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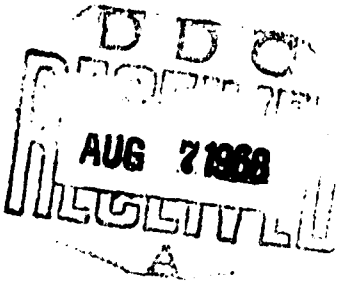

DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

TRANSLATION

INVESTIGATION CONCERNING THE CAUSE OF DEATH BY APOPLEXY IN ANTHRAX

BY: F.W.K. DE MOULIN

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(From the Department of Antiserum and Vaccine Preparation and Control, of the Veterinary Medical Institute for Overseas Assistance. Director: Prof. Dr. F.L. Huber

Information on the physiology and pathology of the syndrome.

In an objective study of the course of anthrax, there is little agreement in the literature concerning some basic problems, and a great difference of opinion exists even in other respects. For the very reason that the anthrax bacillus is not supposed to be "true" toxin producer, the actual cause of death remains a puzzle in very many cases. This is the case above all with apoplectic death, a form of malignant anthrax, in which sometimes no or very few sporadic bacteria can be observed in the blood. Animals, especially hogs, can also die from local anthrax, without our finding any contagion in the circulation. These cases are important, the more so because at the same time they are the denial of those views concerning the death from anthrax according to which the cause of death shall be sought in a bacterial obstruction of the capillaries in the lungs or brain, or even that the circulating bacteria should cause the death by asphyxia as a result of oxygen depletion of the blood. These opinions about the cause of death in anthrax become still more problematic if we take notice of the cases described in the literature, according to which in the blood of small experimental animals fully virulent bacilli can be found during a long period of time, without their experiencing any damage shown externally (BRESREDKA). In a few fatal forms of experimental anthrax in our laboratory, sometimes in the blood of rabbits no bacteria are demonstrable by reinoculation upon guinea pigs, while locally in the spleen or at the site of inoculation they are very much present. These cases are a support of the view that in anthrax a toxic agent is surely formed. The degeneration of the parenchymatous organs, which is regularly observed in this disease, is also an argument for a "toxic" cause.

The task of this investigation is however not primarily the detection of a possible bacterial product, not even the discovery of its nature, but for the present only to establish the existence of such a fatal effect upon the animal organism and to understand that therewith the puzzling apoplectic death could be explained. Here, first of all the following consideration is true. When we study the anthrax syndrome, it is striking that, with the exception of an asphyctic blood picture, no constant clinical symptom is manifested, neither in the same species of animal, nor in those other which are susceptible to anthrax, and even the fever may be absent in the experimental fatally ending anthrax (Test horse No. 981). Herewith, the proper points of approach are indeed extremely limited from where in the study of anthrax we could arrive at a better foundation of the syndrome. Many research people indicated haemolysis as a constant symptom in anthrax. Obviously, some attention should be therefore paid to the occurrence of this. Should we search whether the blood destruction occurs in a sufficiently large number of test animals, then unquestionably the blood-cell count, with subsequent hemoglobin determination according to SAHLI, is the most accurate method. Yet, here we find directly insuperable difficulties which make unfeasible this manner of examination in cases of anthrax. Due to the danger of infection in the septicemic stage, due to the necessity to repeatedly disinfect the used instruments after each individual examination, and due to the time loss thereby, for practical purposes the use of the TALLQUIST haemoglobin scale is therefore to be recommended. As to the finding of expressed blood changes, this color scale is certainly sufficiently accurate, and the errors which are therewith made should amount only to a few percent.

Here are a few figures obtained by this method. After the numbers of the tested animals there are the daily results in percentages, at which the sum in the first column is the figure of color scale obtained before the infection. The horse and the sheep were injected with a dose of the very virulent Poerwakerta anthrax strain which is equal to thousand lethal doses (1000 M.L.D.) for the sheep, while the goats and the rabbits received a single minimum lethal dose (1 M.L.D.) of the same strain as calculated for them.

