the right and above, the slightly affected right anterior horn with infiltration into its substance and into the veins. In the middle, the central canal; just to the left an infiltrated artery; still more to the left, the left anterior horn, slightly infiltrated.

always hæmorrhages into the substance of the cord. The white matter appears quite normal or perhaps slightly œdematous.

The macroscopical appearances in man are so exactly similar to those just described that it is unnecessary to deal with them.

Definite morbid changes appear to be rather less frequent; that they are relatively more marked in the monkey may be due to the intracerebral method of infection.

Microscopic Changes.—In monkeys these are usually much more widespread than would be expected from the macroscopic changes or the clinical symptoms. The microscopic lesions are more intense and constant in the spinal cord than in the brain. I mention this point specially because we are dealing with monkeys infected by way of the brain. In most cases a glance at the section under a low magnification is enough to settle the diagnosis. The most obvious change seen is the remarkable increase in the number

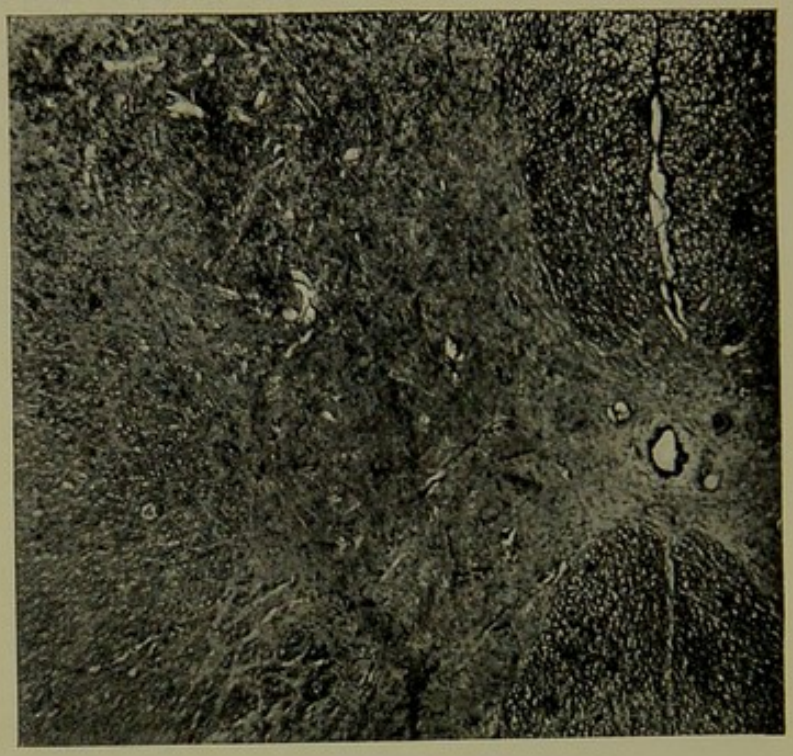


FIG. 19.

Shows marked changes in the left anterior horn and part of the posterior horn of the lumbar cord of monkey No. 24.

of cell nuclei; this is most marked in the anterior horns. In fig. 17* I reproduce the appearances of the normal spinal cord; figs. 18, 19, and 20 represent sections showing the changes due to poliomyelitis under the same magnification. The difference is clear even in the

* The photographs, figs. 17 to 49, were taken by myself by means of a Zeiss microphotographic apparatus kindly lent to me by the firm of Behring in Marburg. The objectives AA, D and E were used, and in order to obtain different enlargements the length of the tube was varied, and not the eye-piece. Unfortuntely, I omitted to note how far the tube was drawn out in each case, so that I am unable to give the exact amount of enlargement.

Most of the photographs were taken with objective AA and a tube of '65 m.

case of monkey No. 58 (for the clinical history see p. 77), in which the changes are only slight; it is very obvious in figs. 19 and 20, taken from the severely affected spinal cords of monkeys Nos. 24 and 4 (*cf.* p. 66 and p. 42), which print more darkly, owing to the increased number of cell nuclei. These illustrations, taken with a low power, show that the posterior horns are also affected. A

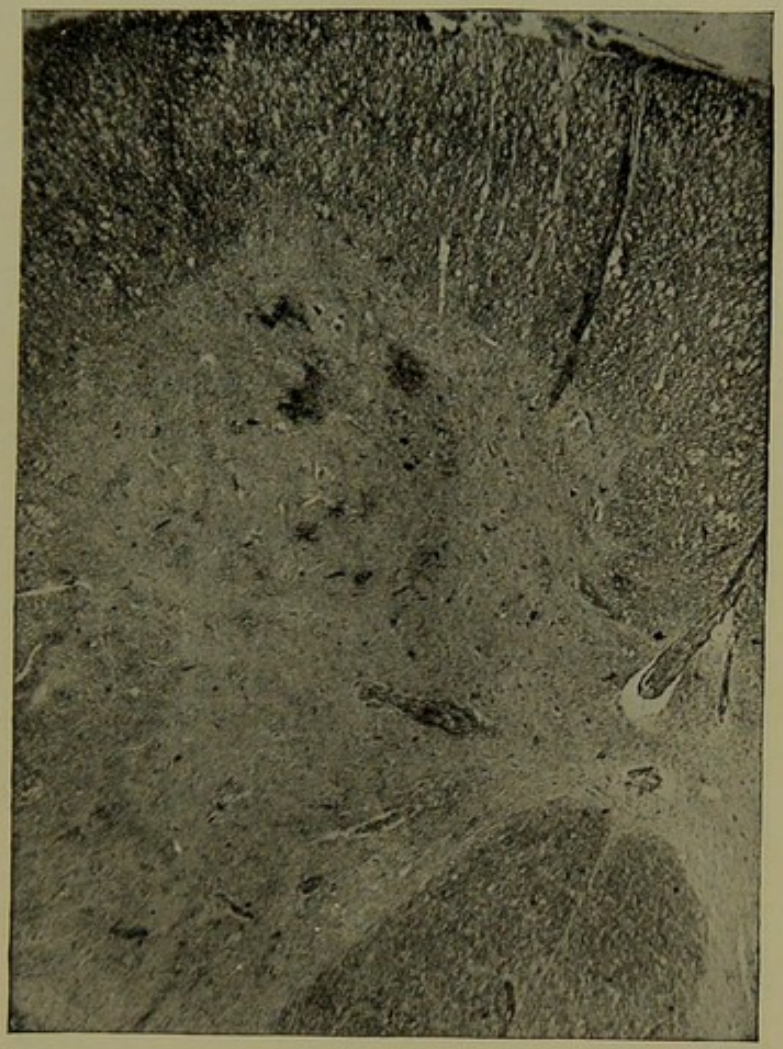


FIG. 20.

Anterior and posterior horns from the lumbar region of monkey No. 4; well-marked changes. The dark areas in the left anterior horn are mainly hæmorrhages. To the right above, a pial septum infiltrated. At the right border, the fold of the pia lying in the anterior longitudinal fissure, much infiltrated. Below, veins with marked infiltration, some of them passing to the posterior horn.

higher magnification is necessary in order to analyse the nature of the lesions.

Pia.—In the lower part of the cord the pia is much affected. I found that involvement of the pia was most marked in the lower lumbar region, and became less in an upward and downward

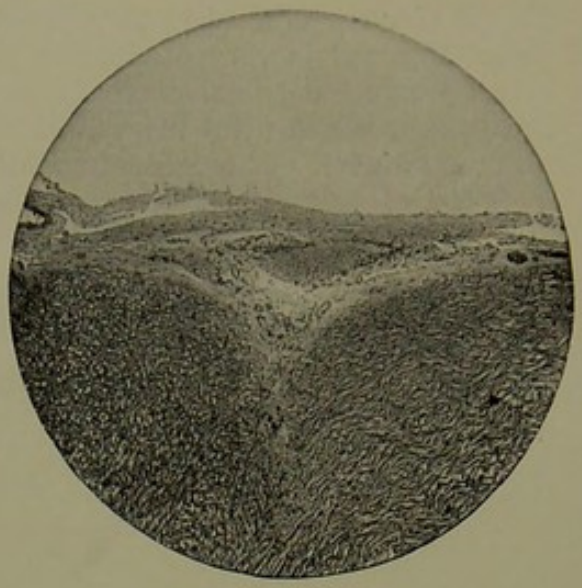


FIG. 21.

Slight infiltration of the pia at the entrance to the anterior longitudinal fissure in monkey No. 2. Also some infiltration within the fissure.

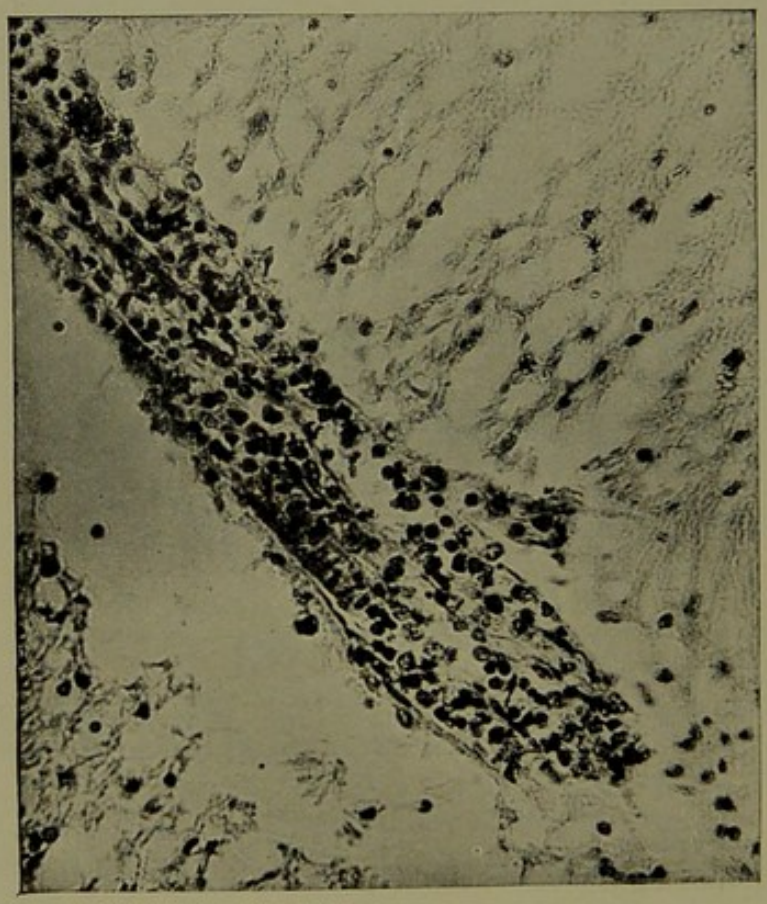


FIG. 22.

Well-marked round cell infiltration in the deeper part of the anterior fissure (from the lumbar cord of monkey No. 2).

direction from that region. Irregularly scattered changes in the pia are found in the upper segments of the cord in varying degrees.

The chief change in the pia is a round cell infiltration, which is partly diffuse and partly in connection with the vessel walls.

This infiltration is more marked on the anterior surface of the cord, but is found also on the posterior surface. A few round cells are found in the posterior septum, but both at the entrance to the anterior fissure and in the deeper parts of the process of pia mater the infiltration is frequently considerable in amount.

Fig. 22 gives some idea of the amount of infiltration. Sometimes infiltration occurs on the antero-lateral aspect of the cord; I found such a condition in a monkey which had been ill for only twelve to twenty-four hours (fig. 23).

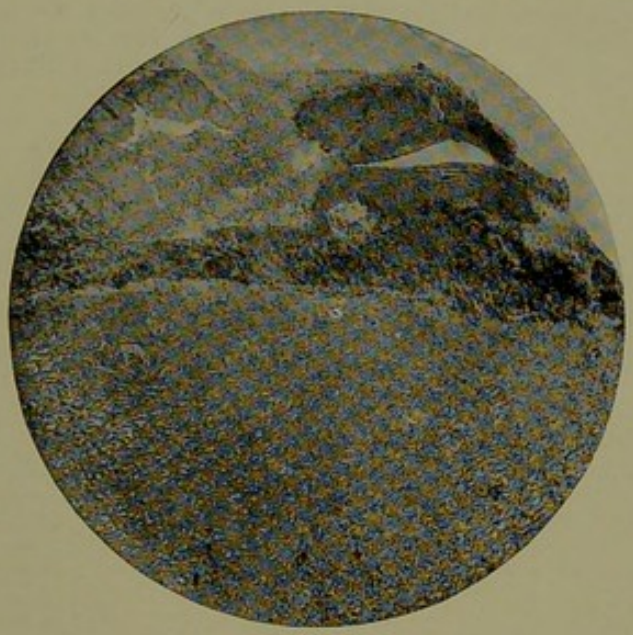


FIG. 23.

Marked round cell infiltration of the pia on the right anterior aspect of the lower lumbar cord of monkey No. 1.

Infiltration of the pia is often seen between the nerve bundles of the anterior or posterior roots. The blood-vessels in the pia are usually distended and full of well-preserved corpuscles. Perivascular infiltration is most marked in the depths of the anterior fissure; the infiltrated vessels can be seen curving outwards to reach the anterior horns. More rarely a pial septum passing through the white matter is seen; I have never observed any direct extension of the infiltration from the pia to the white matter.

The pia mater of the brain shows similar changes, not only at the site of inoculation, where they are invariable, but also on the base of the brain (*vide* fig. 24).

I found the dura mater normal in every case.

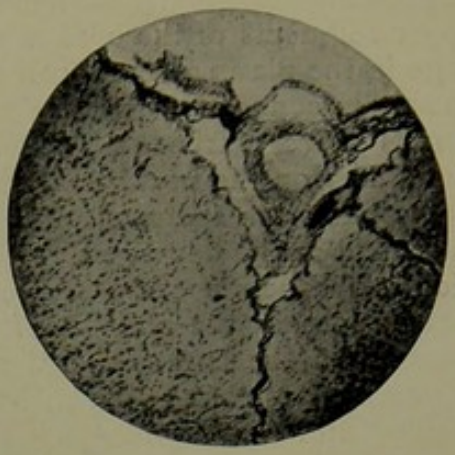


FIG. 24.

Infiltrated pia from the base of the brain of monkey No. 4 at the entrance to a sulcus. Above and to the right there is a septum slightly infiltrated, passing into the cortex. The infiltration is shown surrounding a distended vessel.

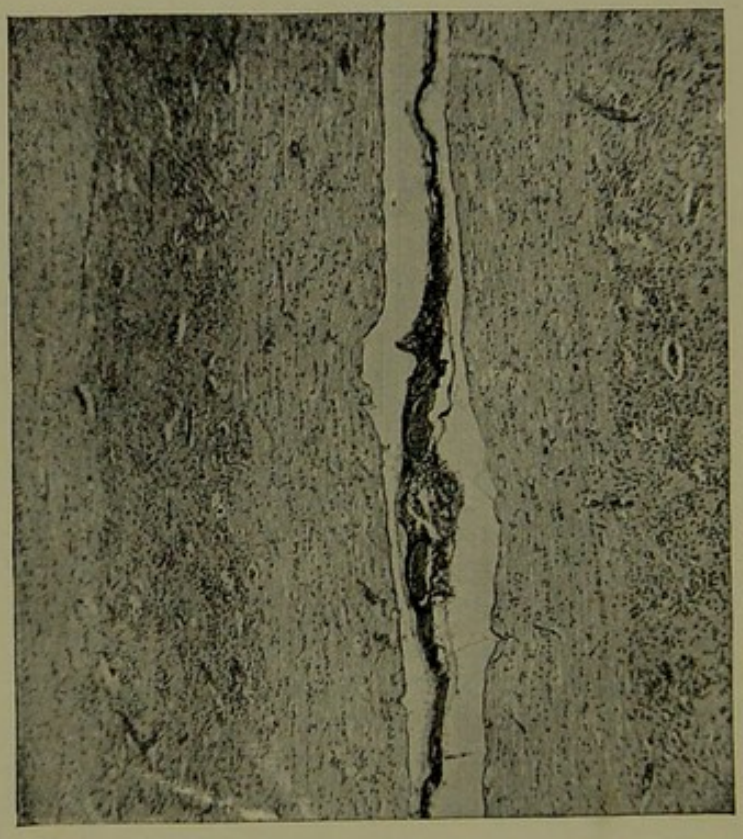


FIG. 25.

General view of a longitudinal section of a human spinal cord from a case of poliomyelitis. In the middle, the pia with much infiltration around the vessels; to the right and left of the pia, normal white matter; still further outwards on both sides, the markedly infiltrated anterior horns. On the left side more white matter is seen.

The condition of the pia is sufficient to explain the irritative symptoms observed in some monkeys (hyperæsthesia and vomiting).

The pathological changes found in the pia in human beings correspond very closely with those just described. The pia mater of the brain appears to be affected more frequently and more markedly in monkeys than in man; the reasons for this are probably those given above.

Spinal Cord.—In the spinal cord itself the grey matter is undoubtedly the part mainly affected. This is very clearly demonstrated by means of longitudinal sections. Professor Beneke has very kindly allowed me to make use of one of his own longitudinal sections of the spinal cord from a case of poliomyelitis from which I have made photographs.

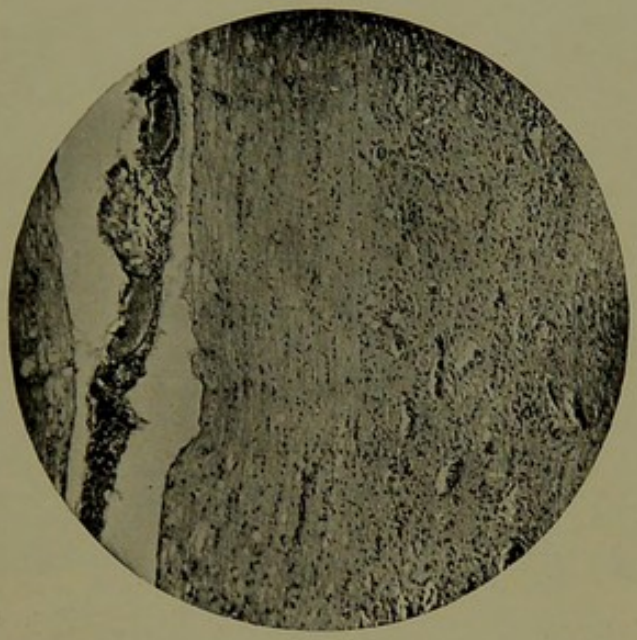


FIG. 26.

Portion of a longitudinal section of the same spinal cord as in fig. 25. From left to right, a portion of the left anterior tract, the fold of pia mater with marked infiltration, the right anterior tract, the right anterior horn invaded by round cells.

The general view (fig. 25) shows the two infiltrated anterior horns lying between bundles of normal white matter. The median fissure contains infiltrated pia mater. The condition is seen more clearly under a higher power (fig. 26).

The increase in the number of nuclei affects the anterior horns most; it is not seen all over the anterior horns, but stands in a definite relationship to the vessels. Very frequently infiltrated vessels are seen passing from the edge of the fold of pia lying in the anterior fissure to the anterior horns and, sometimes, to the posterior horns (*vide* fig. 27). The peripheral vessels are affected as often as the central vessels (*vide* fig. 28). The infiltration usually

affects the adventitia, more rarely the perivascular lymph spaces. I agree with Wickman that the veins are more frequently involved.

The manner in which the infiltration affects the vessels more than the general substance of the cord is well shown in fig. 29.

In fig. 30 a slightly infiltrated artery and several veins with marked infiltration are seen. In some instances the diffuse infiltration does not seem to have any relation to the distribution of the vessels (figs. 31, 32), although it is very difficult to be sure on this point.

Sometimes, more usually in the anterolateral portion of the anterior horns, small infiltrations are seen which are quite unconnected with any vessel; from their situation I judge that they are determined by the presence of the ganglion cells.

FIG. 27.

Lumbar cord of monkey No. 4. (*cf.* fig. 20). Above, the deepest part of the anterior fissure with its pia. In the middle and below, blood-vessels passing to the posterior horn, much infiltrated.

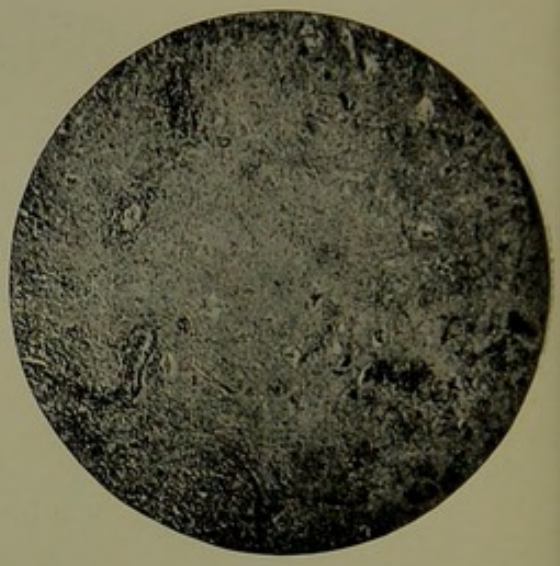


FIG. 28.

Lumbar cord of monkey No. 4. Antero-lateral portion of left anterior horn. To the left, some peripheral vessels, much infiltrated, passing from the white into the grey matter. The collections of cells seen to the right are not made up of round cells, but are hæmorrhages. Markedly degenerate ganglion cells are seen lying in the loose, œdematous tissues of the cord.

The involvement of the vessels is shown further by their engorgement, which is more noticeable in the case of the veins. When stained with van Gieson the vessels are seen filled with well-preserved blood corpuscles. Hæmorrhages into the cord are not rare in acute cases; they are associated usually with interstitial inflammation (*cf.* fig. 20). Finally, the œdema remains to be considered, which sometimes causes considerable loosening of the

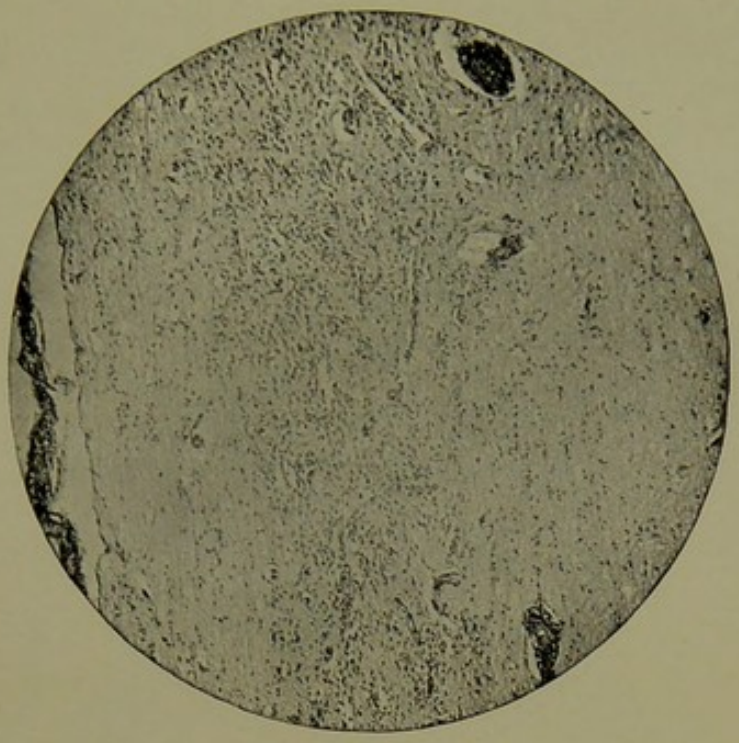


FIG. 29.