	Precontrol percentage	1. day	2. day	3. day	4. day	5. day	6 day
Horse							
No. 2	80	80	80	80	60	+	
Sheep							
No. 69	80	70	55	+			
No. 70	70	68	+				
Goat							
No. 8	80	80	80				
No. 9	80	80	80				
Rabbits							
No. 85	75	75	75	70	+		
No. 88	80	80	80	70	70	70	+
No. 90	80	80	70	70	+		
No. 91	83	80	80	75	75	+	
No. 92	80	80	70	70	70	+	
No. 93	85	80	80				
No. 94	80	80	+	(no bacteria found)			
No. 98	80	80	78	78	+		

With the exception of animal No. 94, all others died from positive anthrax.

It seems that we cannot speak of an anemia in anthrax, although a reduction in the blood count is possible. This finding is contrary to that of BUROW, according to which animals are supposed to die from anthrax when the count of their erythrocytes has dropped to one third of the normal value. Although in the TALLQUIST method we have to count with a certain amount of deviation, this is not so high that the cases in which reduced blood count is found would support the concept of BUROW. Moreover, in his research results, somewhat unexplainable is the fact that, where he finds such a strong reduction in the red count, haemoglobin cannot be found spectroscopically either in the serum, or in the bile and urine. Also, though the reticulo-endothelial system is able to catch haemoglobin, it is striking that a blood destruction which has such a poerful course in a short time should leave no traces of free pigment behind itseld. BUROW explains the haemolysis, found in the anthrax cadavers, as a postmortem phenomenon. PETERMANN is also of opinion that the lysis of the blood does not occur during life, although he recognizes that, after a day long effect upon the erythrocytes, the anthrax bacilli are able to dissolve the red cells. In connection with the above described results of blood examinations according to the TALLQUIST method, in a number of test animals, both during life and directly after death, the serum was examined for haemolytic discoloration. Since some animals died unexpectedly during the night, their serum could not be examined in the moribund stage. This was the case with sheep No. 69 contained in Table I, and with a few rabbits. The effect which a specific serum could have on an incidentally occurring hemolysis was also examined. In the second column, the infective dose is expressed in the amount of minimum lethal dose, which was determined for each animal species in relation to the virulent Poerwakarta anthrax strain.

TABLE I.

No. of test animal	Inoculated with	Examination time	Haemolysis
Horse No. 2	10,000 MLD for sheep	directly after death	-
Sheep 69	1000 MLD	9 hours before death	-
2	1000 MLD	directly after death	#
Rabbit 849	100 MLD	24 h. before death	-
Rabbit 849		right after death	##
Rabbit 852	100 MLD	20 hr. before death	-
Rabbit 851	100 MLD	10 hr. before death	-
Rabbit 826	100 MLD 5 cc serum	3 h. before death	-
Rabbit 16	100 MLD	in agony	-
Rabbit 16		right after death	##
Rabbit 871	100 MLD #6 cc serum	in agony	-
Rabbit 853	100 MLD	before death	-
Rabbit 853		right after death	#
Rabbit 854	100 MLD #3 cc serum	right after death	#
Rabbit 873	100 MLD #3 cc serum	right after death	-
Rabbit 870	100 MLD #5 cc serum	right after death	-
Rabbit 866	100 MLD #6 cc serum	in agony	-
Rabbit 8	100 MLD #4cc serum	right after death	#
Rabbit 12	1 MLD #3 cc serum	right after death	±
Rabbit 14	1 MLD #5 cc serum	right after death	±
Rabbit 722	50 MLD	right after death	##
Rabbit 723	100 MLD	right after death	-
Rabbit 365	100 MLD #5 cc serum	right after death	-
Rabbit 725	1000 MLD #3 cc serum	right after death	#
Rabbit 726	1000 MLD #4 cc serum	right after death	-
Rabbit 111	100 MLD	right after death	±

From these observations it seems that haemolysis as such is not a constant phenomenon, and sometimes it is so slight that it cannot be blamed for being the cause of death. In a few cases it was sure that the process occurs at, or right after death, and it is thus observed more as a sequela than a cause of the lethal outcome. That a dark, laked, asphytic blood with little coagulability still does not mean haemolysis, and that in its determination we have to be very cautious, is shown by the blood examination of most of the rabbits which react negatively in this regard, and first of all by the examination of Horse No. 2. Immediately after death its blood seemed dark-red in color, and its coagulability was very little. Nevertheless, after coagulation in a test tube, the serum seemed to be completely free of any trace of hemolytic discoloration.