Another view of the same section as in figs. 25 and 26. In the right half of the illustration, two peripheral vessels with marked infiltration, lying at the boundary between white and grey matter. Otherwise similar to fig. 26.

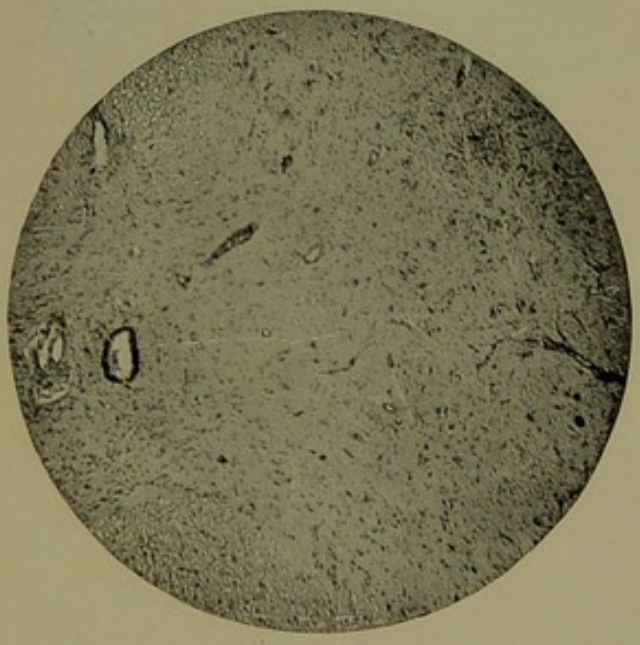


FIG. 30.

Lumbar cord of monkey No. 58 (*cf.* fig. 18). To the left, the central canal; close to it, an artery with slight infiltration. An infiltrated vein is seen running to the anterior horn (upwards and to the right in the photograph). Some diffuse infiltration in the anterior horn (to the right, above).

tissues. This I found most frequently in the region of Clarke's column in the upper lumbar region (*cf.* fig. 33); the tissues were distended and formed a wide mesh-work. It cannot be merely a

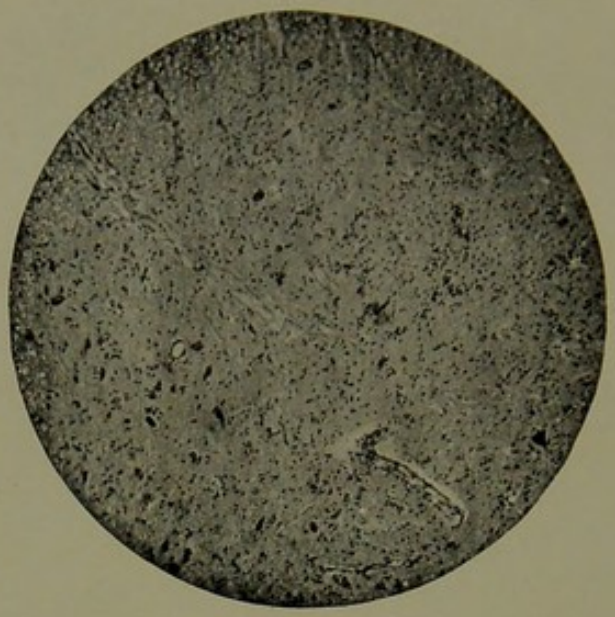


FIG. 31.

Left anterior horn in the lumbar cord of monkey No. 46. The apex of the horn lies above. To the right, a vessel slightly infiltrated. In the middle and above to the right, diffuse infiltration of the grey matter.

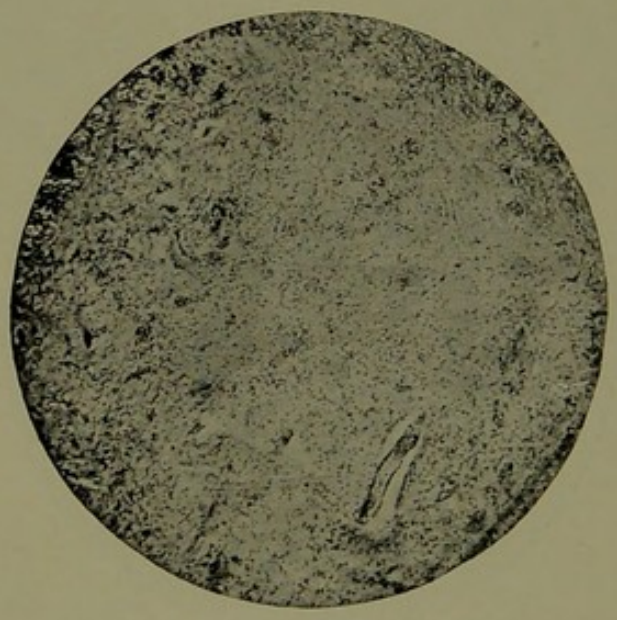


FIG. 32.

Right anterior horn (apex above) in the lumbar cord of monkey No. 24. Marked, diffuse infiltration. The tissues are swollen with œdema. Vessels slightly infiltrated. Ganglion cells have almost disappeared.

matter of chance that Wickman found a similar condition most marked in that region in man also.

Three kinds of alteration of the ganglion cells were to be seen in my preparations. In many instances they had simply disappeared, and it was impossible to say how this had happened. It was as though they had dissolved like a lump of sugar in water. It seems to me not improbable that the œdema is the active agent in this process. In other cases a microscopical change preliminary to disintegration could be seen. The cells lose their polygonal shape, the protoplasm has a washed-out, homogeneous appearance, the nucleus stains poorly. After making due allowance for the possibility of error which Wickman has pointed out, that only portions of normal cells are seen in the sections, I was able by means of serial sections to convince myself that this variety of alteration exists. Strauss has shown that the first change which takes place

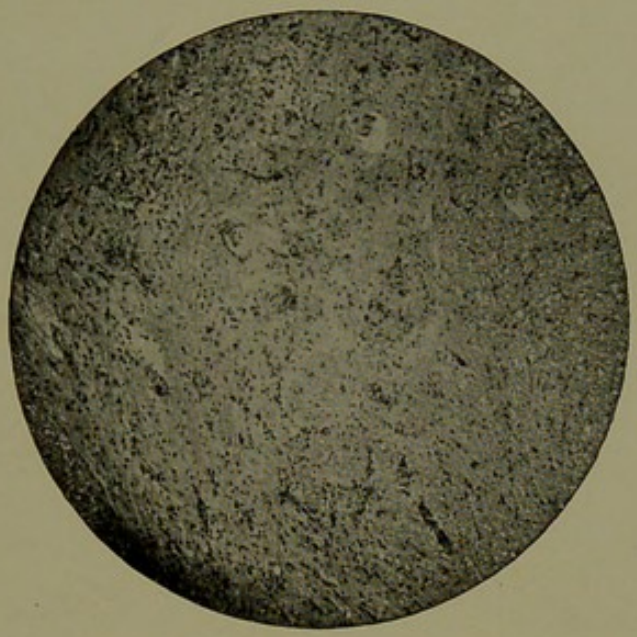


FIG. 33.

Upper lumbar region in monkey No. 48. Near Clarke's column. The tissues are disintegrated. A small hæmorrhage is present to the left and somewhat upwards.

in such cases is a swelling of the intracellular network of neurofibrils. Such a change may be the forerunner of the alterations described above, and lead ultimately to the complete disappearance of the cell. The third method, which is the most unequivocal, is that usually called neuronophagy. It seems to occur more frequently in monkeys than in human beings. In his earlier researches Wickman met with it so rarely that he did not consider it of much pathological importance. In monkeys it occurs frequently, and several stages can be made out. Figs. 34, 35 and 36 show a certain degree of neuronophagy under a low, moderate, and high magnification; in figs. 37, 38, 39 and 40 an advanced stage of neuronophagy is seen.

The illustrations show that neuronophagy consists in invasion of the ganglion cells by round cells; the latter devour the former until nothing is left of the substance of the ganglion cells, and only swollen round cells remain. Wickman's suggestion is correct, that neuronophagy occurs frequently in acute cases of poliomyelitis in monkeys. I believe that it is just because poliomyelitis is so acute in monkeys, as compared with the disease in man, that neuronophagy is so often seen in the former. The following clinical histories show that the examples of neuronophagy recorded above were obtained from monkeys in which the disease ran a particularly acute course.

Monkey No. 35 suffered for a considerable time from the disease, but the paralysis which caused death came on very suddenly in the form of a relapse.

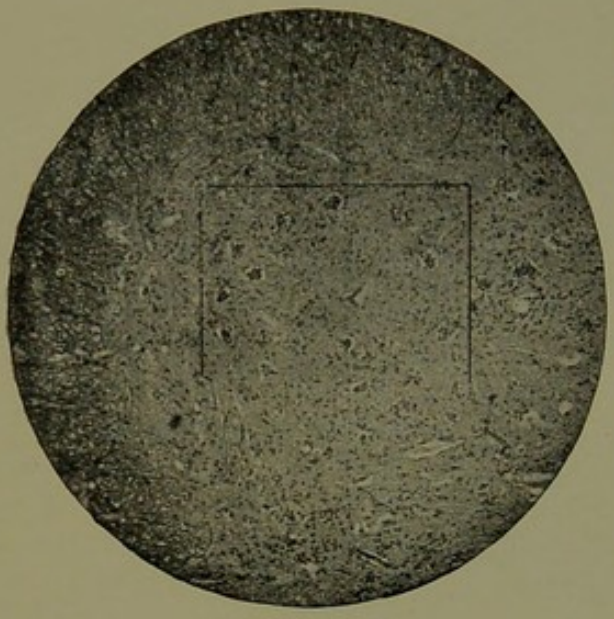


FIG. 34.

Left anterior horn from the lumbar region of monkey No. 35. Active neuronophagy beginning in the ganglion cells. Moderate infiltration of the anterior horn.

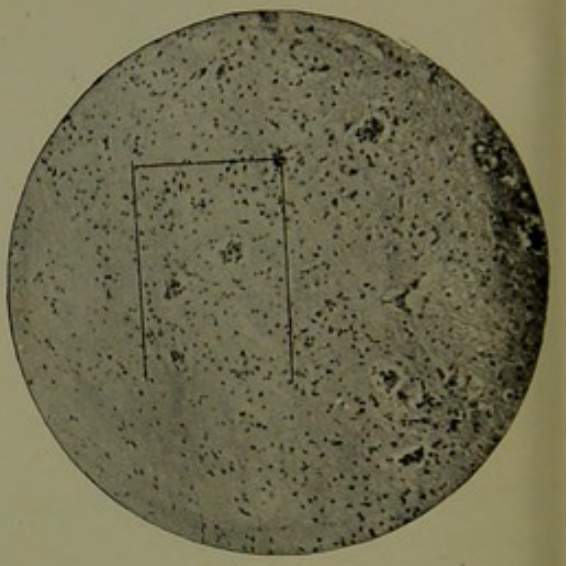


FIG. 35.

Enlargement of part of fig. 34. The neuronophagy is more easily seen.

Monkey No. 24 received an intracerebral injection of the virus on January 25, 1910. On the 29th it became suddenly completely paralysed, and it was found dead on the following morning.

Marked destruction of the ganglion cells was usually accompanied by well-marked interstitial changes. Where this appeared not to be the case I found either that the tissues were much swollen with œdema, or that the vessels in the neighbourhood were markedly infiltrated. Even when there was no connection between infiltration and destruction of the ganglion cells, in almost every case infiltration was present in some part of the section. In order

to come to a conclusion on this point, it would be advisable to kill and examine monkeys in an earlier stage of the disease—directly after the appearance of the paralysis. With our small material we were unable to carry out this plan. In selecting areas for purposes of photography, I tried to find one which showed this destruction of ganglion cells in the absence of infiltration of the interstitial substance; the failure which attended my search has led me to believe that such destruction does not occur. The contrary con-

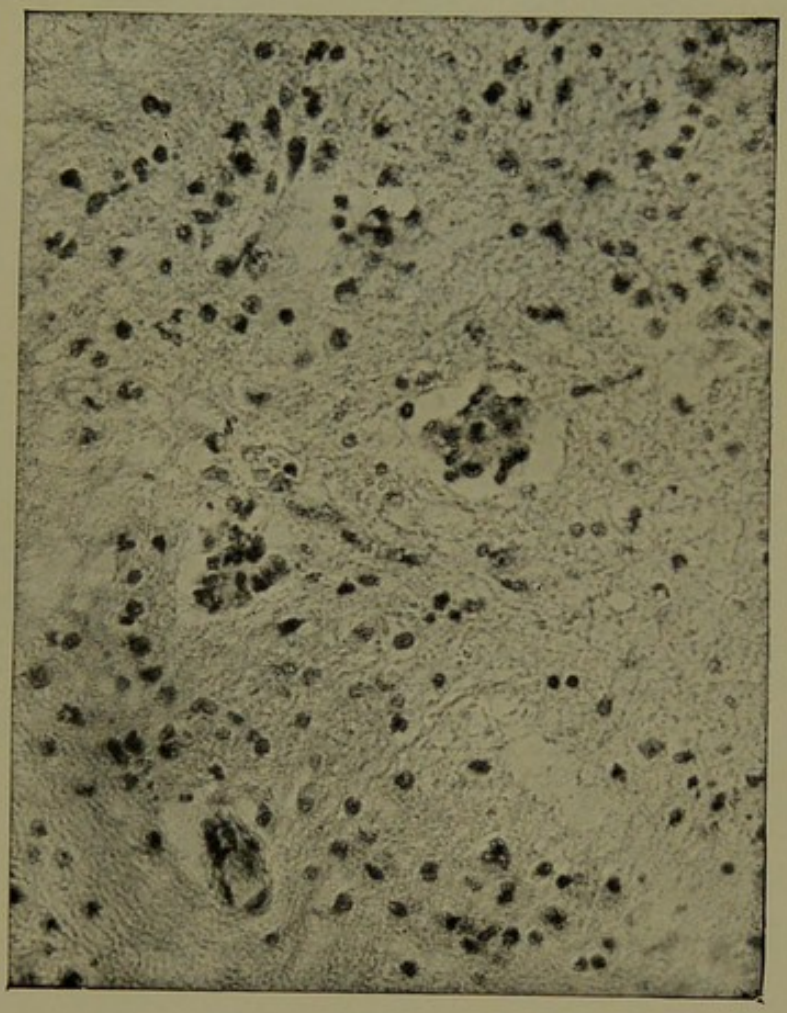


FIG. 36.

High magnification of the part outlined in fig. 35. Four ganglion cells undergoing neuronophagy.

dition is frequently found; cells which are quite normal, as far as can be proved microscopically, are seen near or even in the middle of areas of infiltration.

The posterior horns are usually less affected; they sometimes show one infiltrated vessel (fig. 41).

In confirmation of Wickman's observation in human beings, that in the upper lumbar and lower dorsal regions the posterior

horns seem to bear the brunt of the attack, I may refer to the section made from the upper lumbar region of monkey No. 48; fig. 42

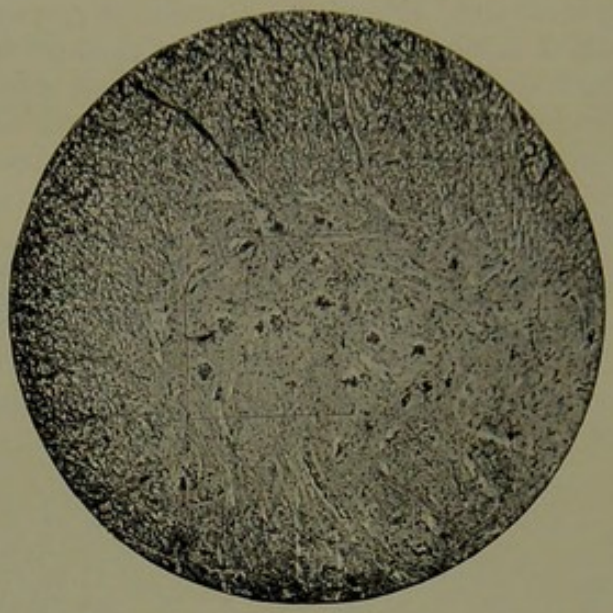


FIG. 37.

Lumbar cord of monkey No. 24. Left anterior horn. An infiltrated septum is passing from the white matter above and to the left to the anterior horn. Marked neuronophagy in the horn.

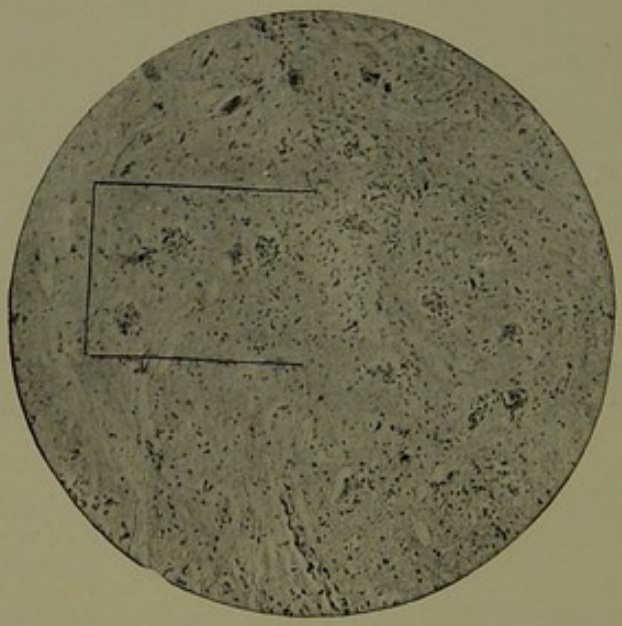


FIG. 38.

Increased magnification of the part outlined in fig. 37.

represents the anterior horn, but little damaged; fig. 33 the marked swelling up of the tissues in the region of Clarke's column; and

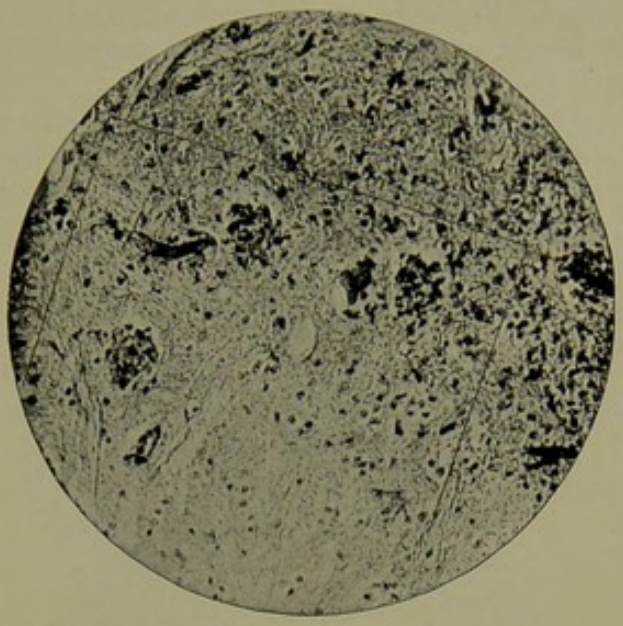


FIG. 39.

Still higher magnification of the part outlined in fig. 38.

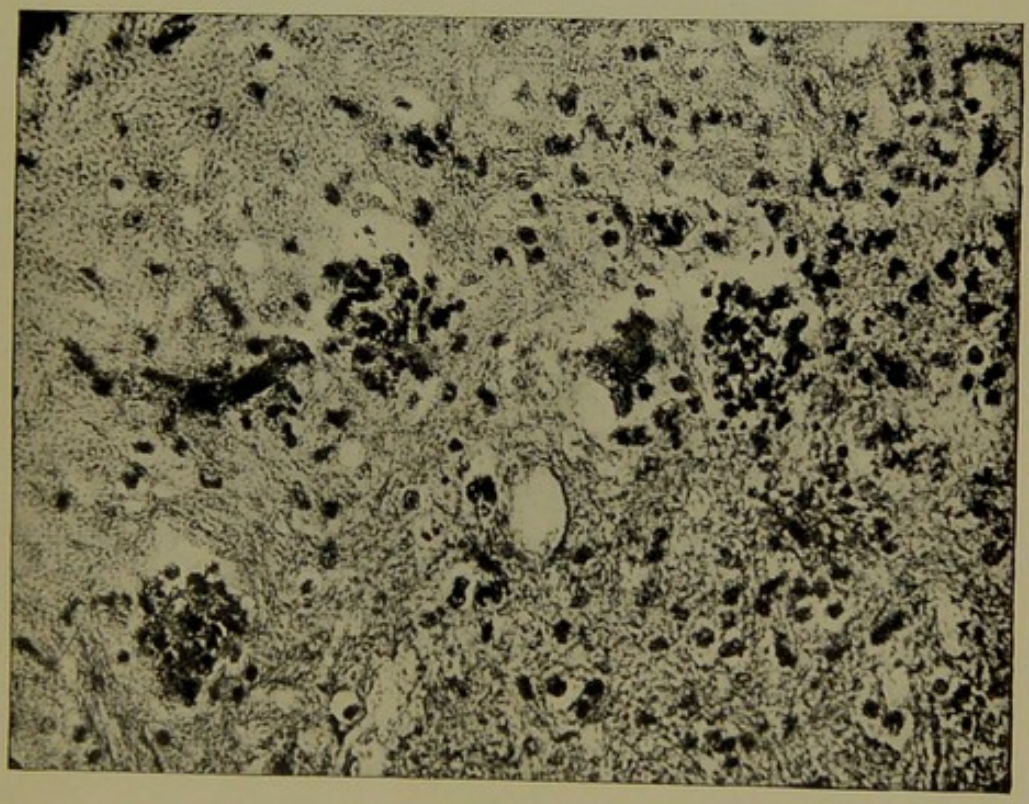


FIG. 40.

Very high magnification of the part outlined in fig. 39.

fig. 43 the changes in the posterior horn in the same section. Speaking generally, however, the changes are much less marked in the posterior horns, and the nervous tissue suffers much less destruction in them.

In the neighbourhood of the central canal, tissue infiltration is generally only slight, but the vessels are much involved, the arteries relatively less than the veins (fig. 30). I always found the ependyma unaffected. Wickman occasionally observed infiltration of it in human beings.

When the white matter is affected at all, it shows only slight infiltration of the tissues or of the vessels. An infiltrated pial septum may traverse the white matter, but the infiltration never invades the white matter itself. I could not find any relation

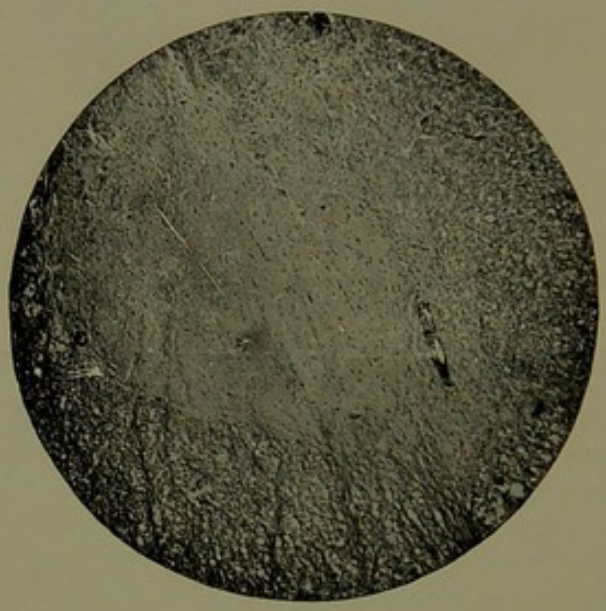


FIG. 41.
Infiltrated vessel in the right posterior horn: from the middle of the lumbar cord of monkey No. 4.

between the areas affected in the white matter and those in the grey.