An effect of the added immune serum could not be detected, nor any slight connection between infective dose and incidental haemolysis.

The supposition that the degree of virulence should favor haemolysis is excluded by the following test. A rabbit and a guinea pig which died from a large dose of anthrax vaccine (B.R.S. vaccine)*, which is harmless to rabbit in a quantity of 1 cc, showed a slight haemolytic discoloration of the serum when examined immediately after death.

On the basis of these results it seems that, particularly to haemolysis in anthrax, no other significance can be attributed but that it is symptom perhaps many times, yet certainly not constantly occurring, which cannot be brought in any casual relation with death.

We are thus forced to search after a cause of a sudden death at which an asphyctic blood picture is supposed to develop, and in that case we have to think of two possibilities: - myocarditis, and a lesion in the respiratory centrum.

Certainly, in this form of anthrax, myocarditis occurs, yet the frequent absence of secondary manifestations such as lassitude, weakness, dyspnea, and general congestion throw a doubt upon this organic affection as the cause of sudden death in anthrax. What is surprising in small laboratory animals and small ruminants is the fact that they seem to be completely normal to the end; they keep on eating and ruminating; they maintain an undistrubed breathing and muscular function, and they pay attention to their environment. The occurrence of an asphyctic blood picture which sometimes arises only in agony, and is known as the typical "anthrax blood", is not a symptom of an apoplectic death from myocarditis.

In about all test animals, finally, at the postmortem a contracted pointed hear is found, without discoloration, dilatation or relaxation. The microscopic image of the cardiac muscle of rabbits and sheep which suddenly died from inoculation anthrax, also shows sometimes actually the picture of a definite myocarditis, but besides this, there are pictures which make it impossible to ascribe the cause of death to the slight cardiac muscular affection (among others, Sheep No. 2).

*FOOTNOTE: Two kinds of anthrax vaccine were prepared at the Veterinary Medical Institute: - one for buffalo, cattle and sheep, this is the so-called B.R.S. vaccine; and a weaker vaccine for the more sensitive animals such as horse, goat, and pig, which is called the P.G.V. vaccine. /NOTE: the initials are Dutch initials of the animals for which the vaccines are useful/.

Degeneration of other parenchymatous organs never bring sudden death; and death is preceded by a series of symptoms which announce the approaching end. Finally, we arrive logically to think of a lesion of the respiratory center. Although haemolysis cannot be demonstrated in all cases, the other symptom of an asphyctic blood picture, the dark, laked blood of slight coagulability is quite evident. The surcharge of the blood with carbon dioxide, which is the result of oxygen deficiency caused by the circulating anthrax bacilli, and the decreasing coagulability of the blood are logically acceptable facts in respiratory paralysis. The incomplete examination of the central nervous system (= CNS), which is striking in the literature of anthrax, seems to be a neglect and a gap in the better understanding of the syndrome.

If we begin to suspect that disorders of the CNS are playing a special role in the anthrax syndrome, then the above mentioned symptoms receive a deeper meaning. Thus, the peripheral disorders are sometimes to be explained not exclusively by the presence of bacteria in the observed lesions. We find splenomegaly in rabbits sometimes of identical degree in cases where an abnormally large number or only sporadic specimens of bacteria of the same strain were found in the pulpa, while splenomegaly can be entirely absent and yet the organ can abound in bacilli (Sheep No. 2). Contrary to this, in a few cases, after experimental infection under the skin, splenomegaly and hyperemia of the small intestines is found, without any chance of finding bacilli in the circulation or in the spleen by means of guinea-pig inoculation. Thus, in the case of lung disorders, be they either pulmonary edema, congestion or emphysema, the number of bacteria that can be found microscopically in the respiratory tract of rabbits, is sometimes so small that we doubt whether the lung symptoms could be ascribed to the regional stimulus of contagion in the organ, since it also happens that the lungs are practically free of pathological changes and yet they have a large number of bacilli of the same strain.