I did not examine the spinal ganglia. According to Flexner and Lewis, Landsteiner and Levaditi, changes are seen in them similar to those observed in man, diffuse infiltration lying between the ganglion cells and between the nerve fibres while the ganglion cells are degenerate.

The peripheral nerves were not examined. Slight degenerative changes have been observed in human beings, but no inflammatory lesions (Redlich, Mönckeberg).

Changes similar to those in the spinal cord are found in the medulla and pons. The areas affected are generally smaller, further apart from one another, and distributed in an irregular manner.

The vessels are most affected, and this is very obvious because of the distance between the areas involved. Wickman's observation that these areas bore no relation to the nuclei of the cranial nerves

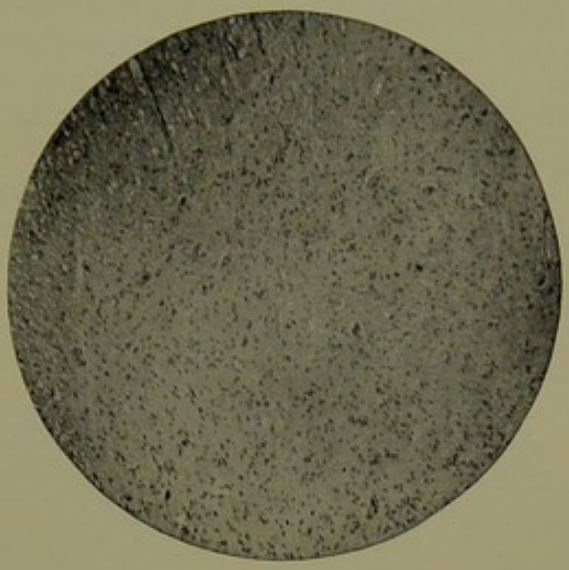


FIG. 42.
Anterior horn, slightly infiltrated, from the upper part of the lumbar cord of monkey No. 48.

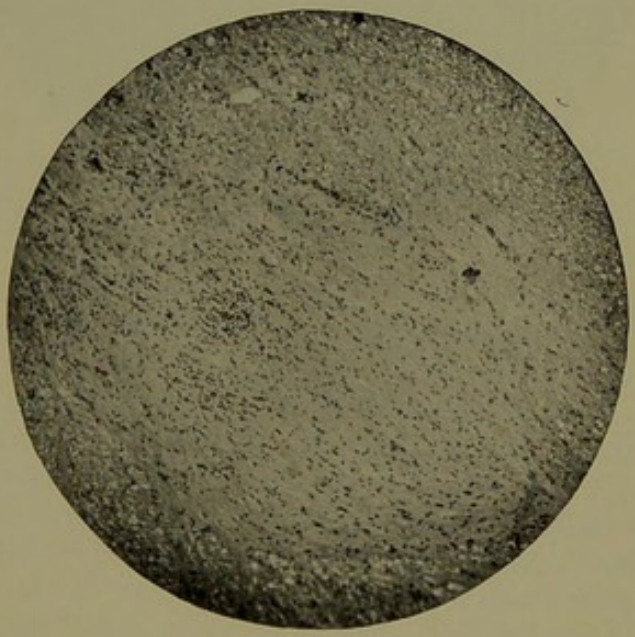


FIG. 43.
Round cell infiltration in the posterior horn from the upper lumbar region of monkey No. 48.

is generally true also in monkeys. Occasionally very distinct, small infiltrations are seen which are clearly in relation to ganglion cells; they are found to be examples of neuronophagy. On the other

hand, infiltration of the vessels in the pons and medulla is common, even when the clinical history does not lead one to expect it.

Brain.—Infiltration is seen most frequently (when it is seen at all) in the cortex near the site of inoculation. It is often not more intense than that found elsewhere in the brain, *i.e.*, in the opposite hemisphere, at the base of the brain, and in the central ganglia. Figs. 44 and 45 represent lesions in the cortex of the side opposite to the injection from a case which appeared, clinically, to be one of cerebral paralysis (monkey No. 27, *cf.* p. 53).

The outstanding feature is the great degree of involvement of the vessels, while the infiltration of the tissues is only slight.

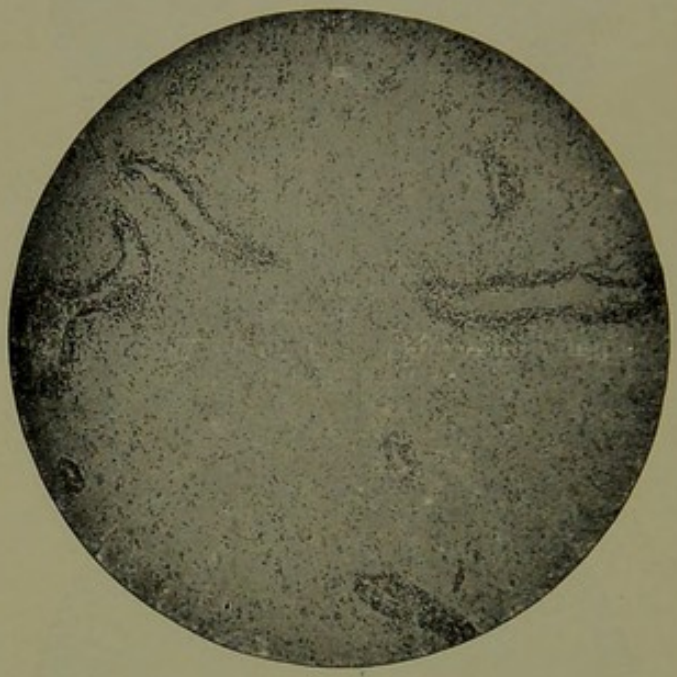


FIG. 44.

Marked infiltration of the vessels of the cerebral cortex of monkey No. 27, with slight general infiltration.

Fig. 47 shows one of the infiltrated vessels in fig. 44 under a higher magnification.

The distribution of the areas is very irregular in the brain, as in the medulla. They are far apart and the component round cells are not numerous or closely massed together in the infiltrations of the tissues. It is remarkable that in many cases, where inoculation was performed by the intracerebral method, no trace of lesions in the brain could be found.

I did not investigate the cerebellum. In man, lesions similar to those in the cerebrum are found. Neither was I able to give much attention to the character of the cells forming the infiltrations. As far as I can judge, Wickman's interpretation applies equally well to the appearances found in monkeys. It is well known that there

has been much controversy as to whether these cells are leucocytes or are derived from the fixed tissue elements. Apart from a few polymorphonuclear leucocytes, Wickman considers the cells to be lymphocytes or lymphocytes which have undergone further development. We were able to demonstrate very clearly that the process is a different one from that which occurs in true suppurative inflammation, in the course of the examination of those monkeys in which a secondary infection had unfortunately taken place at the site of inoculation. The cells which Wickman regarded as being derived from lymphocytes are similar to the "polyblasts" of Maximow. Instead of the round nucleus with much chomatin and the small amount of cytoplasm which characterize the true lymphocyte, these cells have a nucleus which is lighter in colour, contains less chromatin, is not quite round but slightly folded, and a wider margin of cytoplasm. Wickman found cells in all stages intermediate between the true lymphocyte and the polyblast, and concluded therefore that

FIG. 45.

Infiltrated vessel in the cortex of monkey No. 27 (from the side opposite to that on which the injection was made).

the latter is a derivative of the former. The polyblasts are specially numerous in tissue infiltrations; in the infiltrated vessels and pia mater the true lymphocyte predominate (*vide* fig. 22). In neuronophagy many polymorphonuclear leucocytes as well as polyblasts are seen, but Wickman considers that the latter alone act as phagocytes.

As the appearances found in man in the pia mater, spinal cord, medulla, brain, &c., correspond almost exactly with those found in the monkey, it is unnecessary to describe them in detail. I refer the reader to Wickman's description.

In man and in the monkey, therefore, the so-called poliomyelitis has been shown to be a non-suppurative, infiltrative inflammatory process of a lymphocytic type, which may affect the pia mater or any other part of the central nervous system in a disseminated manner, although it tends to involve the grey matter, and, in particular, the anterior horns.

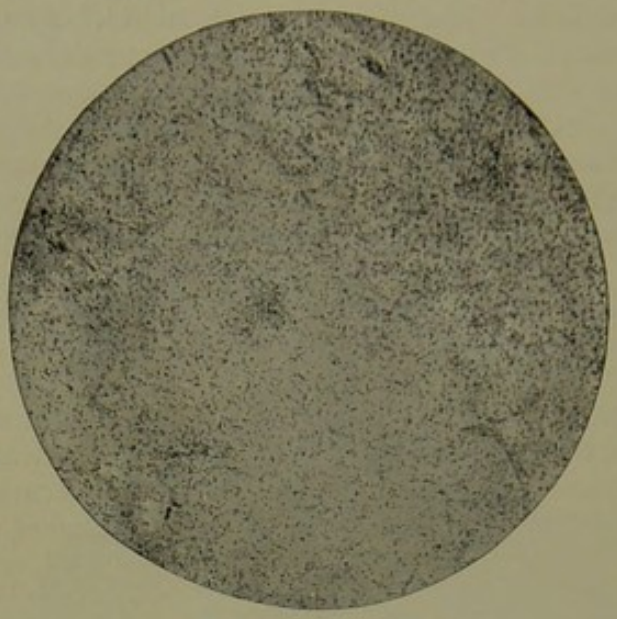


FIG. 46.

Infiltration into the tissues of the brain of monkey No. 27.

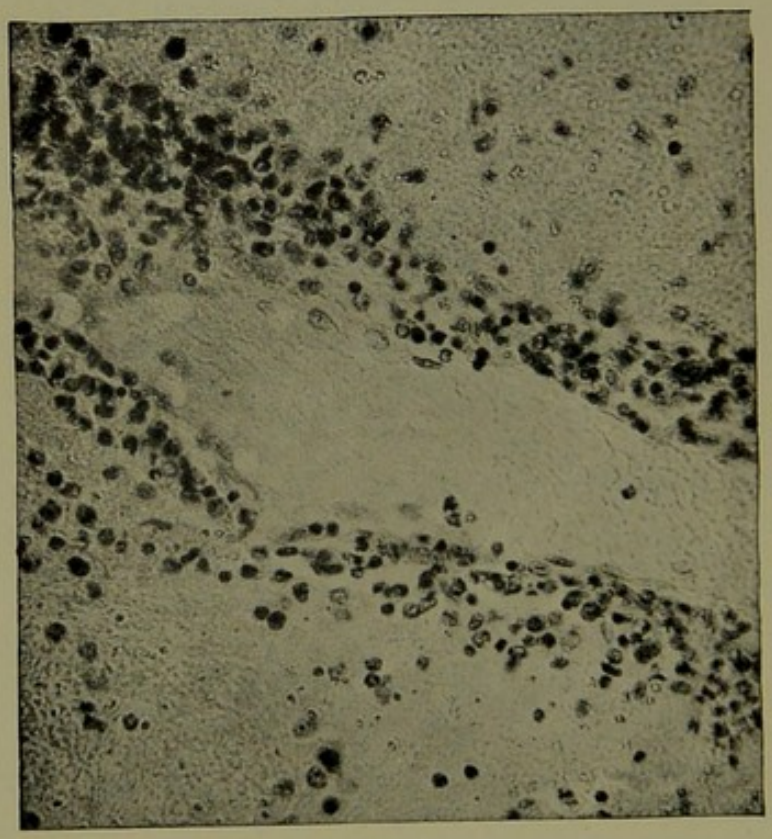


FIG. 47.

Infiltration of a vessel (one of those seen in fig. 44).

The Stage of Repair.—I was able to study this stage in only one instance. Most of the monkeys which became paralysed died in a few days, and even those which survived the first few days died shortly afterwards with symptoms of marasmus. The sole exception to this was monkey No. 37, which was inoculated on March 2, 1910. Paralysis set in on the 9th, and speedily became complete in the hind limbs. The monkey died (for details see p. 57) on April 14, forty-three days after inoculation and thirty-six days after the onset

FIG. 48.

The greater part of the left half of the spinal cord of monkey No. 37. An area is seen at the apex of the left anterior horn.

of paralysis. The brain was not examined. No lesions were found in the medulla, the cervical or the dorsal regions; in the lumbar region almost symmetrical lesions were present, as shown in fig. 48, although the magnification is low.

Under a higher power the lesion is seen to involve the greater part of the anterior horn (fig. 49), particularly in its lateral part.

There is considerable rarefaction of the stroma, the wide meshes of which are filled by a fine network containing small collections of round cells. Ganglion cells are almost entirely absent; it is remarkable that one well preserved cell was found in the middle of the lesion. I have been unable to find any proliferation of the blood-vessels, as has been described in this stage by several authors. In fig. 49 an infiltrated vessel may be seen. After thirty-six days, therefore, a considerable lesion was still present in the anterior horns, but nothing of the nature of scar tissue. Judging by the clinical history of the acute stage of the illness, and by the appearances found in other monkeys, it is very probable that other and more widespread lesions were present at first, which had disappeared with the exception of those in the anterior horns. It may be that

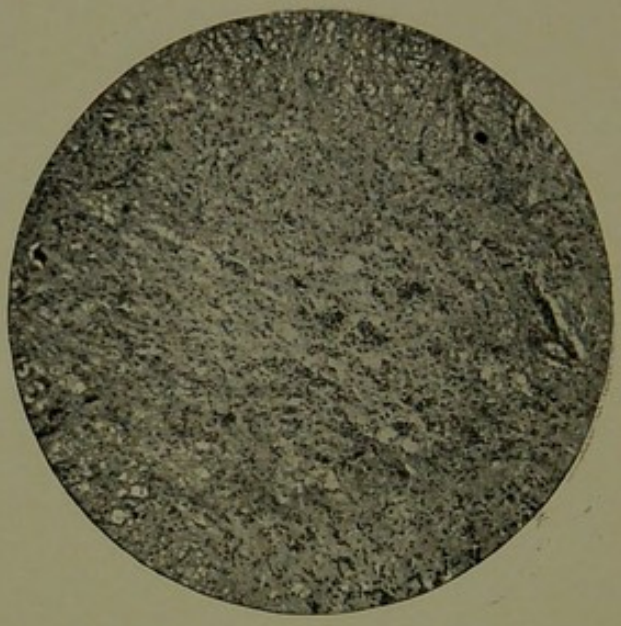


FIG. 49.

The anterior horn in fig. 48 under a higher power. Chronic changes; rarefaction of the stroma; increased number of cells; to the right a blood-vessel with infiltrated walls; marked destruction of the ganglion cells. Below and to the left of the centre, a well preserved ganglion cell.

the peculiar liability to the disease of this part of the spinal cord is shown better in these chronic cases. Levaditi and Stanesco found scar tissue and proliferation of the blood-vessels in monkeys which died sixty-seven days after the onset of paralysis.

According to the more exact descriptions of the stage of repair in man, particularly in those given by Wickman, the lesions are characterized by the presence of cells containing fat granules; such cells are met with frequently in lesions of the nervous system, they are associated with degeneration of the nervous elements and are found close to blood-vessels. The glia cells are increased in number in the later stages of repair. It has been shown during this

stage that the process is not limited to the anterior horns, but takes place extensively in Clarke's column and in the posterior horns. Degeneration of the tracts and of the anterior roots has been demonstrated by means of suitable methods.

In all the monkeys which recovered completely from the paralysis we were unable to find any lesions. It is true that these monkeys were only killed some months after inoculation and several weeks after all paralysis had disappeared. Monkeys which were reinfected without any result after they had recovered from paralysis showed no microscopical lesions, even when they were examined only a short time after reinfection (in one case eighteen days).

I will mention here certain observations which have been made on monkeys killed or dying during the stage of incubation. In my own series there are two such cases. Monkey No. 22 received an injection simultaneously into the brain and peritoneum on January 18, 1910; it died of gastro-enteritis on the 24th before any paralysis had appeared. The monkey used as a control became paralysed on the tenth day. Microscopical examination revealed purely normal conditions.

Monkey No. 62 died four days after infection; the control became paralysed on the ninth day. No lesions were found in the spinal cord.

Landsteiner and Levaditi had a similar experience with four monkeys which received intracerebral and intraperitoneal injections on the same day. Three were killed on the second, fourth, and seventh days respectively. The fourth became paralysed on the eleventh day. The central nervous system of the first three was found normal except that there was a slight traumatic inflammation of the meninges in the case of the two killed on the second and fourth days.

In the light of these experiments it seems clear that lesions occur only just before the onset of paralysis. The experience of Leiner and v. Wiesner was somewhat different; they found changes in the spinal cord (hyperæmia, small hæmorrhages, degeneration of the ganglion cells) on the third day after infection; the control became paralysed on the eighth day. Whether the lesions, which were not quite typical, were really due to the virus cannot be stated with certainty. Further injections made with material from this spinal cord into other monkeys were not successful. The cord of a monkey killed on the fifth day was proved to contain virus.

The Final Stage.—This, the stage of scar formation, I have not been able to observe from reasons which I have given above. In man a scar occupies the anterior horns usually, and makes them appear diminished in size. Under the microscope this scar appears to be composed of fibrillar sclerotic tissue with no nervous elements. In other cases the only change seen is atrophy of the ganglion cells; Charcot's theory of a primary cell lesion was probably based on such cases. The blood-vessels are thickened in the sclerotic

areas. The antero-lateral tracts show some degeneration; much importance was attached to this change by the earlier investigators whose attention was thus turned away from the more important lesions. This degeneration of the lateral tract must not be regarded as evidence that the process had invaded the white matter, but as an endogenous degeneration. It is seen at levels where the grey matter is normal. In rare instances it may be due to small lesions in the white matter. Degeneration and atrophy of the peripheral nerves and muscles are present. Finally, there are traces of atrophy in the cerebral motor area; this is probably a secondary result of the destruction of the lower motor neuron. Wickman, however, has reminded us that the effect of the cerebral lesions must not be overlooked, and our experience with monkeys has shown that lesions are specially liable to occur in the central convolutions.

Poliomyelitis in Adults, Landry's Paralysis, Polyneuritis, Rabies and Borna's Disease in their Relation to Heine-Medin Disease.—I have already mentioned the important contributions to our knowledge of the nature of Heine-Medin disease which have resulted from the investigations into the pathology of the disease by Wickman and others. Wickman was the first to demonstrate afresh the complete identity of poliomyelitis in adults and infantile poliomyelitis; he showed that Landry's paralysis and poliomyelitis acuta are identical from the point of view of their pathology, and produced evidence which made it probable that their etiology is the same also. By means of a critical analysis he showed that in many instances, from purely clinical reasons, the term polyneuritis is used for cases which are caused *de facto* by a poliomyelitis. The clinical symptoms (paræsthesiæ, pains, &c.) can be explained by a poliomyelitic lesion, and the good prognosis which attaches to "polyneuritis" is not incompatible with a poliomyelitic process. As Strümpell suggested a long time ago, Wickman considers that the differentiation between polyneuritis and poliomyelitis is more or less artificial. In Chapter II we have seen how important a recognition of this fact is for clinical work.

Wickman's observations on the similarity of the pathological picture in poliomyelitis and rabies has shown the way in regard to studies into the etiology of Heine-Medin disease. The pathological process in rabies is a disseminated, infiltrative myelitis, which shows a preference for attacking the blood-vessels and particularly the anterior horns.

Again, Joest and Degen have shown that the so-called Borna's disease in horses presents an almost complete pathological analogy to Heine-Medin disease in man. In that disease they found a disseminated, infiltrative meningo-myelo-encephalitis of a lymphocytic type, which specially affected the blood-vessels. The only difference between it and infantile paralysis lies in the fact that it tends rather to involve the brain, by preference the olfactory lobe. But it also affects the rest of the central nervous system, and in the spinal cord the anterior horns are a favourite situation. In other particulars

the pathological features are very similar (slight macroscopic changes, involvement of the meninges, relation to the blood-vessels, the condition of the cerebrospinal fluid). I have already mentioned the bodies which Joest and Degen found in the ganglion cells, and which they regard as specific to Borna's disease. It would be not uninteresting to investigate (*e.g.*, by means of serum diagnosis) the biological relationship between the virus of Heine-Medin disease and that of Borna's disease. I stated in Chapter III that horses are not susceptible to the virus of Heine-Medin disease.

IV.—PATHOGENESIS.

In the first section of this chapter I gave a summary of the historical aspect of the pathology and pathogenesis of the disease; I also formulated four questions. Having sketched the progress which has been made by experiments on animals, I will attempt to provide answers to these questions.

The Point of Attack of the Virus.—At what point in the central nervous system does the virus first have an effect? Controversy has raged around the question whether the ganglion cell is affected primarily, as Charcot believed, or whether the first change is an interstitial one, according to the suggestion made by Roger and Damaschino. Such a controversy is perfectly natural. On the one hand, Charcot's theory explained the clinical symptoms which in great part point to a purely motor paralysis. Such a selective action of the virus was not a new idea; we were accustomed to it in the case of tetanus. On the other hand, pathological investigation showed not only that the lesion was not purely degenerative, but that it was by no means confined to the motor regions of the cord. In that case how was the motor character of the paralysis to be explained? Further, accepting the fact that the pathological process mainly affected the motor regions, why should a virus which acted by producing disseminated lesions show this preference for the anterior horns?

Keeping to the microscopical appearances, the interstitial character of the process appears to be very well marked. The involvement of the blood-vessels is so striking that in many cases one may say that the distribution of the lesions depends mainly upon the vascular supply and particularly upon the situation of the veins. The question arises, whether the disease of the vessels may not be explained by some pathological process affecting the ganglion cells or glia, and secondarily acting as an irritant to the vessels, causing emigration of the lymphocytes. In such a case, an accumulation of lymphocytes around the blood-vessels would be a natural sequence. Against this view, however, the observations made by Wickman and ourselves on the kind of vessel involved are of much importance. According to the theory, the smallest vessels, the capillaries, should be the most affected, but we find it to be the veins. Further, well preserved ganglion cells are often seen in the middle of a markedly

infiltrated area and even quite close to veins which are severely affected. There is little justification for supposing that the cells are really damaged, but that this cannot be seen, because slight changes in the cells are so easily recognized. It is therefore impossible to believe that the involvement of the vessels is secondary to an affection of the nervous elements. The finding of infiltrated vessels in the middle of the white matter, at a distance from the grey matter, is another argument for the primary nature of the lesion in the vessels; so also is the presence of lesions in the pia mater, particularly when they are found on the posterior aspect of the cord, far from the grey matter, and at levels in the cord where the grey matter is scarcely involved at all. Everything points to the change in the vessels being largely independent of changes in the nervous elements; there is no doubt that in at any rate very many places *we are justified in considering the lesion to be primarily vascular or perivascular.*

But this does not mean that the virus attacks the vessels alone and has no direct effect upon the ganglion cells. The general impression is that the changes in the ganglion cells are of a secondary nature; it may be that the infiltrative process extends directly from the vessels to the ganglion cells, or that the cells succumb to nutritional disturbances resulting from the diseased condition of the vessels or from the œdema. The argument drawn from clinical experience, that the occurrence of paralysis so suddenly can be explained only by a primary affection of the ganglion cells, cannot be maintained; the experiments on monkeys have shown that interstitial change is very considerable in those cases where paralysis sets in suddenly and rapidly causes death. Demonstrable lesions in the interstitial tissues may occur therefore quite as rapidly as in the parenchyma. I again call particular attention to the absence of any lesion shortly before the onset of paralysis in monkeys. Sometimes, it is true, the ganglion cells appear to be the only structures involved; but in my opinion enough importance is not attached to the œdema which is frequently present in such cases. *One fact proves conclusively that primary affection of the ganglion cells may occur; that is the neuronophagy which is seen in the most acute cases.* Although here interstitial changes are by no means absent, yet the isolated cells surrounded by round cells give the impression of a localization of the damage to the ganglion cell. Landsteiner and Levaditi observed degenerative change in the cells before the occurrence of neuronophagy, but I was unable to find it. I believe that this type of alteration in the cell is not followed by neuronophagy and is caused indirectly. I saw quite normal cells surrounded by lymphocytes. Nor could I convince myself that the interstitial changes were preceded by recognizable alterations in the ganglion cells, as has been reported by Landsteiner and Levaditi, and on which they base their argument that the process always begins in the ganglion cells. [They quite recognize that the changes in the vessels and the pia may appear independently.] On the contrary, I

have frequently seen well preserved ganglion cells lying within the infiltrated areas. In the atypical (marantic) forms of the disease Leiner and v. Wiesner found no cell infiltration but hyperæmia, hæmorrhages and degeneration of the ganglion cells. In discussing the pathogenesis of the typical, paralytic form of the disease it seems to me to be an important observation that the non-paralytic form presents appearances indicative of essential involvement of the ganglion cells.

The general conclusion arrived at is this: The process is mainly primarily interstitial; the ganglion cells are affected primarily in some degree, but this is small compared with the interstitial change. Our position is the same as that taken up by Fr. Schultze many years ago on the basis of histological and critical studies.

Having arrived at this point, as Wickman rightly says, the difficulty in explaining the clinical symptoms really begins. One would expect from the microscopical appearances to find the clinical picture of a transverse myelitis; instead of which the symptomatology is that of a system disease of the spinal cord. The incongruity between the symptoms and the pathological findings has given much trouble to the adherents of the primary vascular theory. Many hypotheses have been suggested, which all depend upon some cause outside the nervous parenchyma to explain the peculiar susceptibility of the anterior horns. This liability of the anterior horns is a fact admitting of no doubt. A point of special importance arising out of the experimental work is the fact that in monkeys which were inoculated intracerebrally the favourite situation of the pathological process was in the grey matter of the anterior horns of the spinal cord; the symptoms were mainly those of a flaccid motor paralysis, usually of the hind limbs, and so, in spite of the abnormal, artificial point of entry of the virus, the appearances presented by human "spinal" paralysis were reproduced with considerable fidelity. How can this be explained?

In view of the special involvement of the blood-vessels it has been suggested that peculiarities of the vascular supply are the cause of the remarkable vulnerability displayed by the anterior horns. The area of distribution of the anterior spinal artery was said to be particularly liable; Kadyis had shown that it supplied the anterior horns by branches which passed into the cord at the bottom of the anterior longitudinal fissure and then turned outwards. Pierre Marie stated in consequence of this, that the whole process was one of embolism of the anterior spinal artery. Wickman has shown that this supposition is certainly incorrect. Apart from the fact that no embolism or thrombosis is found in the vessel the character of the lesion does not suggest that it is of embolic origin; no necrosis is seen. Again, embolism artificially produced shows no tendency to affect the grey matter more than any other part. Further, it has been seen that not the arteries but the veins are the more affected and, finally, the process is by no means confined to the central regions of the cord; the peripheral portions

are hardly less affected. For these and other reasons the theory of embolism must be rejected, and no cause operating by way of the anterior spinal artery alone can be accepted. Wickman's theory is worthy of more consideration; he associates together the vulnerability and the vascularity of the different parts of the cord. The greater the blood supply is, the more intense the pathological process. When the arrangement of vessels changes the localization of the lesions is found to change also; in the lower lumbar regions the lesions are found mainly in the anterior horns, but in the upper lumbar and lower dorsal regions the process is more in the region of Clarke's column, which at this level is much more richly supplied with blood-vessels. I shall return later to certain difficulties which even Wickman's theory does not explain.

The Spread of the Virus within the Central Nervous System.— The microscopical appearances indicate that the vessels constitute the main channel along which the virus spreads. Wickman holds that the clinical symptoms contra-indicate this route; there is a certain regularity in the way the paralysis spreads which indicates that the pathological process underlying it is advancing in a continuous if rapid manner. This continuity of spread of the lesion is shown in microscopical sections (compare the photographs of longitudinal sections), and leads one to suspect the lymph channels. Experimental studies have shown that the virus has a special affinity to the lymphatics, and Wickman has shown that in the central nervous system the blood-vessels are surrounded by perivascular lymph channels in which the first signs of a lesion appear. Further, the lymph channels which lie in the nervous matter itself must be considered. Some of the observations made on monkeys have a bearing on this point; after intracerebral inoculation into the central convolutions on one side, the paralysis appeared usually on the contralateral side. This leads me to the difficult question of explaining how it is that monkeys when inoculated into the brain suffer subsequently from paralysis which is mainly spinal. I imagine that the virus passes along the perineural lymph spaces as well as the perivascular ones; on reaching certain regions in the spinal cord which are richly supplied with lymph (the grey anterior horns) it finds there a particularly suitable soil. The objection, that there is plenty of opportunity for the virus to develop in the brain itself, is not justifiable; in the first place, cerebral lesions are certainly more common in monkeys which have received an intracerebral inoculation than in man; in the second place, the motor cells in the brain have not the same close relation to the blood-vessels which is found within the narrow limits of the spinal cord, with its complex network of vessels. While I agree with Wickman that richness in vascular and lymphatic supply causes the peculiar liability of the anterior horns, I am inclined to explain the predominance of spinal symptoms in monkeys which have received intracerebral inoculation by the direct passage of the virus along the perineural lymph spaces down to the anterior

horn of the opposite side, where it finds a soil suitable for its further development. Joest's observations on Borna's disease lend some support to this view; he found the most severe lesions in the olfactory lobe and connects this with the entrance of the virus through the nose. In Borna's disease the virus spreads along the perivascular and perineural lymphatics, and finally becomes localized in the anterior horns of the grey matter of the cord.

In short, *the virus spreads along the lymph channels in the central nervous system, along those which surround the vessels as well as those running in the substance of the brain and spinal cord. The virus develops more freely wherever there is a rich supply of lymph.*

Hoche assumes that the central canal serves as a channel for the virus. His theory is founded upon experimental evidence, and he considers that the patency of the canal in children is the cause of the frequency with which they suffer from the disease. This explanation cannot be accepted. In the first place, the poliomyelitis of adults, in whom the central canal is closed, is quite similar to that of children, and in the second place the central canal is only rarely involved in human beings and never in monkeys, according to my own experience.

The Route by which the Virus reaches the Spinal Cord.— At first sight, considering how extensively the vessels are affected, it seems as though the virus must have been brought to the cord by the blood-stream. However, Wickman has shown that it is not the capillaries, as one would expect in such a case, but the veins which are principally, and sometimes exclusively, involved. That the blood and the organs rich in blood contain no virus, or at most the minutest quantity, is strong evidence against the theory of hæmatogenous infection. Virus has never been found in the blood during the stage of incubation. The following observation made by Rénault is further evidence against this possible method of transmission of the virus: A pregnant woman had a severe attack of poliomyelitis, recovered, went to term and bore a healthy child with no signs of paralysis. As the virus is capable of passing through the most perfect filters known, one would expect that it would be transmitted to the fœtus, if it circulated in the blood-stream. It has been clearly shown by experiment, that inoculation into nerves is commonly successful, the virus passing up within the nerve to the spinal cord and causing paralysis of the muscles supplied by that nerve. Further, it has been demonstrated that there is a definite relationship between the situation chosen for inoculation and the part of the spinal cord which is first affected; the virus always chooses the shortest way to the cord, *i.e.*, the path of the nerves.

On page 100 I have shown that the occasional success attending intravenous inoculation does not contradict the theory of transmission by the nerves. Consequently the conditions are almost exactly those which obtain in the case of rabies. [Some authors

recently have revived the hæmatogenous theory for rabies, on the ground that the lesions first observed are vascular in type; the above critical analysis makes it clear that this is no valid argument in favour of transmission by the blood-stream.]

Harbitz and Scheel, as well as Flexner, accept the suggestion made by Schultze a long time ago, that the virus first settles in the meninges and then causes the lesions in the cord by direct extension of the meningitic lesion. According to our views, it is quite possible and probable that the virus, proceeding along the nerves, first reaches the pia mater and gives rise to lesions in it. But that the spinal cord is affected only directly from the meninges seems to us, as it does to Wickman, exceedingly unlikely; there is no exact correspondence between the lesions in the pia and those in the cord, and the pia in the depths of the anterior fissure is usually more affected than that covering the exterior of the cord. It is by no means rare to find the infiltration of the fold of pia cease when the pia reaches the surface of the cord. If we bear in mind the knowledge gained from experiments, that the virus tends to follow the lymph-stream, we shall not be far wrong in saying that *the virus of Heine-Medin disease travels centripetally in the lymphatics lying round and in the peripheral nerves until it reaches the central nervous system, where it attacks the pia mater and simultaneously gains entrance into the cord along the spinal roots.*

Joest's observations on Borna's disease in horses give valuable support to this view. After a most careful consideration of all the probable paths along which the virus could travel he arrives at the conclusion that the active agent reaches the brain by way of the interstices and the sheath of the nerves. In Borna's disease infection begins in the nasal mucous membrane; hence the early and intense involvement of the olfactory lobe. The virus passes in a centripetal direction to the subarachnoid space, causes a certain amount of meningeal irritation, and then passes along the nerve into the brain. Joest denies that the further extension of the process within the central nervous system is due to direct involvement from the pia mater.

The Portal of Entry of the Virus.—The initial symptoms of the disease point to the mouth and throat and the respiratory tract or to the alimentary tract as the situations where the virus enters the body. The occurrence of lesions, which are clearly due to the virus, in the gastro-intestinal tract after inoculation by any method and the appearance of the virus in the mucous membrane of the throat under the same condiions, lead one to believe that these symptoms are the result of a secondary inoculation with the virus. But since these symptoms almost invariably precede an attack of Heine-Medin disease in human beings, I cannot but think that they are symptoms of primary infection. The experimental results do not put these situations out of court as points of entry of the virus, although it is not easy to produce infection by these routes. In

consideration of the known predilection of the virus for lymphatic tissue, it is quite probable that the mucous membranes of the throat and of the intestinal canal constitute the chief portals of entry of the virus because they are so richly provided with lymphatics. It is difficult to say which of the two is the more common portal. Different epidemics differ in this respect. If our theory is correct, that the virus always takes the shortest route to the central nervous system, we are inclined to consider the gastro-intestinal tract as the main point of entry, because the large majority of cases are affected in the lower limbs. The fact that the lower limbs are usually affected, wherever inoculation has taken place, must not be ignored. In future, therefore, it will be of the greatest importance to notice carefully where paralysis first shows itself. Particularly it must be noted whether cases, which have symptoms first in the mouth and throat, develop paralysis first in the upper limbs. It would not be remarkable if such cases ultimately were affected in the lower limbs more than in the upper, because we know that the segments of the spinal cord which correspond to the lower limbs are so much more easily affected than the rest of the segments. It is improbable that the virus often enters through the nasal mucous membrane, because the cerebral forms of the disease are rare.

Conclusions.—None of the deductions we have drawn can be considered conclusive. In the natural sciences it is rare to find a certainty. Many steps in our arguments are based on hypotheses. The following is the most probable of all the theories advanced to explain the pathogenesis of the disease.

The virus enters the body by way of the lymphatics of the throat or of the intestinal tract, or of both (this varies in different epidemics). Thence it passes in the lymphatics within or around the peripheral nerves to the spinal cord. Here it causes slight infiltrative inflammation of the pia mater, and then enters the cord along the spinal roots. It spreads within the cord chiefly along the lymph spaces round the veins, but also in those lying in the nervous tissues themselves. It develops freely in parts of the cord, such as the anterior horns of the grey matter, in which the vascular and consequently the lymph supply is rich and where the texture of the tissues is loose. Here the virus gives rise to infiltrative inflammation of the lymphocytic type, which causes degeneration and destruction of the ganglion cells either by interference with the nutrition of the cells, or by direct involvement in the infiltrative process. In other cases, particularly those in which the process is very acute, the ganglion cells are affected primarily, the cells being always destroyed by the action of phagocytes which are usually lymphocytes.

CHAPTER V.

Epidemiology.

I.—HISTORY OF THE EPIDEMICS.

Early Reports.—The disease has certainly existed for a very long time. Heine mentions patients who had suffered from the disease more than fifty years before his time; he says that the disease "is not rare" and quotes an author, Shaw, who met with it in India, Egypt, and other extra-European countries. "Another author, Colman," writes Heine, "even mentions an epidemic." Wickman considers that this latter statement requires considerable reservation; an author named Colmer (not Colman) reported that he had heard from the mother of a child suffering from hemiplegia, that several cases of hemiplegia and paraplegia in children had occurred in the district within a space of three or four months. The report therefore contains little that is of value as evidence.

It is curious that the older literature contains not a single reference to any epidemic, although infantile paralysis most certainly occurred. After the appearance of Heine's monographs, and at a time when the literature of the disease was becoming extensive, no mention was made of any epidemic before 1880. It may have been because small groups of cases were not recognized as such, owing to the infectivity of the disease being unknown, or because the clinical differences between the cases caused them to be regarded as examples of different diseases. But when the symptomatology of the commonest type of the disease had been fully described under the name of spinal "infantile paralysis," the absence of reports of epidemics can be explained only by the fact *that such epidemics did not occur before* 1880.

The Scandinavian authors were the first to draw attention to the epidemic occurrence of the disease. At about the same time reports were received from other countries concerning groups of cases and the occurrence of several cases in one family. The following is a short summary of the epidemics recorded in the different countries.

Sweden and Norway.—These two countries dispute one another's claim to priority in the matter of recording the first epidemic. Netter states that a Norwegian author, Ch. Bull,

recorded a small epidemic of fourteen cases, four of which were fatal, in the year 1868; Bull is said to have called the disease "meningitis spinalis acuta," but to have described it so that there can be no doubt of its being infantile paralysis. Unfortunately I have not been able to read the report. The epidemic lasted from May to August, and reached its climax in July, when eight cases occurred. According to Wickman, the Swedish physician Bergenholtz was the first to report an epidemic in 1881; he described eighteen cases from Umea in the north of Sweden. In this case there is no doubt of the disease being Heine-Medin disease. The epidemic remained unknown, as the report was only sent to the local health authorities. The observations of Oxholm (Norway) and Cordier (France) also passed unnoticed; they include some statements pointing to an epidemic outbreak of the disease.

Medin first made widely known the epidemic which he observed. He published his exhaustive clinical studies on forty-three cases which occurred in and near Stockholm during the months May to November, 1887, and on twenty-one cases which came under his notice in 1895. The subsequent epidemics in Sweden were studied very thoroughly. Wickman obtained unexampled experience during the epidemics of 1899 (fifty-four cases in Stockholm), 1903 (twenty cases in Göteborg), and 1905-1906 (about 1,100 cases spread over a great part of Sweden). His description has become a classic. During the years 1907 and 1908 many more cases were reported from Sweden.

Oxholm observed a small epidemic of five cases in 1886. It is doubtful if he recognized the true nature of the disease. In the same year Leegaard reported a small epidemic in Mandal, a small Norwegian town. In 1893 Bülow-Hansen and Harbitz made a careful pathological examination of three cases which occurred in one family. Looft observed a small epidemic in 1898-99 in Bergen. The first large epidemic in Norway took place from July to October, 1899, fifty-four cases in Bratsberg, which were studied by Leegaard. *On this occasion he made the remarkable discovery that the infection spread along the lines of traffic.* In 1904 Nannestad examined forty-one cases and Platou twenty-four.

Finally, at the same time as the great Swedish epidemic, about 1,000 cases occurred in Norway in 1905-06 (Leegaard, Harbitz and Scheel, Geirsvold, &c.).

Assuming that earlier epidemics had not occurred unnoticed, a gradual increase is found, from 1880 onwards, in Scandinavia. At first only small groups of cases, some in families, were noticed, then small endemic outbreaks, later a true epidemic in Sweden in 1887, still later a larger epidemic in both countries in 1899, and, finally, a big epidemic over a great part of Scandinavia in 1905. In proportion to the population this was certainly the most serious epidemic. The progress of the epidemics is comparable to that of the North American prairie fires, which begin with a small outbreak, spread insidiously, and finally burst into a mighty conflagration.

Germany.—The epidemics in Germany have followed on similar lines.

In 1882, Möbius and Sänger saw a brother and sister, one of whom suffered from the spinal, and the other from the cerebral form of the disease.

Strümpell observed three cases in one month in 1886; two of the cases were brother and sister, which lent support to his theory that the disease was infectious. Two further reports were due to the influence of Strümpell's theory. Briegleb in 1890 published five cases which occurred close together near Jena within a period of four weeks. Briegleb published these cases "because they seem to support Strümpell's theory, that a disease which makes its appearance in several places in the same neighbourhood and at the same time is probably caused by some organized morbid agent." The paper by Pleuss is very similar; in 1897 he observed four cases in the neighbourhood of Kiel within three months. Hoffmann in 1904 observed a small familial group of cases in Düsseldorf. A brother and sister became ill on the same day; the six-year-old boy suffered from a cerebral hemiplegia, the four-year-old sister from spinal paralysis. Up to this time only small groups of cases had occurred in Germany.

But matters seemed to be becoming serious when Auerbach reported no fewer than fifteen cases in the months May to December, 1898, in Frankfurt alone. The number was large when one considers that from 1892 to 1897 Auerbach had met with only eleven cases. The groups of cases reported in 1908 were larger, one occurred near Heidelberg (thirty-six cases—Hoffmann), one near Hamburg (twenty-two cases—Nonne). These small epidemics proved to be the forerunners of the great epidemic of 1909 in Germany. This mainly affected Westphalia and Rheinland, where certainly 700 cases occurred. The epidemic was studied by many authors (P. Krause, Meinicke, Grober, Reckzeh, Wollenweber, Gasters, Lasch, Vieten). It then passed on to Hesse-Nassau, where Ed. Müller saw 130 cases, and used them for his clinical and epidemiological studies. Thirty-four cases in Hanover (Eichelberg) followed, about fifty cases in Schleswig (O. Förster), and fifty-one cases in Pomerania (Pieper). At least 1,000 cases occurred in Germany during 1909. It appears from the proceedings of the medical societies of Berlin that further groups of cases occurred near that city towards the end of 1910. The progress of the epidemics was similar to that in Scandinavia, at first only small groups of cases, then small epidemics, and finally a large epidemic.

Austria.—In 1898, the first year in which infantile paralysis was met with in Germany in a somewhat epidemic form, Zappert and Neurath reported on groups of cases, which "almost constituted an epidemic," in the neighbourhood of Vienna. Forty-two cases were seen during the summer of 1898, chiefly in August and September, while only 129 instances of the disease had been met with during the preceding ten years. During September there were twelve

cases, a figure larger than the average yearly number for the ten years before. In Austria also this was only a warning of what was to follow. In 1908 there was an epidemic of about 300 cases in Vienna and Lower Austria, which was investigated by Zappert, Neurath, Frankl-Hochwart, Löcker, Lindner and Mally, and many others. The epidemic began in July, and reached its greatest height in September and October. It is of particular historical interest, because it was the occasion on which Landsteiner and Popper successfully transmitted the disease to monkeys. In 1909 the epidemic passed on to Upper Austria and the Steiermark; according to Fürntratt and Potpeschnigg, at least 600 cases occurred. Kärnten was also affected. Potpeschnigg made the interesting observation that the large epidemic was preceded by several small ones during 1906 and 1907. In Austria, as in the other countries, the same warning is given before the occurrence of a great epidemic.

Holland and Switzerland.—The other European countries have not suffered from widespread epidemics. Groups of cases have occurred in 1906 and in 1909 in Holland, but no epidemic. During 1909 there were twenty-four cases in Leyden, and fourteen cases in Warnsweld and Zutphen. During 1910 cases occurring in groups were observed in Switzerland by Eichhorst and Hagenbach.

England.—There are few reports from England. The experience of Pasteur in 1896 was remarkable. Seven children in one family became ill within ten days; some suffered from the cerebral, some from the spinal form; the others had only indefinite feverish symptoms, and belonged to what we should call now the abortive type. In 1897 Buzzard observed four cases in London, two of which were brother and sister, while two lived in adjacent streets. Batten saw nine cases within six weeks during July and August, 1902. In the same year Mitchell Stevens made a similar observation in Cardiff. In 1909 Treves reported a small epidemic in Upminster, and Parker collected thirty-seven cases in Bristol. During 1910 outbreaks occurred in Carlisle (thirty-four cases—Beard), Edinburgh (sixty-two cases—Low), Tillycoultry (five cases—Currie and Bramwell), Barrow (thirty-seven cases—Garrow), Maryport (thirteen cases—Garrow), and South Shields (five cases—Mostyn). In 1911 the number of small epidemics was larger. The disease appeared in epidemic form in Huntingdonshire, Hampshire, Stowmarket, Derbyshire, Devon, Cornwall and Dorset. In Devon and Cornwall no less than 224 cases occurred within the year (Reece). Thus in England the same phenomenon is seen as in other countries. The small epidemics have become more frequent and involve an increasing number of cases, but so far we have been spared from a large epidemic. The disease was made compulsorily notifiable in London in September, 1911, and in some provincial centres since then.

France.—The French observations are not without interest as they are analogous in many respects to those made in Scandinavia,

Germany, and Austria. Cordier reported thirteen cases in 1888; they were collected after the epidemic in Sainte-Foye d'Argentière, a village with 1,400 inhabitants near Lyons; there were four fatal cases. Cordier's observations make it probable that in two cases infection could be traced to visits made to patients already ill. The cases occurred largely in adjacent houses. It was at this time that the contagiousness of the disease was indicated. In 1893 André saw four cases near to Saint-Girons, and several cases in Toulouse in 1895, in which there was probable infection from neighbours. In the same year Beclère received a reliable report of a dozen cases which occurred within three months in one village. The same author observed the disease in brother and sister in 1898; Guinon and Rist the same in 1903. In the year 1909 there was a definite epidemic of the disease in Paris and its surroundings; Netter states that at least one hundred cases occurred.