The more we pull the CNS into the research of the whole pathological picture, the more careful we should be that we should not be inclined to seek the primary cause of organ deviations in the local peripheral action of bacteria, especially in the cases where the observed lesions, including circulatory disturbance, hyperemia or inflammation, are very sharply demarcated, and moreover they may coincide with a definite neural area. A small-intestinal disease which is sharply limited to the stomach or cecum, or one which is exclusively limited to the colon or cecum, as it is many times found in rabbits, a paralysis and a secondarily arising inflammation of the esophagus which was observed in a horse at the stage of hyperimmunization, bronchial cramps, ruminal atonia, splenomegaly, anuria and abortion are so many indications of the share which the nervous system can have in the origin of functional disturbances of the organs. Other clinical symptoms which are of special interest in this connection are the following: tremor, muscular cramps, lowering of blood pressure, and rapid, almost imperceptible pulse, vascular paralysis and edema, meteorism, diarrhea or constipation, dyspnea, salivation and epiphora.

Reduced sensitiveness (hypoesthesia) of the skin can be observed in rabbits after experimental infection, before the sensorium appears to be disturbed. A few hours to one day before death, while the animals still do not show any locomotor involvement in their movements, they sometimes do not react any more, or only imperfectly, to needling stimulation. The sensations in the cornea, eyelids, upper lip and nose remain the longest. With an otherwise almost anesthetic hind portion, at a scratch in the interior hip angle a sensory reaction can be still observed for a while. Among the animals examined in the above described manner, there were two with expressed inability to correct the unnatural body positions. When brought in a supine position, they remained in this position, even when the forepart and the hindpart were turned at 90 degrees with regard to each other, without any resistance or any attempt at correction, until they were again brought in the usual lateral position.

Undoubtedly, all these symptoms are based upon neural disturbance, either of the cerebro-spinal system or of the sympathetic system. For a better understanding of the development of the great diversity in the symptom complex of anthrax, here follows a brief recapitulation of the position and the function of the most important neural centers.

The cerebral cortex puts the organism in equilibrium with its environment. It dominates the reactions to stimulation which are originating from the external world and for which a dose of experience is required by which the organism has a series of reflexes at its disposal which are not innate but they rest upon experience and/or memory, the so-called conditioned reflexes. In this way, the look at food is supposed to cause in a reflex way a secretion of the gastric juice as a proof that the body adjusts itself to the stimulus from the outside. (In opposition to these conditioned reflexes are the unconditioned reflexes for which the cooperation of the cortex of the cerebrum is not required and which arise, e.g., by chemical and mechanical stimuli). Next to the conditioned reflexes, we also know of typical cortical reflexes, including the eyelid reflex, lacrimation reflex and the corneal reflex.

Although the cerebral cortex is injured, yet in the experimental animals adequate movements will still remain as a result of the working up of the impressions picked up by the sense organs. Nevertheless the ability of apperception and intelligence are supposed to be decreased or to disappear.

The corpus striatum and the pallium rule a system for affective impulses of the whole bodily musculature, and chiefly of such movements of the limbs as walking, jumping, throwing. Lesion of the corpus striatum are also supposed to cause fever.

The thalamus has a very manyfold function. In addition to sensory and motor pathways, it includes also secretory, vasomotor and still other paths which are in connection with the sympathetic system, and to a certain extent they are also playing a role in the heat regulation of the body. Stimulation of the caudal portion of the thalamus in the animals will result in roaring, bellowing, and so on.

The cerebellum plays a certain special role as an auxiliary system in the maintenance of equilibrium, without itself being a centrum of equilibrium in the proper sense. It regulates the muscular tonus of the trunk and the limbs. The Purkinje cells and the granular cells are linked with the cortico-spinal pathways, and impulses from the whole body reach along here the motor centers of the medulla oblongata and the spinal cord. The cerebellar tonus is based in a great part upon the so-called depth sense, the complex of sensory impressions, which results from the tensions and pressures upon the sole of the foot, in the joints, the periosteum, muscles and ligaments at every position and condition of the body. Disorders of the cerebellum are supposed to be manifested also in: - atonia, ataxia and asthenia. Without causing a general inhibition of the motility, an uncertainty in the control of the standing, walking, and equilibrium is observed thereby.

The medulla oblongata includes the centers for: - mastication, swallowing, vomiting, respiration, regulation of the heart, and the vagus nerve, the vasomotors, the secretion of saliva, perspiration and glycosuria and furthermore the centers of the caudal cerebral nerves. Furthermore, we assume there the presence of a general center for convulsions which controls a special irritability of the total musculature, and is in connection with the center of respiration. The digestive apparatus from the pharynx down to the colon is under the effect of the medulla oblongata (nervous vagus). The centers in the pons and the spinal cord collaborate in the condition of the animal. From the lumbar and sacral spine originate the nerves for defecation, urination and parturition.

The vasomotor neural centers which are chiefly under the control of the medulla oblongata are still able tow work more or less independently. All these centers are in close direct or indirect connection with the sympathicus system which, mostly in cooperation with other neural pathways and the parasympathicus and chiefly its n.vagus, is charged with the regulation of the unconscious processes. At present we do not separate any longer the autonomous system so sharply from the cerebrospinal system, for the vegetative centers are situated in the latter and functionally are very closely connected with it. Generally, we should say about the autonomous nervous system that the centers for positive activity are situated in the vertebral and praevertebral ganglia, while those for the negative activity are placed in the praevertebral and terminal ganglia.

If now we look over the whole markedly varying sympton complex of anthrax in connection with what we recalled briefly above then practically everything can be referred to lesions of the cerebrospinal and vegetative nervous system, and thus to excitation or paralysis of the functions which by the mentioned centers and neural pathways are controlled in such a sense that the initial stage is characterized by increased excitability which in case of the continuation or intensification of the stimul passes over into a lowering of irritability. This is yet a known fact that the initial stage of anthrax in the cattle and buffaloes can be associated with strong excitation, roaring, jumping, tossing, kicking, while later the results of a depressed sensorium will come in the foreground. How much one has to watch that in pregnant animals no abortion is provoked by the vaccination against anthrax for the reason that the center for the uterine contractions is stimulated in the lubar spine! In pregnancy the uterus has an increased irritability, and it can be brought to contractions by influences which would normally remain without any effect. Even the well known splenomegaly is supposed to result from a neural cause. The nerves for the spleen have probably their origin in the medulla oblongata and in the cervical part of the spinal cord (LUCIANI et al.). Peripherally they pass through the splanchaic nerves and stimulation of these nerves brings the capsule of the spleen and the trabeculae into contraction; these movement will otherwise occur as rhythmic physiological movements. Nerves are also assumed which at their irritation will cause dilatation of the spleen. The splenomegaly in anthrax has not to stand in any relation at all with the destruction of red cells in case of anthrax, but in many cases, where the cell destruction is absent or it cannot be considered important, it can be the result of a degeneration of neural centers and thus a result of loss of muscular tonus of the capsule and of the traveculos, and perhaps at the same time of the arterial walls. The arterial blood keeps on flowing under a definite pressure, while by the muscular relaxation in the spleen this will be inflated sometimes to a multiple of its volume, depending upon the tonus reduction, so that outwardly the organ looks as a gigantic haematoma as it was often found in thee big domestic animals. The softening of the contents of the cell necrosis are the inevitable sequelae of the obstructed blood circulation and of the accumulation of metabolic products. This explanation will become still more acceptable in the cases where splenomegaly is found without speaking of any destruction of the circulating blood (cf.Sheep 70 p.128 of this article. The lack of splenomegaly in cases which show many bacteria of very virulent character (Poerwakarta strain) in the pulpa, can be explained by the fact that the above described neural lesions have not developed.