Spain.—Only small epidemics have occurred in Southern Europe. Roset reported a small epidemic of eight cases from the neighbourhood of Valls in 1896; curiously enough five cases were hemiplegic in type.

Italy.—There are many reports from Italy, but they all concern groups of cases or quite small epidemics (1895, thirteen cases from the surroundings of Padua, observed by Cerevesato; in the same year seven cases in fifteen days in Montespertoli near Florence, reported by Pieraccini). In 1895, Buccelli saw seventeen cases in Genoa, which all occurred in the same part of the town, several in one house and in one family. Further observations are those of Fabris (twenty-two cases in the years 1897, 1898 in Conegliano), Simonini (twenty cases in September and October in Vicence), and Lorenzelli (twenty-six in 1901 in Parma).

Russia.—There is one communication by Jogichess that grouped cases of infantile paralysis occurred in St. Petersburg in the years 1909 and 1910.

North America.—Great epidemics have occurred in North America, but they were preceded by warning outbreaks in the shape of groups of cases and small endemics. Thirty-eight cases were observed in Massachusetts in 1892. Caverley and Macphail reported an epidemic of 126 cases from Vermont in 1894, which they diagnosed incorrectly as cerebrospinal meningitis. In 1896 there were groups of cases in Alabama and Maine. In 1897 H. L. Taylor observed twelve cases in a small district of New York; in 1898 M. Taylor saw four cases, two of these were brother and sister and one a cousin of the same. In the same year Newmark and Packard observed the disease in families, in 1899 Chapin saw seven cases in Poughkeepsie, and Mackenzie seventeen cases in Dutchess County, in 1900 Painter thirty-eight cases in Boston, and Bondurand and Woods fifteen cases in Alabama. During 1901, fifty-five cases were reported from San Francisco; in 1906 there were large groups of cases of infantile paralysis in New York (Collins and Romeiser).

The large American epidemics began in 1907. In New York 2,500 cases occurred (Collins, Gibney, Wallace, Romeiser, Koplik, Starr, Berg, Clowe, and others), in Massachusetts there were 234 cases, and the disease spread to New Jersey and Connecticut. There was a small epidemic of 136 cases (Lovett and Emerson) in Massachusetts in 1908, also in Pennsylvania, Iowa, Wisconsin, Michigan, and Minnesota. The Nebraskan epidemic occurred in 1909, and during these three years (1907-1909) the number of children affected had risen to the considerable total of 20,000.

Flexner says that few of the States have been spared; the Southern States appear to be free, but this is probably due to faulty reports. Flexner further points out that the epidemic began in the States on the east coast, which receive many emigrants from Scandinavia.

Cuba.—Lebdreo and Recio reported an epidemic in 1909.

South America appears to remain free from the disease.

Australia.—Small epidemics have been reported here and there. In 1895, fourteen cases in Port Lincoln (Alston); in 1904, chiefly during March and April, thirty-four cases in Sydney and Brisbane (Wade); in 1908, 135 cases in Melbourne (Stevens).

The Origin of the large Epidemics.—The preceding facts lead to the conclusion that it is the northern countries, particularly Scandinavia and North America, which are most attacked by the disease. Large epidemics occurred first in Scandinavia. The occurrence of small epidemics shows that southern countries are by no means immune to this disastrous scourge. It is, perhaps, only a question of time before they are afflicted by a great epidemic.

We see that all large epidemics are preceded by warning outbreaks in the shape of small groups of cases. It is doubtful therefore whether the view that Flexner seems to take is correct, that the outbreak of a severe epidemic is determined by the importation of the disease from Scandinavia, although the fact that the Scandinavian epidemics antedated the others seems to give some support to this view. But since the so-called sporadic form of the disease has always been found extensively in each country before the outbreak of an epidemic, and since we know that the sporadic and epidemic forms are identical, there seems to be no conclusive proof that the epidemics in Germany, Austria, and North America have been due to importation of the virus from Scandinavia. It is most remarkable that a disease, which had been well known in its sporadic form for many years, should attack groups of cases in 1880 and onwards, and should appear in epidemic form first in 1905. Any attempt to explain this must remain more or less a hypothesis. Some suggest that the cause of the disease became more virulent, and instance, in support of this theory, that fatal cases are more frequent during epidemics and adults are more often attacked than by sporadic poliomyelitis. It is probable that both these statements are incorrect; when there was no epidemic the cause of death was not diagnosed as due to poliomyelitis, nor was the disease diagnosed

as such in adults before the works of Medin and Wickman became well known. The following is a possible explanation of the sudden appearance of the disease in epidemic form; owing to a particular chain of causes a group of children becomes affected, and the resultant accumulation of infective material makes a wider distribution of the disease possible. But there still remains the question why it is only in the last few years that these unknown factors have caused this accumulation of the virus. Possibly, the great increase in the network of railways has resulted in a wider distribution of infective material. In truth, we are quite ignorant of the causes which have produced this result, and can only confess the fact.

II.—THE EPIDEMIOLOGICAL CHARACTERISTICS OF THE SEVERAL OUTBREAKS.

Season.—In almost all the outbreaks mentioned above we find certain definite relations between the outbreak of an epidemic and the time of year. The disease is pre-eminently one of the summer and autumn, in particular of the late summer and early autumn. The following curve made by Wickman demonstrates very clearly the great increase in the number of cases which occurred during the months of July to October, 1905, in Sweden (fig. 50).

The highest point of an epidemic may be somewhat delayed. This happened with our own cases in Hesse-Nassau which were observed by Ed. Müller; he found many more cases during October and November than in August and September (fig. 51). The comparative distribution of the cases in the Swedish epidemic observed by Wickman and of those of our own epidemic in Hesse-Nassau has been put into tabular form by Ed. Müller (figs. 52 and 53).

Müller is probably correct in surmising that the delay in reaching its highest point which was seen in our epidemic was due to the fact that the contagion passed over to us from Westphalia rather late in the year.

Wickman mentions that the maximum in an epidemic may be reached during the winter months. Such an epidemic was recorded in the north of Sweden. The onset of winter does not guarantee that an epidemic will cease in some cases. Here I may mention again the extraordinary resistance to cold shown by the virus. The Australian epidemics are no exception to the rule that the disease occurs during the summer months, because March and April in Australia correspond to our summer.

Age, Sex, Predisposition.—Reports from the different epidemics agree as regards the usual ages at which patients are attacked by the disease. Children are most affected, although the epidemics show very clearly that adults are attacked more often than was formerly supposed. The percentage rate of incidence of

the disease cannot be expressed more clearly than by the curves constructed by Ed. Müller (figs. 54-57).

Ninety-six per cent. of all cases occur during the first decade (fig. 54), and nine-tenths of these children had not reached the age of five years (fig. 55). More than three-quarters of the cases occurred during the first three years of life, of these most in the second year (fig. 56), and mainly in the second half of that year

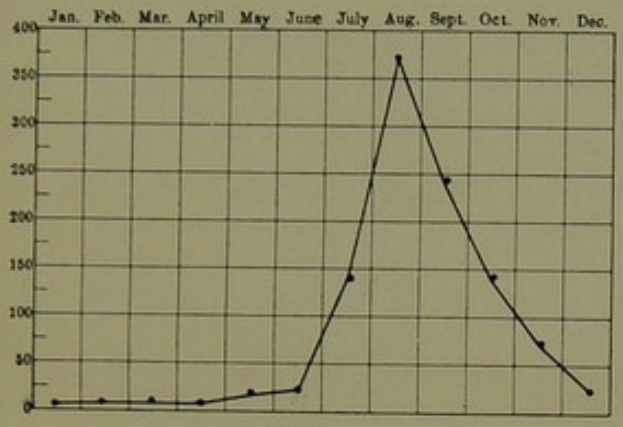


FIG. 50.

Monthly number of cases of Heine-Medin disease in Sweden (after Wickman).

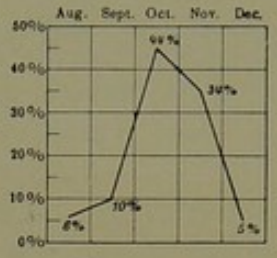


FIG. 51.

Percentage of frequency of cases in Hesse-Nassau from August to December, 1909 (after Ed. Müller).

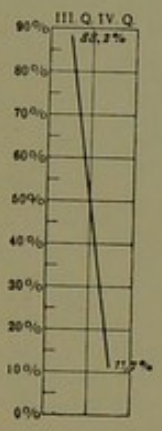


FIG. 52.

Distribution of Wickman's cases in the third and fourth quarters (Swedish epidemic, 1905). (After Ed. Müller.)

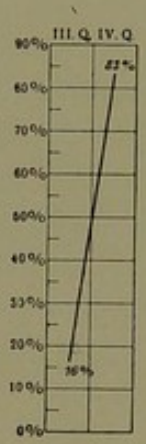


FIG. 53.

Distribution of cases in Hesse-Nassau in the third and fourth quarters. (After Ed. Müller.)

(fig. 57). The experience of other investigators at other places coincides with this.

Males are somewhat more affected than females, but the difference is not large. Most observers have been unable to detect any

indications that predisposition plays any *rôle* in the disease. Strong and healthy children are affected quite as often and as severely as weakly children; in particular, children with a neuropathic taint show no special liability to the disease.

While discussing the pathogenesis of the disease I have already touched on the question: Why children are so easily and frequently attacked.

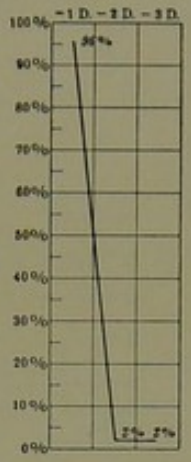


FIG. 54.

Percentage distribution of the cases among the first three decades of life. (After Ed. Müller.)

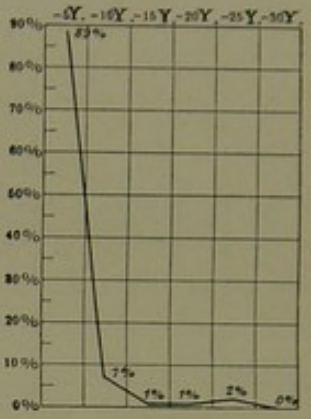


FIG. 55.

Percentage distribution of cases in the first six 5-yearly periods of life. (After Ed. Müller.)

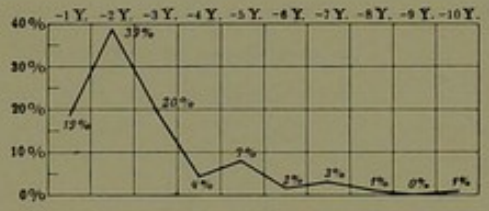


FIG. 56.

Percentage distribution of cases in the first ten years of life. (After Ed. Müller.)

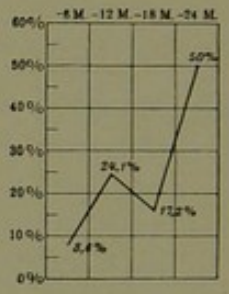


FIG. 57.

Percentage distribution of cases in the first four half years of life. (After Ed. Müller.)

Proof of Contagiousness.—Now that a living micro-organism is known to be the cause of Heine-Medin disease, the question arises as to how infection takes place and what are the sources of contagion.

The first observations to be mentioned are those which relate to the occurrence of paralysis in certain animals, chiefly in dogs, fowls and rabbits, at the same time as epidemics of infantile paralysis in human beings. Such a coincidence is very hypothetical, and is rendered still more unlikely by the number of epidemics

which have been observed which were not associated with any such disease in animals. The evidence obtained from experimental work all points in the opposite direction, all these kinds of animals being proved to be not susceptible to the cause of Heine-Medin disease in man. It would be of scientific interest to determine in what relation the active agent of Borna's disease in horses stands towards the virus of poliomyelitis in man, because of the extraordinary similarity, not to say identity, of the microscopical lesions in the two cases.

Since it is exceedingly doubtful whether the disease may be transmitted from an animal to man, it becomes necessary to determine whether infantile paralysis can pass from man to man and so belong to the contagious variety of diseases. In this connection the older observations offer a certain amount of evidence, *e.g.*, Cordier's statement that he saw the disease in one patient who had previously visited another. The occurrence of several cases in one family pointed in the same direction; further, Leegaard observed that an epidemic followed the lines of traffic.

All these examples were only significant, and until 1905 there was no clear proof of the contagiousness of the disease; up to that time observers were inclined to take rather the opposite view, *e.g.*, Medin thought that direct infection was exceedingly rare, and Zappert was definitely opposed to the idea.

The exemplary investigation into the Swedish Epidemic of 1905 *by Wickman turned the current of opinion in a contrary direction.*

Wickman worked under particularly favourable conditions; owing to compulsory notification being enforced by the Government he was able to investigate every single case. Further, the lonely parishes of Sweden with their isolated farms and houses made it possible to trace the course of the epidemic under very simple conditions. Wickman did not shirk the labour of tracing every case, and he made it possible to obtain a clear general view of the individual cases by the use of maps. No one, who wishes to gain a thorough knowledge of the epidemiology of the disease, can avoid the trouble of carefully examining the studies of Wickman.

We shall only summarize Wickman's arguments, by which he proved that Heine-Medin disease is contagious, *i.e.*, communicable from man to man.

In the first place, in the Swedish epidemic it was possible to prove contact between the individual cases almost universally. It is true that contact was not direct in every case, frequently there were intermediaries who remained healthy. Wickman would never have been able to establish this fact if he had not known of the abortive cases from his clinical studies and had not taken them into consideration. When this is not done it happens too often, as I mentioned in the first chapter, that the hasty and incorrect conclusion is reached that no contact has occurred between the cases. Wickman made a careful analysis of the circumstances accompanying infection in almost every case, 1,031 in all.

His observations in the little parish of Traestena have become specially celebrated, because they form a classical example of his theory that the disease is contagious. Out of 500 inhabitants, living in 102 houses, mostly isolated from one another, 49 persons (= 10 per cent.) became ill, 26 of these (= 5 per cent.) had definite paralysis. The source of infection in most cases was the school; the disease was carried to the different houses by the children, some of whom became ill themselves, while others remained well. Wickman therefore arrived at the important conclusion that the disease could spread by means of "carriers," as in the case of so many other infectious diseases. Where it was not possible to trace the infection directly to the school, it could be proved that visits had taken place to houses which had already been infected from the school. The infection spread from this parish in a radial manner, in the same way as was observed in larger affected areas.

Even when it was not possible to trace the spread of the epidemic so clearly as in the above example, yet the grouping of the cases was important; in many instances several persons in one house or in adjacent houses were attacked. Further, the connection between the chief roads and railways and the spread of the disease was very evident, particularly among the more scattered cases.

From all these facts Wickman came to the conclusion that Heine-Medin disease behaves exactly like other contagious diseases as far as its method of spread is concerned. Wickman explained also why this had not been recognized before. The earlier small epidemics had not given opportunities for such observations, and the importance of abortive cases and of healthy carriers had not been recognized.

Wickman considers that indirect transmission, *i.e.*, by non-living objects, is a great rarity. He himself only met with one case in which the infection was carried by a picture, and one in which the milk was blamed. These observations have remained unique; no similar examples of indirect transmission have been reported.

Confirmation of Wickman's Statements.—Subsequent epidemics provided excellent opportunities of testing Wickman's conclusions. In our epidemic in Hesse, Müller succeeded in tracing very clearly the track of the epidemic, because the number of cases was not very great, and in many villages only one case occurred. A tendency to grouping of the cases was observed. As in Sweden, it was abundantly clear that the infection followed the lines of the railways and the great roads. Müller was able to find cases in which the infection was brought by healthy carriers and could have been brought in no other way.

A particularly instructive example was provided in the case of the small epidemic in the little town of Frankenau. The midwife of the town had visitors from Westphalia from September 11 to the 13th. On the 20th one of her children was stricken with paralysis and two others suffered from gastro-intestinal symptoms. Some time later a neighbour's child, who had

played with the children of the midwife who had remained unaffected, became ill, so also a child of the schoolmaster (the healthy children of the midwife attended the school); finally, the child of a workman became ill, who had been in the same schoolroom with the midwife's children. The track of the epidemic was therefore as follows: The virus was brought by healthy carriers from Westphalia; in the village it was disseminated by the healthy children of the midwife.

Direct transmission of the disease by the patient was more rare, a fact which had been observed by Wickman. Müller found the disease less among the peasants who remained on their land than among those who followed a trade, particularly those that came much into contact with the rest of the world (inn-keepers, coachmen, postmen, and railway workers); shoemakers or their children were curiously often affected, a fact noticed also by Eichelberg.

Confirmation of Wickman's observations, particularly of those with reference to the subject of the healthy carrier, was given by the reports of Krause (Westphalia), Leegaard (Norway), Netter (France), of Löcker, Lindner and Mally (Upper Austria), and also of Emerson, Armstrong, Jones, Shidler, and, to a certain extent, Lovett, who all reported American epidemics.

Zappert is very reserved in his opinion on the contagiousness of the disease. He observed grouping of the cases in Lower Austria; in Vienna itself the disease appeared in certain quarters of the city and in certain groups of houses; occasionally he saw more than one case in the same family; but he was quite unable to trace any connection between the different cases. It must be remembered that he had to carry out his research in a large capital and in a thickly populated province.

No proofs of the contagiousness of the disease could be obtained in the great epidemic in New York in 1907, nor in the epidemic in the Steiermark (Fürntratt, Potpeschnigg) nor in Pomerania (Peiper). Wickman quite rightly emphasizes the fact that all these observers were unable to prove any other method of transmission of the disease.

The reasons usually brought forward against the theory of contagion are the occurrence of completely isolated cases, the observation that so often only one child in a family is affected, the absence of any epidemics in hospitals, and the occasional appearance of the disease among the "most isolated" people (prisoners!). It is, however, questionable whether these isolated people are really so isolated as they appear to be; in particular it must be remembered that abortive cases may have occurred in the neighbourhood and that contact with healthy carriers is possible. Serum diagnosis may throw some light on these cases (see following chapter).

Wickman justly draws the comparison between Heine-Medin disease and cerebrospinal meningitis; the epidemiology of the two diseases has many points in common; in both, children are chiefly affected, adults are not entirely immune, only one or, at most, two

children in a family are affected, the disease is certainly transmitted by healthy carriers, "sporadic" cases occur, and finally, no completely satisfactory explanation of the epidemic occurrence of the diseases has ever been found. Scarlet fever might be instanced for comparison on many points.

No sound argument has been brought against the contagion theory so far.

All attempts to find another way by which the infection travels have failed, such as transmission by drinking-water (epidemics in towns with a faultless water supply), by fruit (epidemics at a time when there was no fruit), by cow's milk (children at the breast have contracted the disease, see Wickman's exception quoted above), and by other articles of food. Transmission by insects is not probable because of the occasional epidemics during the winter.

Certain observations seem to support the idea that the virus may remain in a house (*i.e.*, on non-living things) and thus be transmitted. That the virus has been proved experimentally to remain active for a long time is an argument in favour of this view, which deserves consideration.

We agree with Wickman that the chief method of transmission of the disease is the direct one, from human being to human being.

It is very difficult to say how infection takes place. When discussing the pathogenesis of the disease we arrived at the conclusion that probably the lymphatic tissues of the mouth, nose, throat, and alimentary tract, served as the portal of entry of the virus. Many things point to the virus remaining for a long time in the mucous membrane of the mouth and throat of infected individuals. One might think of infection by the saliva in speaking, coughing, sneezing, or in more direct contact. Unfortunately there is as yet no proof that the virus is contained in the saliva. I have given monkeys an intracerebral injection of saliva filtered through a Berkefeld filter from cases of poliomyelitis and have not succeeded in producing the disease. Considering how little we really know about the pathogenesis of the disease, any attempt to explain how infection occurs under the conditions of an epidemic must be fraught with almost insuperable difficulties.

One fact may be accepted as practically proved by Wickman—the disease is contagious. No one knows how infection takes place, whether by direct contact, by the breath, by virus which has adhered to non-living objects, clothes and shoes, or finally, by some animal carrier which has been overlooked. We are still at the beginning of this question.

There are two mysteries awaiting an explanation. The one is general in character, the question how the great epidemics arise. The other is particular, how does infection take place in each epidemic?

[Kling, Wernstedt, and Pettersson have since succeeded in producing the disease in monkeys by using saliva and intestinal contents. Neustaedter and Thro succeeded in using dust from the sick-room for this purpose.—*Translator.*]

CHAPTER VI.

The Fight Against the Disease.

I.—IMMUNITY AND IMMUNIZATION.

Clinical and Epidemiological Experience.—Before attempting to produce artificial immunity to an infectious disease, it is necessary to consider whether the evidence points to the development of a natural immunity in the course of the disease. In the case of Heine-Medin disease this inquiry leads to no definite conclusion and is beset with difficulties. In the first place, we have only recently become acquainted with the epidemic form of the disease; secondly, the total number of cases is, fortunately, relatively small, and they occur within narrow limits of age. Even though many children survive one epidemic, by the time that another occurs these patients have attained an age in which infection is rarely found. It is consequently very difficult to prove by figures that one attack of Heine-Medin disease protects against a second attack.

However, it is worth placing on record that observers who have paid special attention to this point and who have had the opportunity of observing large epidemics, have never seen the disease attack the same child twice (Wickman, Ed. Müller, Stiefler). Harbitz and Scheel observed the great Norwegian epidemic, and state that "it seems proved beyond doubt that when a district has been visited by the disease in one year, it remains free during the following years." Zappert came to the same conclusion in the course of his extensive studies. In 1898 there was an epidemic in Vienna, and in the following year the number of cases was much below the average; this corresponds also with our experience with regard to other infectious diseases: the number of cases in the years following an epidemic is always remarkably small.

There are a few records which indicate that the same individual may suffer twice from the disease. Eshner saw a patient who had the first attack at the age of three and the second at fourteen. The exact nature of the second illness is, however, not quite clear; it is not impossible, though improbable, that it was really a traumatic neuritis. Eckert reported another case, unfortunately giving very meagre details: "H. Sch. was attacked by poliomyelitis in

September, 1903. Tenotomy and a mechanical support were necessary for the left leg, which was paralysed. At the beginning of April, 1909, he suffered from a second attack, in which the right leg was paralysed." Unfortunately I have been unable to see the original paper by Sterne, quoted by Netter and Levaditi, in which a large number of cases were reported in adults, who had suffered from poliomyelitis during childhood. In these cases the second attack followed 9, 17, 19, 23, and 54 years after the first.

It is quite possible that if immunity be established it does not last throughout a lifetime; Sterne's results might be explained on this assumption. Further, it must be remembered that increase of paralysis does not always mean a second attack of the disease; a spinal cord which has once been damaged is particularly liable to further damage of a non-specific kind, with destruction of those elements which had remained capable of functioning. But even although isolated cases of reinfection do occur, that does not do away with the possibility that survival of one attack leaves behind it a specific protection against another. Even in the case of diseases, such as small-pox, in which this occurs to a very marked degree, occasional exceptions to the law of immunity are met with. Biological laws are not mathematical in their application.

Relapses, which are very rare, constitute no proof that immunity is not conferred by an attack of the disease. Medin and Neurath both observed relapses. Wickman found them exceedingly rarely, and Ed. Müller not at all. I once saw a relapse in a case of experimental poliomyelitis (see p. 59). Under these circumstances they appear to be extremely rare, and I believe that the two cases described by Levaditi and myself are the only instances known.

All these observations fail to prove that immunity is not conferred, and yet it is very difficult to obtain exact proof of the opposite, if one ignores the general impression obtained from the study of epidemics. In the case of monkeys, which behave towards the virus in other respects just like human beings, it is quite certain that immunity is present. This makes it probable that in man one attack produces immunity for a longer or shorter period against a second attack.

The existence of such immunity may explain some of the observations made during epidemics. Wickman was struck by the small incidence rate of the disease. In the district which was most severely affected only 5 per cent. of the inhabitants became paralysed; the inclusion of all abortive cases only brought the figure up to 10 per cent. Now, Wickman's observations offer convincing proof that the virus may be transmitted by healthy carriers; we know also, from our experience with typhoid fever, cholera, and other diseases, that these clinically healthy carriers have suffered from the infection in some way or another, because specific products of reaction to the virus can be found in their blood-serum. It seems to me worth considering whether we shall

not eventually find specific antibodies in the serum of a large number of apparently healthy people during an epidemic. Such a discovery would be of the greatest importance epidemiologically and, merely as a working hypothesis, such a consideration will be of value to future investigators.

Attempts to Reinfect Monkeys.—Apart from all epidemiological considerations it would have been natural to make investigations into the question of immunity in experimental poliomyelitis. The existence of a successful method of protective inoculation in the case of the analogous disease of rabies, although the epidemiology of that disease offered no evidence of the occurrence of immunity, would in itself have stimulated us to make the experiment. The following is a series of experiments in which monkeys which had survived the first infection were given a second injection of the virus.

Experiment 1.—On December 28, 1909, the following monkeys received an intracerebral injection of ·5 c.c. of an emulsion of virus No. 11.

(*a*) Control monkey No. 16 (*Macacus rhesus*).

December 29-January 2.—Well.

January 3.—In the evening rather tired, looks cross.

January 4.—Severe flaccid palsy of both arms and the neck; slight weakness in the hind limbs.

January 5.—Lies on the floor, apparently completely paralysed. Death at noon. Microscopical appearances typical.

(*b*) Monkey No. 6 (*Macacus rhesus*) received an intracerebral injection of ·8 c.c. of virus of Case 3, passed through Berkefeld filter, on December 2 and 4. Remained perfectly well. Interval between the two infections twenty-four to twenty-six days.

Course of the infection on December 28:—

December 29-January 7.—No symptoms.

January 8.—Spares the right hind limb.

January 9.—Paresis of right hind limb more noticeable.

January 10.—Paresis scarcely to be seen.

January 11.—Still slight paresis.

January 12 *et seq.*—Well. The monkey lived until June 15, 1910; occasionally a trace of weakness was noticed in the right hind limb.

Experiment 2.—The following monkeys received an intracerebral injection of ·5 c.c. of virus No. 12 on January 3, 1910:—

(*a*) Control monkey No. 17 (*Macacus rhesus*).

January 4-15.—Well.

January 16.—Sad and cross.

January 17.—Flaccid paralysis of both hind limbs.

January 18.—Lies on the floor of the cage with all limbs apparently paralysed. Death in the evening.

Microscopical appearances typical.

(*b*) Monkey No. 8 (*Cercopithecus ruber*) received ·4 c.c. of virus No. 3 (intracerebral injection) on December 4, 1909; afterwards suffered from the abortive type of the disease (see p. 38).

Interval between the injections, thirty days.

Result of injection January 3.—Remained quite well.

Experiment 3.—The following monkeys received an intracerebral injection of an emulsion of virus No. 11 on January 6, 1910:—

(*a*) Control monkey (*Mangabey*) received ·2 c.c. January 7-17. No symptoms.

January 18.—In the afternoon, definite flaccid paresis of both hind limbs.

January 19.—Paresis more marked. Slight paresis of the arms.

January 20.—Total flaccid paralysis of both hind limbs; definite slight paresis of the arms.

January 21-23.—Gradual increase of paralysis.

January 24.—Total paralysis of all limbs. Death in the afternoon. Microscopical appearances typical and extensive.

(*b*) Monkey No. 9 (*Mangabey*) received a subcutaneous injection of 1 c.c. of an emulsion of the virus of Case 3 on December 4, 1909, and remained well.

Interval between the two inoculations thirty-three days.

Result of re-infection (·2 c.c. intracerebral).—Remained permanently well.

(*c*) Monkey No. 10 (*Mangabey*) received an intraneural injection of ·2 c.c. of the virus from Case 3 on December 4, 1909, and remained well.

Interval between the inoculations, thirty-three days.

Result of reinfection (·5 c.c. intracerebral, *i.e.*, two and a half times the dose given to the control):—

January 16-19.—Trace of paresis of left fore limb.

January 20 *et seq.*—Quite well. General condition remained normal throughout.

Experiment 4.—The following monkeys received intracerebral injections of ·35 c.c. of virus No. 12 on February 7, 1910.

(*a*) Control monkey No. 29 (*Macacus rhesus*).

February 8-14.—Well.

February 15.—Paralysed.

February 22.—Death. (For details, see p. 47.)

(*b*) Monkey No. 9 (*Mangabey*). For previous inoculation see Experiment 3. Period between the second and third infection on February 7 was thirty-two days. Result of last infection—Remained permanently well.

(*c*) Monkey No. 10 (*Mangabey*). For previous infection, see Experiment 3. Period between that infection and the one on February 7 was thirty-two days. Result—remained well.

(*d*) Monkey No. 6 (*Macacus rhesus*). For previous infection see Experiment 1. Interval between inoculations, forty-one days. Result of last infection—Remained well.

Experiment 5.—The following monkeys received an intracerebral injection of ·6 c.c. of virus No. 11 on March 15, 1910:—

(*a*) Control monkey No. 41 (*Macacus cynomolgus*).

March 16-25.—Remained well.

March 26.—Paresis of the legs.

March 27.—Paresis more marked.

April 1 *et seq.*—Gradual improvement (for details, see p. 59).

(*b*) Monkey No. 32 (*Macacus rhesus*) received an injection, causing a paralysis which gradually improved, on February 7 (*cf.* p. 58). Interval between first and second inoculation, thirty-six days.

Result of infection on March 15.—Remained permanently well.

Experiment 6.—The following monkeys received an intracerebral injection of ·6 c.c. of virus No. 11 on July 13, 1910:—

(*a*) Control monkey No. 102 (*Macacus rhesus*).

July 14-24.—Well.

July 25.—Flaccid paresis of hind limbs and weakness of the trunk. In the evening paralysis of the hind limbs and of the left fore limb; right-sided facial palsy.

July 26.—Found dead. Microscopical appearances typical.

(*b*) Monkey No. 59 (*Macacus rhesus*) received an injection on June 13, 1910, which caused paralysis which improved. Interval between the infections, thirty days.

Result of reinfection.—Remained permanently well.

In six different series of experiments nine reinfected monkeys proved to be immune to an infection which caused severe paralysis in the control monkeys and, with one exception, caused death. The interval between infection and reinfection varied from twenty-four to forty-one days in my experiments.

The work of other experimenters provides further proof that a monkey that has survived infection with poliomyelitis is immune. Landsteiner and Levaditi reported the following experiment on January 3, 1910:—

Three monkeys (*Macacus rhesus* and *Macacus cynomolgus*), of which two had been paralysed for twelve days and the third for twenty-five days, together with a control monkey (*Macacus cynomolgus*), were reinfected. The control became paralysed in five days, and died on the sixth day. The three reinfected monkeys remained well.

The experiment shows that immunity is present twenty-one days after the first infection and twelve days after the appearance of paralysis.

Flexner and Lewis were the first to report a reinfection experiment on January 1, 1910:—

Monkey 45, paralysed as a result of an intracerebral infection on November 6, 1909, was reinfected, together with two control monkeys, on November 30, 1909. The latter became typically paralysed, the reinfected monkey remained well.

In their summary of later date Flexner and Lewis report that they had found monkeys to be immune from eight days to two months after the onset of paralysis.

The experience of Leiner and v. Wiesner was similar. They published no less than twelve separate experiments with a positive result; reinfection was performed 2, 7, 9, 25, 31, 41, 52, 55, 60, 66, 87 and 99 days after the occurrence of paralysis. They have performed the service of showing that immunity is present as early as two days and at least as late as ninety-nine days after the appearance of paralysis.

The summation of all these similar results leaves no doubt that the survival of an attack of poliomyelitis which is accompanied by paralysis confers immunity upon monkeys. The condition laid

down by Krause and Meinicke is not necessary, *viz.*, that long series of experiments in more suitable animals are required before the fact of immunity can be conclusively proved. There is also no doubt that Krause and Meinicke are wrong in believing that increase in the age of the monkeys can be the cause of the immunity in the experiments detailed above.

Immunity after an attack which has caused paralysis seems to be the rule in monkeys. The only experiment with an opposite result is one quoted by Leiner and v. Wiesner: Monkey No. 172, infected on February 11, 1910, was paralysed on February 23. It was reinfected on March 12, and became ill and more paralysed on March 30. (The control became paralysed on March 17.) In this case the shortness of the incubation period in the control renders it probable that the infection was very severe, and this single case does not disprove the rule of immunity. After all, every immunity is relative.

It is more difficult to determine whether an infection which does *not* cause paralysis confers immunity. I have the impression that an unsuccessful inoculation increases the resistance of the animal (*cf.* Experiment 3 above); but I have no doubt that the immunity thus conferred is neither so certain nor so powerful as that which follows definite paralysis. The following experiments show that reinfection may be successful when the first infection has had no result: —

Experiment 7.—The following monkeys, on December 14, 1909, received an intraperitoneal injection (3 c.c.) and an intracerebral injection (·5 c.c.) of a 20 per cent. emulsion of virus No. 11.

(*a*) Control monkey No. 13 (*Macacus rhesus*).

December 15-25.—Well.

December 26.—Paresis of the hind limbs.

December 27.—Marked paralysis of the hind limbs, commencing paralysis of the fore limbs.

December 28-January 2, 1910.—Slight improvement.

January 3.—Paralysis more marked.

January 4.—Total paralysis.

January 5.—Found dead. Microscopical appearances typical.

(*b*) Monkey No. 4 (*Macacus rhesus*) received, on November 27, 1909, an intracerebral injection of an emulsion of virus from Case 2 (see p. 37), and suffered subsequently from a doubtful (? abortive) poliomyelitis from the fifth to the seventh day after the infection. Interval between the infections, seventeen days.

Result of reinfection on December 14.—

December 15-22.—No symptoms.

December 23.—Definite paresis of all limbs.

December 24.—Total paralysis of all limbs; death.

Microscopical appearances typical.

Experiment 8.—The following monkeys were given an intracerebral injection of ·5 c.c. of virus No. 6 on December 17, 1909.

(*a*) Control monkey No. 14 (*Macacus rhesus*).

December 18-25.—Well.
December 26.—Paralysed.
December 30.—Death (for details, see p. 48).

(*b*) Monkey No. 5 (*Macacus rhesus*) was given an intracerebral injection of virus No. 6 on December 1, 1909, and remained well. Interval between the two infections, sixteen days.

Results of the reinfection :—
December 18-23.—No symptoms.
December 24.—Paresis of the right hind limb.
December 25.—Paralysis of all limbs.
December 28.—Death.

I believed at first that the shortness of the interval between the two injections would explain the successful reinfection of monkeys Nos. 4 and 5. Now, however, that it has been proved that immunity, if present at all, is fully developed by the time at which I reinfected the monkeys, I believe that after unsuccessful inoculation immunity is established only in an irregular and feeble manner; Leiner and v. Wiesner, Landsteiner and Levaditi, Flexner and Lewis, have also found that monkeys which had been unsuccessfully inoculated could be reinfected successfully. At the same time I believe that immunity does follow unsuccessful intracerebral injection in some cases and under certain conditions. It is possible that the amount of virus used has some bearing on this matter. As far as I can see, most experimenters have used emulsion of spinal cord, filtered through paper or centrifugalized for a short time; on the other hand, I myself have used the virus unfiltered or have merely allowed the coarser particles to settle. Flexner and Lewis have shown in their later work that unsuccessful inoculation confers immunity if large doses of virus have been used. They believe, further, that injection of fresh virus into the brain, if not followed by paralysis, does not produce immunity, but that virus preserved in glycerine does do so. As their experience became more extensive, Flexner and Lewis appear to have come to believe that immunity does follow unsuccessful inoculation, but not with the same certainty as after successful infection.

For practical purposes it does not much matter whether unsuccessful intracerebral inoculation is followed by immunity; such a method of immunization is not practicable. But it is of importance to know whether immunity can be produced without causing the disease. It was from this practical point of view that I called attention to the existence of immunity in some of my cases of unsuccessful inoculation. It will be only if no serious symptoms are caused by the proceeding that any method of preventive inoculation can be of any practical use. Subsequent events have given support to the optimistic view, which I adopted on perhaps somewhat slender grounds. Authors, who at first denied the possibility of such a thing, have published methods of immunization which confer specific protection without causing an attack of the disease.

I have already touched on the question of the duration of the immunity. Landsteiner and Levaditi showed that it was still present after twenty-five days, I myself after forty-one days, Leiner and v. Wiesner after about 100 days, and Flexner and Lewis found it four to five months after the onset of paralysis.

Methods of Immunization in Monkeys.—The attempt to discover a method of immunizing monkeys which might be used in human beings is not at present of great practical importance. Only a small number of the children exposed to infection are affected by the disease even in times of epidemic, and parents are not likely to agree to preventive inoculation while the risks are so small. On the other hand, it is possible that future epidemics will be much more violent than they were in Scandinavia; the character of the epidemics has changed very much even in the last ten years. If we consider what a panic the disease causes during an epidemic, and, further, how powerless we are when faced by the disease in its acute stages, it must be evident that it is not only justifiable, but it is the duty of experimental science to carry out such investigations.

Many authors have endeavoured to find the most effective and least dangerous method of artificial immunization of monkeys. The experiments are still in the initial stages, but they provide a very definite basis for further work on the same lines.

(*a*) Protective inoculation with dry virus. Pasteur's method in rabies depends on the introduction of virus which has been dried for different lengths of time. The analogy between the two diseases led Landsteiner and Levaditi to attempt to produce immunity by similar means. They proceeded exactly according to Pasteur's method; the spinal cord of a monkey with poliomyelitis was dried over caustic potash at a temperature of 22° C. for various periods, and then rubbed up in physiological saline and injected subcutaneously into the monkeys.

Monkeys Nos. 36 and 37 were treated in this manner. From December 3 to December 10, 1909, they received a daily injection of 2 c.c. of the emulsion made from the dried spinal cord in the following way:—

December	3,	cord	dried	for	9	days.
,,	4	,,	,,	,,	9	,,
,,	5	,,	,,	,,	6	,,
,,	6	,,	,,	,,	6	,,
,,	7	,,	,,	,,	5	,,
,,	8	,,	,,	,,	5	,,
,,	9	,,	,,	,,	4	,,
,,	10	,,	,,	,,	3	,,

Ten days after the last vaccination monkey No. 37 was infected together with a control monkey No. 51 (*Cercopithecus*). The control became paralysed after twelve days, and died three days later. Monkey No. 37 remained well.

Monkey 36 was infected together with a control monkey No. 59 (*Macacus cynomolgus*) nineteen days after the last vaccination. The control was paralysed in four days and died on the fifth. Monkey 36 remained well.

As has been shown above, such a method does not diminish the potency of the virus, and since Flexner and Lewis have proved that subcutaneous injection may cause paralysis, such a method should be rejected a priori. As a matter of fact, Landsteiner and Levaditi found subsequently that subcutaneous injection of dried virus does cause paralysis sometimes.

Example.—Monkey No. 87 (*Macacus cynomolgus*) received on:—

January	27,	2 c.c. of virus dried for	21	days	On the 5th, trembling; 6th, paralysis; 7th, death with typical lesions.
,,	31	,,	,, 24	,,	
February	4	,,	,, 24	,,	

Monkey No. 86 (*Macacus cynomolgus*) received on:—

January	27,	2 c.c. of virus dried for	21	days	On February 11 paralysis and death.
,,	31	,,	,, 24	,,	
February	4	,,	,, 24	,,	
,,	9	,,	,, 25	,,	

The fact that the monkeys which were not paralysed by the subcutaneous injection were mainly immune, proves that if sufficient quantities of virus are used an unsuccessful inoculation may protect against the disease. This confirms my own experience (see p. 155).

(β) Immunization by small doses of virulent material. The basis of Pasteur's treatment of rabies is the theory that the virus becomes attenuated by being dried. At the present time there are good reasons for believing that drying does not weaken the individual particles of the virus, but that it does diminish their number; it follows that in Pasteur's method of protective inoculation the principle is really one of giving a small dose of fully active virus at first and later giving larger and larger doses. In accordance with this theory, Pasteur's method has been successfully modified. It was natural that experiments should be made on these lines in the case of poliomyelitis. Flexner and Lewis carried them out. The following example may be quoted:—

A *rhesus* monkey received subcutaneous injections in the following manner:—

January	12	to January	16,	1910	daily	$\frac{1}{30}$	c.c.	virus of full virulence.	
,,	20	,,	23	,,	,,	$\frac{1}{20}$	,,	,,	,,
,,	27	,,	31	,,	,,	$\frac{1}{10}$	,,	,,	,,

The dose was gradually increased; the monkey received $\frac{1}{2}$ c.c., then 1 c.c., and on March 23, 1910, it received 5 c.c. virus of full virulence.

On April 2, 1910, this monkey received an intracerebral injection of 2 c.c. of virus of full virulence and remained permanently well. The virus used in this case was exceedingly active and very constant in its action; a dose of even $\frac{1}{1000}$ c.c. killed a monkey which had not been previously treated, after a normal period of incubation. A high degree of immunity can be attained by the use of the method of Flexner and Lewis; in the example given above the animal was protected against 200 times the lethal dose.

Flexner and Lewis found later that one subcutaneous injection of fully active virus conferred immunity. This was similar to my own experience, as in experiment 3 (*b*) described above. The method proved very inconstant in its action and dangerous, because many of the animals became paralysed instead of only immunized.

(*γ*) Immunization with virus attenuated or killed by chemical means. Kraus was the first to make experiments in this direction. By treating the virus with ·5 per cent. carbolic acid he believed that he had obtained a safe and certain vaccine. He reported the following experiment:—

> On December 18, 1909, a monkey received a subcutaneous injection of 5 c.c. of fresh virus of full strength; on January 2, 1910, it received a further injection of 6 c.c. of *post-mortem* virus mixed with ·5 per cent. carbolic acid. A second monkey received, on January 3, 1910, 6 c.c. of virus mixed with ·5 per cent. carbolic acid. On January 13 these two monkeys and a control monkey received an intracerebral injection of virus filtered through paper. The control became paralysed on the twelfth day and died on the fourteenth. Both the monkeys which had been treated previously remained well.

As a result of his experience with rabies, Kraus lays stress on the use of virus filtered through paper in testing the immunity. It is not clear in the above experiment whether the immunity of the first monkey was due to the injection of the carbolized virus or of the fully virulent virus.

Kraus recognized later, as did also Leiner and v. Wiesner, Landsteiner and Levaditi, that even after five days ·5 per cent. of carbolic acid did not kill the virus in every case (see p. 67), and that this method was therefore not without danger; consequently, in his more recent experiments he always used virus which had been rendered harmless by treatment with 1 to 1½ per cent. carbolic acid for six days, and which had been freed from all coarse particles by centrifugalization before it was so treated. One injection of virus prepared in this way protected monkeys against subdural infection carried out fourteen days to two months later with virus (filtered through paper) which was fatal to the control monkeys.

I made one unsuccessful attempt to produce immunity by the use of virus killed with formalin.

Monkey No. 35 (*Macacus rhesus*) was given an intracerebral injection of virus treated with formalin on February 26 without result.

> On March 22 this monkey, together with a control monkey No. 43, was infected with virus No. 12 (intracerebral, ·6 c.c.; intraperitoneal, 3 c.c.).
>
> Course of the infection:—
>
> Monkey No. 35:—
>
> March 23-April 26.—No symptoms.
>
> April 7.—Weak in the hind limbs.
>
> April 8.—Definite flaccid paresis of both hind limbs and the left arm.
>
> April 9.—Paresis more marked.
>
> April 10-15.—No change.

April 16.—Both arms markedly paretic; both hind limbs completely paralysed.

April 19.—Died with increasing paralysis.

Microscopical appearances typical.

Monkey No. 43:—

March 23-April 4.—No symptoms.

April 4.—Depressed; does not want to climb.

April 5.—Marked paralysis of all limbs.

April 6.—Death.

Microscopical appearances typical.

(δ) Immunization with heated virus. If any method of protective inoculation is ever used it will have to be one which can be guaranteed to be harmless. The monkey is an animal which shows unmistakably the lesions of poliomyelitis after intracerebral inoculation. Although we did not succeed, we aimed at finding a virus which would confer immunity and yet be harmless when injected into the brain of monkeys. For this purpose we studied virus which had been subjected to high temperatures. On page 65 we have already given some of our results. Intracerebral injection of virus which had been heated for half an hour at 55° and at 50° proved harmless to monkeys; when heated at 45° the virus was less active. Subcutaneous injection of virus heated to 45°, 50°, or 55° was quite harmless. Monkeys treated with virus prepared by these methods were tested in many ways.

Experiment 1.—The following monkeys received intracerebral injections of ·6 c.c. of virus No. 11 on March 15, 1910:—

(*a*) Control monkey No. 41 (*Macacus rhesus*). Paralysed on the 26th. Recovered. (Details on p. 59).

(*b*) Monkey No. 32 (*Macacus rhesus*), which suffered on February 7, 1910, from paralysis caused by intracerebral injection of virus heated to 45° (see p. 65). After the infection on March 15 no symptoms observed for two months.

(*c*) Monkey No. 34 (*Macacus rhesus*) received subcutaneous injections of 2 c.c. of virus heated to 45° on February 7 and 9.

Result of the infection on March 15.—No paralysis; died of secondary infection on the 22nd.

No lesions of poliomyelitis could be found.

Experiment 2.—The following monkeys received intracerebral injections of ·6 c.c. of virus No. 11 on May 31, 1910.

(*a*) Control monkey No. 58 (*Macacus rhesus*).

May 31-June 10.—No symptoms.

June 11.—Paralysed.

June 13.—Death. Typical microscopical appearances. For details, see p. 77).

(*b*) Monkey No. 51 (*Macacus rhesus*) had had an intracerebral injection of virus heated to 50° with no result on April 25, 1910 (*cf.* p. 65).

Result of the infection of May 31.—Remained permanently well.

(*c*) Monkey No. 52 (*Macacus rhesus*) received a subcutaneous injection of virus heated to 50° on April 25, 1910, without result.

Result on infection on May 31.—Remained permanently well.

The other monkeys treated without result with virus heated to 50°, monkey No. 53 (3 c.c. on April 25, 27 and 29, subcutaneously), and monkey No. 54 (daily from April 25 to April 30, 3 c.c. subcutaneously), died of pulmonary tuberculosis before their immunity could be tested.