It is well-known that lesions of the spinal cord and of the lumbar cord may cause bladder disorders still before the motor muscular involvement can be found. Urinary retention can be the result of an irritation of the hypogastric plesus, but also of a degeneration of the cells in the cerebral cortex or in the brainstem.

It is not necessary to discuss all symptoms in detail; surely, many of them are complicated by secondary changes in the organs. For instance, in the case of hemorrhagic enteritis the question is whether this is a direct sequela of the bacteria found at this site; for, whether the anthrax bacilli at the penetration in the intestine would be in a position to provoke such a

vehement inflammation of the intestinal wall, this question is now unlikely on the basis of the negative results in a large number of well-known tests (BESREDKA). SANARELLI AND MARCHESINI also came to the conclusion that the intestinal lesions in anthrax did not develope primarily enterogenously. If we are convinced of the great role which the nervous system has in the peripheral pathological picture, then the possibility and even the probability seems to be great that the penetrated anthrax bacilli bring substances into the circulation whose character is still not definitely established, and which exercise a fatal effect upon the central and perifpheral ganglion cells. Both by motor and vasomotor paralyses, sharply delimited intestinal portions can sometimes be the site of such circulatory disturbances which result in all grades of inflammation or necrosis. That such intestinal areas have anthrax bacilli, does not prove anything about the enterogenous origin of enteritis. Anthrax inflammations have the tendency to assume a hemorrhagic character. Nevertheless it is very much a question whether this is the typical result of a primary, suddenly destructive action of the contagion upon the tissue; for, bacterial products of such a malignant character are not demonstrated so far in anthrax. In many case, we get the conviction that we have here a merely local reaction. In the localized forms of anthrax, as these were chiefly described in hogs, often we find bacteria nowhere else in the body than in the necrotic or hemorrhagic processes, e.g., in the lymphnodes or the splenic swellings. Even in the experimental inoculation of anthrax, at the site of the inoculation, there will be edema of the skin, in several cases combined with strong congestion and necrosis. From this we must draw the conclusion that the anthrax bacilli give off products which have a paralyzing effect upon the regional vasomotor nerves. In some cases it is nevertheless observed that rabbits infected with a virulent anthrax strain and killed before the bacteria could reach the circulation, -- in spite of a negative course of guinea-pig inoculation or culture medium inoculation with the blood of these animals -- can show marked hyperemia and edema of the small intestines over the entire length and an enormous overfilling of the bladder without finding any local cause. In hogs we see indeed cutaneous hyperemia, either exclusively on the back side, or limited to the abdominal side or to both ears. It is inadmissible that such processes could be local reactions, the more so since the blood and the spleen may contain so few bacteria that the re-inoculation has negative results (CROOKSHANK). Much more probable is to accept for this a primary central vasomotor disorder. The following cases are proof for this opinion.

Rabbit No. 902, subcutaneously inoculated with 100 M.L.D. Poerwakarta strain, was killed 28 hours after the infection. From the blood, spleen, and brain, material was inoculated on guinea-pigs and microscopically examined. The result of this was negative. Yet, there was a sharply circumscribed inflammation of the small intestine manifested in strong hyperemia and edema, without finding any local cause, and at the same time there was marked dilatation of the bladder.

Rabbit No. 893 was killed 30 hours after subcutaneous infection with the same dose. In this animal also, by means of inoculation of blood and emulsions of spleen and brain upon guinea-pigs, which all remained alive, the existence of a bacteriemia could be excluded. Nevertheless, there was a sharpely limited small-intestinal hyperemia and urine retention.