Experiment 3.—The following monkeys received an intracerebral injection of ·6 c.c. of virus No. 12 on March 2, 1910:—

(*a*) Control monkey No. 37 (*Macacus rhesus*).

March 9.—Totally paralysed.

Gradually recovered (see p. 57).

(*b*) Monkey No. 27 (*Mangabey*) received 5 c.c. of virus heated to 55° subcutaneously on January 25 and January 29 without any result.

Result of the infection on March 2, 1910:—

March 11.—Depressed.

March 13.—Cerebral symptoms.

March 14.—Death from cerebral paralysis. (For details, see p. 53.)

[Two other monkeys inoculated with virus heated to 55° unfortunately died of intercurrent disease before their immunity could be tested. Monkey No. 28 received a subcutaneous injection of 5 c.c. on January 25 and January 29 with no effect; monkey No. 26 intracerebral injection of ·5 c.c. on the 25th without result.]

These experiments, which must be confirmed, seem to show that virus heated to 55° is quite harmless, but no longer has sufficient immunizing power. Landsteiner and Levaditi had the same experience. Monkeys treated by subcutaneous injection with virus heated to 55° for half an hour succumbed to infection caused nine days after the last preventive inoculation; the infection appears to have been of a severe type.

Virus heated to 45° for half an hour proved to have definite immunizing power, but not to conform to the necessary degree of safety (*cf.* experiments recorded on p. 65).

Virus heated to 50° seems to meet the requirements of immunizing power and safety better than the others. Further experiments with this virus may lead to more hopeful results.

(ε) Immunization with mixtures of virus and serum containing antibodies. As we shall see later, it is possible to demonstrate the presence of antibodies in the serum of immune monkeys and human beings which, when mixed with virus *in vitro*, destroy the activity of the latter. It was natural to attempt to produce immunity by the injection of such mixtures. I have had some success in this direction. Flexner and Lewis obtained no result in similar experiments, and so I wish to emphasize the fact that the following experiments are the only ones performed by me along these lines and that they were not performed *ad hoc*.

Experiment 1.—The following monkeys were given an intracerebral injection of ·6 c.c. of virus No. 11 on March 15, 1910:—

(*a*) Control monkey No. 41 (*Macacus rhesus*).

March 16-25.—No symptoms.

March 26.—Paralysed.

March 28.—Paralysis more marked; then gradual improvement. (Details, see p. 59).

(*b*) Monkey No. 30 (*Macacus rhesus*) had received an intracerebral injection of a mixture of virus and specifically active serum, without any subsequent symptoms, on February 7, 1910.

Result of the injection on March 15, 1910.—Remained permanently well.

(*c*) Monkey No. 31 (*Macacus rhesus*) received the same preliminary treatment as monkey No. 30.

Result of infection on March 15.—Remained permanently well.

Experiment 2.—The following monkeys were given an intracerebral injection of ·6 c.c. of virus No. 11 on July 13, 1910:—

(*a*) Control monkey No. 102 (*Macacus rhesus*).

July 13-24.—Well.

July 25.—Paralysed.

July 26.—Death. Microscopical appearances typical. (Details on p. 77.)

(*b*) Monkey No. 57 (*Macacus rhesus*) had received an intracerebral injection of a mixture of virus and human serum containing antibodies on May 31, 1910.

Result of the infection on July 13.—Remained permanently well.

(*c*) Monkey No. 60 (*Macacus rhesus*) had received an intracerebral injection of a mixture of virus and serum containing antibodies (see p. 171).

Result of the infection on July 13.—Died on July 30 as a result of a cerebral abscess (see p. 52).

It is remarkable that no changes indicative of poliomyelitis were found in this animal even on July 30. (The control had died on July 26.)

Experiment 3.—On May 31, 1910, the following monkeys were given an intracerebral injection of ·5 c.c. of virus No. 11:—

(*a*) Control monkey No. 58 (*Macacus rhesus*).

June 1-6.—No symptoms.

June 11.—Paralysed.

June 13.—Death. Microscopical appearances typical. (Details on p. 77.)

(*b*) Monkey No. 39 (*Macacus rhesus*) received an injection of a mixture of virus and monkey's serum containing antibodies on March 2, 1910, without any subsequent symptoms (see p. 164).

Result of infection on May 31.—Remained permanently well.

In my experiments, therefore, four monkeys (if monkey No. 60 is counted the number is five), which had previously received an injection of a mixture of virus and serum containing antibodies, survived an infection which produced paralysis in the controls in the usual way. Landsteiner and Levaditi obtained the same result with a monkey which had been inoculated with such a mixture subcutaneously; the animal was found to be protected against reinfection, while two control monkeys became paralysed.

Flexner and Lewis say that they were unable to produce immunity with a mixture of virus and serum; they suppose that the serum prevents that development of the virus which is necessary for the production of immunity. As far as I can judge from the communications of these authors, the monkeys which they tested had been vaccinated with serum obtained from *highly* immunized

monkeys. But it is well known that the proportion of virus to antibody is of the greatest importance for success in serum-vaccination. In my experiments, in which serum from convalescent cases was used, a small quantity only of antibody was present in all probability, and thus, by chance, favourable conditions prevailed.

(ζ) Immunization during the incubation period. Protective inoculation against rabies stands in a unique position compared with inoculation against other diseases, in that it is used after infection has taken place, *i.e.*, during the incubation period of the disease. That this is possible is explained by the difference between the virus which causes hydrophobia and the virus *fixe*, used for vaccination. Landsteiner and Levaditi, following Pasteur's method, tried to protect monkeys after they had been given an intracerebral injection of virus. These animals, however, all became paralysed on the eighth day, like the controls.

Following the same train of thought, Flexner and Lewis tried to immunize monkeys by giving simultaneously an intracerebral injection of fully active virus and a subcutaneous injection of virus heated to 60° for half an hour, or of virus heated to 55°-57° for one hour. These experiments were without result. The same thing happened in Krause's experiments; simultaneously with, or after, intracerebral injection he gave monkeys his carbolic acid vaccine. Attempts to immunize monkeys during the incubation period have failed so far.

(η) The biological connection between poliomyelitis and rabies from the point of view of immunity. Owing to the apparently close relationship between the active agents of rabies and poliomyelitis, and because of the many analogies between the diseases, Landsteiner and Levaditi tried to find out whether there was any biological connection between them from the point of view of immunity.

Rhesus No. 6 had been proved immune to reinfection after having survived an attack of poliomyelitis, and its serum contained antibody. On May 17 ·25 c.c. of rabies virus (virus *fixe*) was injected. After nine days the animal became paralysed, and died on May 29. The course of the disease was the same in the control.

This experiment proves the essential biological difference between the two diseases in spite of the many points of analogy between them.

II.—SPECIFIC ANTIBODIES.

Fixation of Complement.—It is usual to demonstrate the presence of specific antibodies in the blood of cases of acquired immunity. It is very difficult to be successful in the case of poliomyelitis because the cause of the disease cannot be cultivated, and a large number of reactions, which ordinarily are carried out in a test tube, are impossible. We ourselves began by testing the

reaction of fixation of complement, because this is one of the most sensitive reactions and serves to indicate extremely small quantities of antigen and antibodies.

We used the ordinary procedure; as indicator we used the known hæmolytic system (1 c.c. of 5 per cent. sheep's blood corpuscles, well washed; specific hæmolytic amboceptor obtained from rabbits in twice the necessary amount, and fresh guinea-pig serum as complement, also in twice the necessary amount). Extracts of the spinal cord of monkeys and human beings, who were certainly suffering from poliomyelitis, were used as antigen; we used not only watery extracts, but also antiformin extracts. We made use of the experience gained by Altmann and Schulz in making the antiformin extracts (*Zeitsch. f. Immunitätsforschung*, vol. iii). We examined the blood and cerebrospinal fluid of human beings in various stages of the disease for antibodies which would fix the complement; we also examined the serum of monkeys which had survived infection, and of monkeys which had received repeated large doses of virus for purposes of immunization. I will only mention summarily that the existence of antibodies which would fix the complement was not proved in a single case. We did obtain fixation of the complement by mixing the watery extract with the serum of a sheep which had been treated many times with poliomyelitic spinal cord. However, the serum of this sheep showed fixation of the complement when mixed with a similar extract of the spinal cord of a normal monkey, so that the occurrence of fixation of the complement was due merely to a specific reaction between the albumin of the sheep's serum and of the monkey's spinal cord, and it was not a reaction specifically of the virus of poliomyelitis. Starr and Wollstein had already examined the spinal fluid of a large number of patients with the same result. They used spinal cord, nerves, muscles and extract of the liver from cases of poliomyelitis as antigen.

Specific Hypersensitiveness.—We have investigated the question whether there is any specific hypersensitiveness shown by cases of experimental poliomyelitis analogous to the tuberculin reaction. We investigated the skin particularly. We had found that in tuberculosis the method of subcutaneous injection gave very reliable results. We injected into the skin of monkeys during the incubation period, directly paralysis set in and during convalescence, 2 c.c. of a 5 per cent. emulsion of monkey's spinal cord containing living or dead (55°) virus. We never had any positive result. Leiner and v. Wiesner also had negative results by this method.

These negative results in the search for specific antibodies are of importance, because they constitute another analogy between poliomyelitis and rabies. In rabies the reaction of fixation of complement has never been obtained even when serum has been used which has been proved, by other methods, to contain antibodies.

Successful Demonstration of Antibodies.—The antibodies in rabies have been demonstrated by mixing the virus with the serum of individuals who have undergone specific treatment. On injection

of this mixture, under certain conditions, it is found to be non-virulent to certain sensitive animals. The necessary conditions are, that the emulsion should be as finely divided as possible (*i.e.*, passed repeatedly through filter paper), and that contact between the virus and the serum should be sufficiently long.

I mixed virus from poliomyelitic spinal cord, usually of a strength of 5 per cent. and repeatedly filtered through paper, with equal parts of the serum to be investigated; the mixture was kept for one hour at a temperature of 37°, and then for twenty-three hours in an ice-chest or at the temperature of the room. The mixture was given to monkeys as an intracerebral injection of ·6 or ·8 c.c. The control experiments were made with a similar mixture prepared with serum from a normal monkey; the mixture was allowed to stand for the same length of time, and the same doses were given to normal monkeys by intracerebral injection. The results were as follows:—

Experiment 1.—The following monkeys received intracerebral injections of ·7 c.c. of a mixture of serum and virus No. 12 prepared as above:—

(*a*) Control monkey No. 29 (*Macacus rhesus*). A mixture containing serum of a normal monkey.

February 8-14.—No symptoms.

February 15.—Paralysis, which ended in death on the 22nd. (Details, see p. 47.)

(*b*) Monkey No. 30 (*Macacus rhesus*). The virus was mixed with serum withdrawn on February 5 from monkey No. 6, which had repeatedly been proved to be immune to reinfection (see pp. 151 and 152).

Result of the infection on February 7.—Monkey No. 3 remained permanently well.

(*c*) Monkey No. 31 (*Macacus rhesus*). The virus was mixed with an equal part of a mixture of the sera of monkeys Nos. 9 and 10 (equal parts), which had been proved to be immune (see p. 152).

Result of the infection on February 7.—Monkey No. 31 remained permanently well.

Experiment 2.—On March 2, 1910, the following monkeys received an intracerebral injection of a mixture of serum with virus No. 12 (·6 c.c.):—

(*a*) Control monkey No. 37 (*Macacus rhesus*). The serum of a normal monkey was used.

March 3-8.—Well.

March 9.—Paralysed.

March 11.—Total paralysis of the hind limbs.

April 14.—Death from marasmus. (Details, see p. 57.)

(*b*) Monkey No. 38 (*Macacus rhesus*). The virus mixed with serum from monkey No. 27, which had been unsuccessfully inoculated with killed virus (see pp. 53 and 160).

March 3-9.—No symptoms.

March 10.—Ill.

March 11.—Paralysed.

March 12.—Death. (Details, see p. 54.)

(*c*) Monkey No. 39 (*Macacus rhesus*). Virus mixed with sera of monkeys Nos. 32 and 34. Monkey No. 32 had survived infection on February

7, 1910, and consequent paralysis (see p. 65); it was immune against re-infection (see p. 159). Monkey No. 34 had received subcutaneous injections of virus heated to 45° on February 7 and 9 for immunizing purposes.

Result of the injection on March 2.—Monkey No. 39 remained permanently well.

These experiments show that serum from monkeys, which have survived paralysis or which have been successfully immunized, when mixed with virus under these conditions, will destroy the infective power of the virus.

Landsteiner and Levaditi, Leiner and v. Wiesner, Flexner and Lewis have proved by similar methods that specific antibodies are present in antipoliomyelitic serum. Certain differences in the methods used, and particularly in the duration of contact between the virus and the serum, make it necessary to refer more in detail to these experiments. In the first place those of Landsteiner and Levaditi:—

Experiment 1.—3 c.c. of the serum of immunized monkeys, the immunity of which had been tested, were mixed with 3·5 c.c. of virus emulsion filtered through paper; the mixture was allowed to stand for four hours at the room temperature and was then injected into the following animals:—

(*a*) Control mandril No. 73 (virus mixed with saline), paralysed in thirteen days, dead in fifteen days.

(*b*) *Macacus rhesus* No. 74 (virus mixed with serum from immune monkey).

Remained permanently well.

In the second experiment serum and virus were mixed in the same way, but the mixture was allowed to stand on ice for a night (*i.e.*, at least twelve hours). It was injected into the following:—

(*a*) Control monkey No. 90 (*Macacus cynomolgus*), virus mixed with saline; paralysed in nine days; microscopical appearances typical.

(*b*) *Macacus cynomolgus* No. 88. Virus mixed with immune serum. Remained well.

(*c*) *Macacus cynomolgus* No. 89. Virus mixed with immune serum. Remained well.

Leiner and v. Wiesner found that when a mixture of virus and immune serum was kept for four hours at the temperature of the room, the intracerebral injection caused only slight paresis in monkeys, while control animals became severely ill. After contact of virus and serum for six hours the monkeys remained well and the controls became ill.

Flexner and Lewis proved that normal monkey serum mixed with the virus had no effect upon it, but that immune serum added to virus, the mixture being warmed for one hour at 37° and allowed to stand on ice overnight, rendered the virus innocuous. This was practically a corroboration of my own experiments.

The unanimous verdict of all these authors is that the serum of monkeys which have survived the disease, or which have been successfully immunized against it, when mixed with virus for a

sufficiently long time renders the latter completely innocuous. We do not know how the serum produces this result. Some authors talk simply of an "antimicrobial" serum; but we know of no means to prove that the serum kills the virus in the test-tube. The only reagent which we possess is the body of the living monkey. It is possible that the virus is killed in the test-tube, but it is also possible that it is not killed at all, but merely rendered non-infective because its reproductive power is destroyed. It is going too far to say that the serum is "antimicrobial." However, it is quite certain that the antipoliomyelitic serum prevents infection in some specific way.

In this instance also we find that the correlation of results obtained in different laboratories enables us to formulate definite general conclusions and renders unnecessary the long series of experiments on various animals, which Krause and Meinicke consider to be essential.

It is probable that the antibodies are the cause of the immunity; from the above experiments we see that only sera obtained from immune animals proved capable of abolishing the infectiveness of the virus; serum from normal monkeys, or those in which preventive inoculation had proved unsuccessful, did not have this action (*cf.* my experiment 2 (*b*)).

Flexner and Clark found antibodies in the cerebrospinal fluid sometimes, usually just after recovery from infection. They hold that this is due to the abnormal permeability of the diseased vessels. According to their observations, specific antibodies are present also in the bile of immune monkeys.

Flexner and Lewis examined the serum of other animals (horses, rabbits and fowls), but found that it had no effect on the activity of the virus. The natural immunity which these animals show towards the virus of poliomyelitis therefore cannot be due to the presence of specific antibodies in their blood. Flexner and Lewis found that normal sheep's serum was slightly active, and they believed that they increased its activity by specific treatment of the animals. Krause proved that the serum of a sheep which had been treated subcutaneously for months with emulsion of poliomyelitis virus, had a specific antipoliomyelitic action (the degree of activity appears to have been small).

Serum Diagnosis.—Possessing as we do a method of demonstrating the presence of antibodies, it becomes possible to make the attempt to use it for diagnostic purposes. The first question which must be decided is, whether antibodies are present in the serum of patients who have had Heine-Medin disease. I performed the following experiments with human serum in conjunction with Professor Eduard Müller, who consents to the publication of the results in this place.

We first made the following experiment: The mixtures of virus and serum were made in an exactly similar way to that used in my experiments with monkeys. The control serum used was taken from a new-born child, whose mother's past history contained no indication of poliomyelitis.

Experiment 1.—On May 19, 1910, the following monkeys received intracerebral injections of mixtures of virus and serum :—

(*a*) Control monkey No. 56 (*Macacus rhesus*) was given ·4 c.c. of emulsion of virus and ·4 c.c. of serum of the new-born child intracerebrally, and simultaneously 5 c.c. of emulsion of virus intraperitoneally.

May 20-June 1.—No symptoms.

June 2.—Paralysed.

June 10.—Death (see p. 76).

(*b*) Monkey No. 55 (*Macacus rhesus*) injected in a similar manner. The serum of the patient, Alois H., was used in the mixture.

Result of the injections.—Monkey No. 55 remained permanently well.

A *résumé* of the history of Alois H., aged 2¾ years (after Ed. Müller) :—

The child became ill on September 10; fever, rapid pulse, vomiting, headache, and constipation. He cried out when taken hold of : " Leave me alone, that hurts," or even when he was only touched. There was marked sweating. At first the case was diagnosed as rickets and intestinal catarrh. During the first few days the child appeared to have difficulty and pain on micturition.

October 11.—Eyes and cranial nerves normal. Internal organs normal.

Complete flaccid paralysis of both arms and both legs, said to have appeared on the second day of the illness. Deep reflexes absent in all limbs.

Abdomen is soft. Epigastric reflexes absent.

Can sit up only with difficulty, the head rolling in all directions.

Swab from the throat shows mainly pneumococci, a few colonies of *Staphylococcus aureus*. Leucocyte count 3,000; blood-film shows nothing abnormal.

Lumbar puncture : Clear, colourless fluid under high pressure; albumin and sodium chloride present in large amount; microscopically a few lymphocytes; cultures made from the fluid all remained sterile.

Within a week the general condition improved; the child remained apathetic. Appetite good; there was a tendency to vomiting and a remarkably frequent pulse. After three weeks a scarlatiniform rash appeared suddenly on the chest and arms; no sore throat, no rise of temperature. Eight days later the rash appeared on the thighs and disappeared completely five days later. Definite peeling in small flakes was seen on the parts affected. Sweating remained profuse. The condition of the nervous system remained practically unchanged; some improvement in the arms; the hands and fingers showed some return of voluntary movement. At the end of six weeks, some distal improvement in the legs. No reaction of degeneration.

The flaccid paralysis of the legs remained, and the child died in a marasmic condition at the end of May, 1910.

Experiment 2.—On July 13, 1900, the following monkeys were injected with mixtures of virus and serum :—

(*a*) Control monkey No. 102 (*Macacus rhesus*). Virus mixed with physiological saline.

July 14-24.—Well.

July 25.—Paralysed.

July 26.—Death (see p. 77).

(*b*) Monkey No. 63 (*Macacus rhesus*). Virus mixed with serum of Elfrida G. The serum was withdrawn on June 23 and kept on ice.

Result of the injection on July 13 : Monkey No. 63 remained permanently well.

(*c*) Monkey No. 64 (*Macacus rhesus*). Virus mixed with serum of Heinrich P.

Result of the injections on July 13: Monkey No. 64 remained permanently well.

Short abstract of the clinical histories of the two patients:—

(1) Elfrida G., 8 years old, from Lüdenscheid, suffered from infantile paralysis at the age of two. In November, 1908, tendon transplantation performed.

Condition on June 23, 1910: Internal organs normal. The whole right leg atrophic; power and muscular tone diminished. The limb feels cold; the patellar, Achillis and plantar reflexes are absent on the right side. Epigastric reflexes present. Power of abdominal muscles good. Talipes equinus on the right side with inversion of the foot (paralysis of the peronei). No sensory loss.

Diagnosis: Old-standing spinal infantile paralysis.

(2) Heinrich P., 5 years old; from Frankenau.

In September, 1909, bilateral complete flaccid paralysis of the legs. (Details may be found in Müller's monograph, p. 36.) By November the paralysis had disappeared; tone of the muscles good; plantar reflex present. Infantile paralysis recovered from.

Our experiments show in the first place that normal human serum has no effect on the virus, but that the serum of individuals who have survived an attack of Heine-Medin disease contains specific antibodies just as in the case of monkeys. Antibodies are present even when the paralysis is completely cured, and even so long as six years after the acute illness.

Netter and Levaditi have paid particular attention to this last point. They allowed their mixtures of virus and serum to stand for three hours at a temperature of 15° and for twelve hours on ice.

In their experiments serum was taken from the following patients:—

(*a*) Girl, aged 3 years, H.-M. disease middle of January, 1910
(*b*) Girl, aged 3 years, H.-M. disease end of December, 1909
(*c*) Man, aged 38 years, H.-M. disease beginning of September, 1909
(*d*) Boy, aged 5 years, H.-M. disease in 1907

} Injection of virus and serum mixture on March 9, 1910.

Result.—Control monkey No. 66 (virus mixed with normal serum), paralysed in seventeen days, dead on March 30.

Monkeys injected with virus mixed with serum obtained from cases (*a*) to (*d*) all remained well.

The experiments show that antibodies are present six weeks after the acute illness, and that they are still demonstrable after three years. Netter and Levaditi arrive at the following important conclusion: The virus was obtained from Landsteiner, *i.e.*, from the Austrian epidemic, while the antibodies were present in the serum taken from patients in France. The activity of the antibodies against the Austrian virus shows that the active agent in the two epidemics was the same. Case (*d*) was a so-called sporadic case, and yet the serum promptly neutralized the virus. This affords the final proof that the sporadic and the epidemic cases belong to

identically the same disease. Our own experiment 2 (*b*) proved the same point, the serum being derived from a sporadic case. These experiments also prove that the demonstration of antibodies may be used as a clinical test.

Netter and Levaditi give the further interesting facts in relation to the question of the persistence of the antibodies in human beings:—

Monkeys were injected in a similar manner as in the preceding experiments with serum from the following cases:—

(*a*) Boy, aged 6½ years, H-M disease middle of January, 1910
(*b*) Boy, aged 12 years, H-.M. disease 11 years ago
(*c*) Baby at the breast, brother of case (*a*), who suffered from an atypical poliomyelitis of the abortive variety

} Monkeys injected on April 5, 1910.

Result.—Control monkey (mixture of virus with normal serum), paralysed in seventeen days, died on April 23.

Monkeys injected with virus and serum of cases (*a*) and (*c*) remained well.

The monkey injected with virus mixed with serum of case (*b*) had paralysis limited to the left hind limb and survived.

Netter and Levaditi draw the conclusion that antibodies are still present, but in diminished quantity, after eleven years. These observations, together with our own experiment 2 (*b*) throw much light on the question of duration of immunity discussed above.

The investigation of Netter and Levaditi of case (*c*) shows that specific antibodies are formed in abortive poliomyelitis. Müller and I were able to bring further evidence on this point.

On May 31, 1910, the following monkeys received intracerebral injections of a mixture of virus and serum:—

(*a*) Control monkey No. 58 (*Macacus rhesus*). A mixture of virus and serum from a normal new-born child.

June 1-10.—No symptoms.

June 11.—Paralysed.

June 13.—Death (see p. 77).

(*b*) Monkey No. 57 (*Macacus rhesus*).—Mixture of virus and serum of the patient, Erna B.

Result of the inoculation.—Remained permanently well.

Erna B. was a child 2 years old, who suffered from a rudimentary form of poliomyelitis.

The fact that antibodies are formed even when the poliomyelitis is abortive is of great practical importance. In our own case, for example, the result of the test made the diagnosis certain, which it was not before the test was made. Anderson and Frost were able to prove that atypical poliomyelitis was present in six doubtful cases in the same manner. It is impossible to estimate the value of serum diagnosis in future epidemics. In particular, it will be necessary to find out if antibodies are present in the blood serum of people who live with the sufferer from poliomyelitis, but who are unaffected. In this way many obscure points in the epidemiology of the disease may be made clear.

In other cases a negative result may be of value, as in the following instance. The patient, Daniel Sch., aged 7, and three of his brothers and sisters suffered from the same symptoms, cough, vomiting, and diarrhœa, without any neurological symptoms. The diagnosis was: Neuritis and acute bronchitis; the suspicion of poliomyelitis cannot be excluded.

The mixture of the patient's serum and virus No. 11 was made in the usual way and given to monkey No. 61 (*Macacus rhesus*) by intracerebral injection.

June 14-17.—Well.

June 18.—Paralysed.

June 19.—Death. (Details, see p. 52.)

In this case the negative result of the test enabled poliomyelitis to be excluded; the diagnosis was not very probable because the patient came from a village in which there were no cases of poliomyelitis.

Clinical and epidemiological investigation, particularly by Medin, has shown that Strümpell's old theory was correct, namely, that there are cerebral forms of Heine-Medin disease. But undoubtedly there are also polio-encephalitic processes which are not connected etiologically with Heine-Medin disease. In such cases serum diagnosis may be of much value. The following serves as an example of this:—

On July 13, 1910, the following monkeys received intracerebral injections:—

(*a*) Control monkey No. 102 (*Macacus rhesus*).—A mixture of virus and saline.

Death from paralysis on July 26. (See Experiment 2, p. 161.)

(*b*) Monkey No. 65 (*Macacus rhesus*).—A mixture of virus and the serum of George K.

The result of the injection on July 13.—Monkey No. 65 remained permanently well.

Short abstract of the clinical history of George K.—Age 33 years, had infantile paralysis during the first year of life, otherwise no important illness.

Condition on June 28, 1910.—Internal organs normal. Reflexes all brisk except the pupil reflexes. Patient appears mentally dull. Speech is slow and stammering. Comprehension fairly good. The whole of the musculature on the right side is weaker than on the left (leg, arm, face).

Diagnosis.—Long-standing cerebral infantile paralysis.

In this case, therefore, proof was brought forward by means of serum diagnosis that the cerebral form of infantile paralysis is identical from the etiological point of view with the typical spinal form of the disease. Further, in this case antibodies were present in the blood of a patient thirty-two years after he had suffered from the acute attack.

A number of authors have maintained that the etiology of herpes zoster is the same as that of poliomyelitis. In herpes

zoster infiltration of the intervertebral ganglia is found, which is similar to infiltration of these ganglia found in spontaneous and experimental poliomyelitis by Swedish and American authors (Forssner and Sjövall, Strauss, Flexner). We have therefore examined some cases of herpes zoster.

On June 13, 1910, the following received intracerebral injections:—

(*a*) Control monkey No. 59 (*Macacus rhesus*).—A mixture of virus No. 11 with serum from a new-born child.

June 15-21.—Well.

June 22.—Gastro-intestinal symptoms.

June 24.—Paralysis.

Gradual improvement. (Details, see p. 56.)

(*b*) Monkey No. 60 (*Macacus rhesus*).—A mixture of virus No. 11 with serum of the patient, Adam St.

Result of the infection.—Monkey No. 60 remained permanently well.

Short abstract of the clinical history of the patient, Adam St., farmer.—Some days ago he had feelings of cold, pains in the knees, and swelling of the glands in the inguinal region; next day a red rash on the left thigh. Anorexia; furred tongue. Otherwise no symptoms. Vesicular eruption over a saddle-shaped area on the buttocks.

Diagnosis.—Herpes zoster.

We have examined two other patients with herpes zoster by this method. Both monkeys which were injected with a mixture of virus and serum in the usual way remained well (Nos. 104 and 105). This did not amount to proof, because unfortunately the control monkey did not become ill either (injected with a mixture of virus and serum from a normal new-born child). Possibly this monkey was one of the few (5 per cent.) which are refractory. We therefore cannot lay much stress on this experiment, although the results are of interest, and the subject must be investigated more fully.

We are convinced that this method will prove of use in many other doubtful conditions, *e.g.*, in some cases of facial palsy. Further, it may be applied in order to determine whether the cases of poliomyelitis which occur with measles and scarlet fever are cases of true Heine-Medin disease; whether they are due to accidental double infection, or whether there is some other etiological factor at work. In the differential diagnosis of poliomyelitis and cerebrospinal meningitis the serum test will be of the greatest value.

The clinician can call to mind many other conditions which are, as yet, little understood. We are only at the beginning of such investigations, and the preceding research is meant chiefly to indicate the importance of such investigation and the methods by which it may be carried out.

Serum Therapy.—It would be still more gratifying if the antibodies could be made use of in therapeutics as well as for purposes of diagnosis. Experience with the virus of rabies does not seem to hold out much hope in this direction; Kraus has shown that although the antibodies of this disease prove very efficacious *in*

vitro they have no therapeutic effect either as a preventive or a curative measure. On the other hand, Heine-Medin disease in man runs a much more benign course than rabies. The lack of any other means of treating the disease during the acute stage is an argument in favour of trying the effect of treatment with antibodies. I have no experience in this matter; my experiments came to an end owing to lack of material just when I had reached the stage of investigation of the therapeutic action of the serum.

Leiner and v. Wiesner gave monkeys simultaneously intracerebral injections of virus and intraperitoneal injections of large quantities of serum containing antibodies. The monkeys so treated became paralysed quite as quickly and as severely as the controls. Subcutaneous and intraspinal injection of the serum also proved useless.

Levaditi and Landsteiner had similar negative results:—

Monkeys No. 79 (*Mangabey*) and No. 80 (*Callitrichus*) were infected on January 19, 1910. Monkey No. 79 received on January 19, 20, and 24 5 c.c., 10 c.c., and 5 c.c. of the serum of a monkey which had survived an attack of poliomyelitis. Both monkeys became paralysed in five days. Simultaneous intraspinal injection of serum and intracerebral infection also proved useless.

Monkeys Nos. 92 and 93 (*Rhesus*) were given intracerebral infection on February 12, 1910.

Monkey No. 92 received 2 c.c. of the serum of a highly immunized monkey into the theca on February 12, 13, and 15. Monkey No. 92, together with the control monkey, became paralysed on February 17.

Intraperitoneal and intraspinal injections of the serum thus proved to be of no curative value. Kraus found that his specifically active sheep serum had no prophylactic effect (see p. 166).

The outlook for serum therapy does not seem bright. Flexner and Lewis are the only authors who have obtained any positive results. It is true that serum injected into the theca had no effect on monkeys which had been infected by intracerebral injection, even when treatment was begun very shortly after infection. But when the monkeys were infected in a way more approaching the natural method, according to these authors, the serum was found to exert a definite influence on the course of the disease. Monkeys were infected through the scarified mucous membrane of the throat, and were given repeated intraspinal injections of serum, beginning not later than twenty-four hours after infection; in these animals the incubation period of the disease was found to be as long as twenty-six days, while the control monkeys became paralysed in from nine to eleven days. Flexner and Lewis suggest that if treatment had been carried on longer the occurrence of paralysis might have been prevented.

They obtained these results not only with the serum of monkeys which had survived the disease, but also with serum from monkeys which had been artificially immunized and from human beings who had suffered from the disease. They hope to raise the antibody

content of the serum by specific treatment and thus to provide a serum of therapeutic value. They consider that Heine-Medin disease produced artificially in monkeys is a much more serious disease than that occurring naturally in man. On the other hand, we must remember that we are not in a position to use the serum so early in the disease in man as Flexner and Lewis were able to in monkeys.

The only experiment carried out with human serum in man, as far as I know, was performed by Nobécourt and Darré. They gave an intraspinal injection of the serum, and state that symptoms of marked meningeal irritation set in three hours after the injection and continued for several days, but that no definite effect on the course of the paralysis could be observed. Considering how extraordinarily variable the course of the disease is, and how impossible it is to give a prognosis from the symptoms of the prodromal stage, it is evident that the value of serum therapy can be established only by means of a very large collection of statistics. At present the question is still in the experimental stage.

[Netter, Gendron, and Touraine report that the administration of serum from an old case of poliomyelitis into four acute cases resulted in improvement of three and the death of one case.—*Translator.*]

III.—EXPERIMENTS WITH DRUGS.

Fermi stated that the course of rabies, produced artificially in rabbits, was influenced in a favourable way by certain dyes, particularly by Trypan red. I therefore made some experiments on monkeys with this substance, but they were quite unsuccessful.

Landsteiner and Levaditi used other substances, firstly arsacetin:—

Two *Macacus* monkeys received, on the same day and in the same manner, intracerebral and intraperitoneal injections. The control became ill in seven days, and paralysed in eight. The other monkey was given subcutaneous injections of from ·075 to ·2 gr. arsacetin on the third, fifth, and sixth days after infection. It became ill on the seventh day and paralysed on the eighth.

In a similar way they used arsenophenylglycin.

Two *Macacus* monkeys were infected in the same way as in the preceding experiment. The control became paralysed in twelve days. The other monkey received a subcutaneous injection of ·3 gr. arsenophenylglycin at the same time as it was infected. It became ill six days afterwards, and was completely paralysed in seven days.

Radium and X-rays proved equally useless both for prevention and cure.

Flexner and Clark recently turned their attention towards urotropin. Cushing and Crowe have shown that urotropin injected

subcutaneously passes to the cerebrospinal fluid, and they have used this drug as a prophylactic antiseptic in their operations on the brain and spinal cord. Moris in Baltimore is said to have used urotropin with success in poliomyelitis. Flexner and Clark therefore used this drug in the case of monkeys. The animals took it well, and it appeared in the cerebrospinal fluid. These authors infected monkeys which had been treated with urotropin, and they continued the treatment. In some cases the period of incubation was prolonged to twenty-four days, instead of the usual six to eight days. They hope to achieve better results by combining serum treatment with the administration of urotropin.

In any case, these American experiments show that a certain amount of therapeutic effect can be produced on acute poliomyelitis. So far, the experiments have only been carried out in animals and have been protective, and not curative, in character. Both serum and urotropin had no effect on poliomyelitis in monkeys when the disease had once begun. In the absence of any known method of combating the disease they deserve consideration.

Other therapeutic measures are purely symptomatic and it must be left to the clinician to judge of their usefulness (rest, careful nursing, plaster jacket (Hohmann), even a plaster of Paris bed (Machol), sodium salicylate, antipyrin, aspirin, phenacetin, &c.). Lumbar puncture appears to me to be a rational method of treatment, because I have found increase of fluid sometimes in monkeys.

It is not within my province to judge of the purely physical methods necessary during the period of convalescence (baths, active and passive movements, electrical treatment, &c.), which are all directed towards the prevention of contractures, nor of the orthopædic treatment which may become necessary at a later stage.

IV.—PROPHYLAXIS.

The methods to be adopted for prophylaxis against the disease are all the more important because we possess no means of influencing the disease when once started. We are driven to adopt special measures against infantile paralysis, not only by humane reasons, caused by the miserable spectacle of the paralysed children themselves, but also by purely economic considerations. As Eduard Müller says, the disease is more to be feared than many other infectious diseases of childhood, because the majority of those who survive remain paralysed; their wage-earning capacity is diminished or destroyed, and they remain chronic invalids. Heine-Medin disease produces a large number of persons who are physically unfit and are a burden to the State. Although the truth of this is obvious, it seems to me necessary to write it, because I have heard even physicians say, that the small number of persons affected by the disease does not justify any special measures. It is true that so far we have not been visited by an epidemic on the same scale as those in Norway and Sweden, but this may happen at any time.

Even from the humane standpoint alone, it is our duty to take measures for an efficient prophylaxis. The feeling, often expressed by mothers during our own small epidemic, that they would rather that their children should suffer from a disease more dangerous to life than from infantile paralysis, is based on a very sure and instinctive appreciation of the consequences.

In the face of the recognized necessity for efficient prophylaxis, it is particularly painful to have to realize how little we know of the usefulness of the measures proposed, and how difficult it is to carry them out. The following suggestions are put forward with full knowledge that they are not in any sense final, and that they will need revision and correction when more is known of the nature and mode of occurrence of the disease.

Private Prophylaxis.—It will be useful to distinguish between the advice which may be given by the private practitioner and the measures which may be taken by the State. Both must depend upon the result of studies in the epidemiology and pathogeny of the disease. Wickman has proved that the disease is transmitted from one human being to another; consequently all contact with persons who may be carriers of the virus should be avoided. The patient should be isolated, and he should be looked after by only one person, if possible. This will not be enough to stop all possibility of further infection. We know from experience that in epidemics the virus is transmitted more frequently by persons suffering from the slight, abortive type of the disease, or by healthy carriers, than by the patient himself. Isolation of the patient must not be omitted on this account, because he may at any time become the source of spread of infection, but it is impossible to isolate all the persons around him. We possess no practicable method of separating those who are infected from those who are not. The method of serum diagnosis cannot be used extensively, because it would be too costly and because the result of the test would be known too late to be of any use. All we can do is to warn those who have been in contact with the patient that they may carry the infection to other people, and to advise them to avoid all communication as far as possible. For how long this should be done I shall discuss later. Unfortunately such advice is rarely followed.

Careful cleansing of the mouth is clearly of importance, when we consider that the virus gains entrance in all probability through the mucous membrane of the mouth, throat, and alimentary canal. For this purpose I advise the use of a 1 per cent. solution of perhydrol because of its disinfectant action on the virus of poliomyelitis (*cf.* Chapter III). The mechanical cleansing effect of this preparation is of great use because, during the act of gargling or rinsing the mouth, the contact between the virus and the drug is necessarily short. Preparations of menthol have a destructive effect upon the virus, but thymol, which is much used as a mouth-wash, has no effect. In all these measures any excessively active use should be avoided, in order that the mucous membrane may not

be damaged. Experimental experience shows that the presence of any lesion of the mucous membrane renders the entrance of the virus much more easy.

In this connection I may refer once again to the greater incidence of the disease during the first two years of life. It is possible that there is a germ of truth in the idea of the older English physicians, which Heine adopted, that troubles of dentition have some etiological significance; there is no doubt that lesions of the mucous membrane are very frequently present at that age. The greater permeability of the mucous membranes, which is physiological in infants, must not be forgotten. Such measures as are taken to prevent entry of the virus from the alimentary tract are all based upon the avoidance of lesions of the mucous membrane. Errors in diet should be avoided. Articles of food do not convey the infection, nor can water be blamed. Milk from an infected house may be contaminated (Wickman), but milk is usually boiled before it is taken nowadays. Nervous persons may be reassured by telling them that a temperature of 60° is sufficient to destroy the virus.

In making further regulations to prevent the spread of infection from the patient or from people in contact with him, we must use our experience in connection with the excretion of the virus. Unfortunately our knowledge is still limited in this respect. Experiments with monkeys have shown that virus is found in the nasal mucous membrane, but it has never been demonstrated in the nasal secretion. As we have no definite knowledge it would be wiser to do too much rather than too little. When asked, I always advise the patient and all persons who come in contact with him in any way to cleanse the mouth and throat with the utmost care, because of eventual spread of the disease by the secretion.

How long the patient and the "carriers" remain infectious it is impossible to say.

Osgood and Lucus found virus in the mucous membrane of the throat in monkeys six months after intracerebral injection. At that time they were able to show that virus had already disappeared from the central nervous system. If this is also correct for human beings it explains many "sporadic" cases, but it emphasizes the necessity for disinfection of the mouth as a prophylactic measure.

Medical men should practise the most careful prophylaxis, they are peculiarly liable to act as carriers of the virus. It is advisable to disinfect the fæces, vomit, and urine of the patient. A 2 per cent. solution of potassium permanganate destroys the virus, and solutions of a high degree of concentration will disinfect the dejecta. The underlinen and bedclothes, and particularly the pocket handkerchiefs, of the patient must be disinfected; ordinary boiling in the wash is sufficient owing to the peculiar sensitiveness to heat of the virus. The foregoing measures must be used also by the nurse.

It has been found that the house in which cases of poliomyelitis

have lived may retain the infection. In most instances in which this is said to have happened it is probable that the virus was conveyed by direct contact with a human being. However, the possibility cannot be excluded that virus was given off in some secretion or excretion from the patient and remained active owing to its powers of resistance. Wickman brought forward some evidence in support of this view. It is therefore advisable to carry out a disinfection of the house. We have tested the value of formalin for this purpose.

The experiment was carried out in the usual way by means of Flügge's Breslau apparatus. The dimensions of the room chosen were 4·93×3·4×3·84 metres. The formalin and water necessary were calculated according to Flügge's tables. The poliomyelitis virus was exposed in the middle of the room in an open Petri dish; it was obtained by drying the spinal cord of a monkey suffering from poliomyelitis *in vacuo* and rubbing it down in a mortar. Silk threads covered with the spores of anthrax were placed close to the dish as a control. The formaldehyde was allowed to act for seven and a half hours. Culture tubes inoculated with the anthrax spores which had been exposed to the formalin vapour showed no signs of growth in thirty days. Tubes inoculated from threads which had not been thus exposed showed definite growth in twenty-four hours. Monkey No. 35 was given an intracerebral injection of ·5 c.c. of a 5 per cent. emulsion of the spinal cord exposed to the formalin. At the same time monkey No. 36 received ·5 c.c. of a 5 per cent. emulsion of the spinal cord not so exposed. Monkey No. 36 become paralysed after fourteen days, and died on the seventeenth day after injection. Monkey No. 35 remained well permanently.

The usual disinfection with formalin is therefore sufficient to destroy the virus under these conditions. It is to be supposed that other modern methods of disinfecting rooms, when carried out in the same energetic way, will prove equally efficacious.

State Regulation.—It remains to be seen in what way prophylaxis may be furthered by the State. I believe that notification is of the first importance; Eduard Müller also agrees with me that it should be carried out not only in times of epidemic, but always. Quite apart from the usefulness of this measure in making known the number of sporadic cases which occur, and thus keeping the disease before the minds of practitioners even when there is no epidemic, it will enable us to take steps immediately a case occurs and even prevent the development of an epidemic by prophylactic means in some instances. It is very much to be hoped that some reliable method of early diagnosis will be discovered. Flexner's proposal, that lumbar puncture should be used early for diagnostic purposes, should be more widely followed. In one case Flexner was able to assist materially towards a diagnosis by discovering an increase in the quantity of albumin present and an absence of bacteria.

For the rest, we shall do well to proceed cautiously in introducing any further State regulation of the disease. Compulsory isolation is not justifiable in the present state of our knowledge.

For the same reason I do not think it necessary that the public should be alarmed by the introduction of compulsory disinfection of clothes, household linen, and of rooms. Müller rightly draws attention to the damage to property which this entails, and to the loss which results from declaring a place of business to be infectious. Although we can ignore such considerations when dealing with the subject from the purely hygienic standpoint, yet from the practical point of view they are of very considerable importance. On the other hand, the physician in charge of a case may do much by impressing on the relatives, in a tactful way, the importance of simple, practicable prophylactic measures. The uniformed inspector, carrying out these proceedings in as conspicuous a way as possible, is not a sight we should wish to see.

In another direction the sanitary authorities may well take action. The brothers and sisters of children suffering from the disease should be forbidden to attend school for a period of some weeks (unfortunately we cannot say exactly for how long). In times of epidemic the schools should be closed. The objection has been raised to this, that the children meet at play if they are not at school. I do not think that this is relevant, because it is well known that children from all parts of the town do not flock to one place to play, as they do in the case of the school. Wickman's experience at Trästena has proved how the school favours the spread of infection. During epidemics children should not be allowed to attend church (Müller); the evil practice of permitting children to attend the funerals of comrades who have died of Heine-Medin disease should be stopped; on such occasions contact with the house and with the relatives is usually impossible to avoid. Vaccination should not be performed during an epidemic, and no children's parties should be given.

It is the duty of the sanitary authorities to give full information concerning the measures which are considered advisable to all doctors in some suitable form.

This represents all that it is wise to do at the present time in fighting Heine-Medin disease along hygienic lines. If we carry out these measures we shall feel at least that we have done our duty. Only practical experience can tell us whether thereby we really reach the virus.

CONCLUSION.

The attempt made in this book to give a comprehensive description of Heine-Medin disease shows how impossible it is to do so, in spite of the many remarkable advances which have been made during the last few years. The study of poliomyelitis provides us with another example of the manner in which additions to our knowledge make us conscious of further and further regions of the unknown.

The clinical aspect of the problem may be regarded as having

been investigated almost in its entirety, thanks to the labours of Heine, Medin, and Wickman. Observation of the last great epidemics has shown that there is not much more to be discovered in that direction. There is one important gap, however, which remains to be filled in, the discovery of a certain means of early diagnosis. The studies of Eduard Müller show that progress is possible (he lays stress on the heavy perspiration, the hyperæsthesia, and the leucopenia).

From the pathological point of view the study of the disease is complete, except in so far as refinements of microscopical methods may yield fresh discoveries. In spite of the investigations of Wickman, and in spite of the results obtained by the experimental method, the question of the pathogenesis of the disease remains obscure and debatable on many points. Systematic experiments with animals will do much to make clear this part of the subject.

I have tried to emphasize the many points in the epidemiology of the disease which are still doubtful, even after Wickman's researches. We will not hope that opportunities will arise in which we shall be able to study the epidemiology on a large scale; but we may hope that, if our fears are realized, all will be done which is possible to furnish us with new weapons for prophylaxis.

The main object of this book was to bring forward proofs that the method of experiment with animals, the most recent branch of research, is able not only to confirm the results obtained by the older methods of investigation, but also to throw fresh light upon them and to yield new results in its turn. If the reader should feel disappointed that the actual results are not larger and more important than he finds them, I would ask him to consider that this method is still young, and that the peculiar characteristics of the only animal which is suitable for the experiments limit the range and variety of the investigations very strictly. This is surely a field in which the authorities might render practical assistance, in order that the therapeutics of this pest—until now the most obscure chapter in poliomyelitis—may come to be understood. There is no doubt that the answer to many unsolved problems will be given ultimately by experimental research.

May the experimental study of Heine-Medin disease be in a position to fulfil the *nobile officium*, which devolves upon it from the great series of pioneers named in the first chapter of this book, who have brought our knowledge to its present pitch by other means. The study of their works recalls to one's mind the comparison made by Goethe, by which he used to express the sensation which seized him while studying the profound writings of Kant. They give one the sensation as of entering a brightly illuminated room.

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