Rabbit No. 806 was killed 20 hours after the subcutaneous infection with the same dose, and inoculation of blood and organ emulsions upon the guinea-pigs likewise did not give any result. In addition to the urinary retention it also showed marked pulmonary hyperemia and thickened spleen whose pulpa was not softened. A local cause for the splenomegaly and the disturbed pulmonary circulation could not be found.

Rabit No. 980, subcutaneously infected with only 1 M.L.D. of the same anthrax strain, and thereafter killed in 24 hours, likewise seems to have no bacteriemia on the basis of the negative course of guinea-pig inoculation.

an enormous bladder dilatation points, nevertheless to the existence of a function disorder of that organ.

In addition to this, there are examples in test rabbits, in a sheep and a goat which died from inoculation anthrax, and which demonstrated that the presence of a huge number of anthrax bacilli in the spleen and blood does not necessarily go in combination with any of the above mentioned symptoms. Cases are thus found where, independently from the presence of bacteria, organ affections may occur or be absent. The explanation of this can be found only in a central cause. When by the still undetermined anthrax toxins certain nerve centers are injured, peripheral organ lesions are supposed to develop independently from whether in the attacked parts or in the blood stream bacteria have been already found or not, while the lack of peripheral symptoms in the stage of septicemia is a result of the condition that incidentally no neural centers have yet been attacked. Next, macroscopic and microscopic examination of the CNS, a confirmation of this assertion is looked for.

In a number of experimental animals which died of inoculation anthrax the CNS, a confirmation of this assertion is looked for.

In a number of experimental animals which died of inoculation anthrax the CNS was examined. Since at the opening of the cranium in anthrax animals a large amount of blood pours out due to the reduced coagulability of the blood, and the danger of the contagion's spread is thereby not just imaginary. Complete post-mortem examination of the brains in the domestic animals was limited to a goat and a horse. Both animals showed powerful sero-sanguinolent inhibition not only of the meningeal membranes but also of the cerebral parenchyma itself. In the horse, hugh swelling of the cerebellum was outstanding which according to estimation assumed about 1½ of its normal size. The cerebrospinal fluid was also discolored with blood.

Of a number of rabbits, the brains gave the following postmortem picture. In all animals, the cerebral meninges showed hyperemia, which in most animals was combined with smaller or larger hemorrhages. In a few animals, there was hemorrhage within the meninges, so that the cerebrospinal fluid still remained clear and without discoloration, while in other animals the blood pigment penetrated into the cerebrospinal fluid. The region of the medulla oblongata and that of the cerebral tentorium are visibly predestined for blood extravasates. This is so probably due to the presence of large vascular sinuses which are here located. Under one side of the medulla oblongata the sinus basilaris is located, while in the cerebral tentorium the sinus transversus and the sinus communicans are located. It is not impossible that fatal symptoms of cerebral congestion are demonstrable the most clearly in this area.

In the following rabbits, blood effusions could be found chiefly in the meninges around the medulla oblongata:

Rabbit No. 829, large haemorrhage on the right inferior side; spinal fluid still clear.

Rabbit No, 828, on the inferior and lateral level, with diffuse red imbibition of the meninges; spinal fluid still clear.

Rabbit No. 825, haemorrhagic discoloration of the meninges directly behind the cerebellum; bloody spinal fluid.

Rabbit No. 833, at about the same site hemorrhage, red cerebrospinal fluid. Moreover, also a pin-head sized hemorrhage in the meninges on the cerebral basis.

In a few other rabbits, the most marked affections were found in the region of the cerebral tentorium.

Rabbit No. 831, slight bloody infiltration and marked congestion of the meninges; spinal fluid clear; on the base of the lobus piriformis, pin-head sized hemorrhage.

Rabbit No. 832, at the height of the corpora quadrigemina a few flat hemorrhages, cerebrospinal fluid red. Edema of the meninges, chiefly of the cerebral basis.

Rabbit No. 824, local edematous swelling and slight diffuse bloody infiltration around the sinus transversus, while the upper part of the meninges does not show any affection, and does not seem to be even hyperemic.

Rabbit No. 821, marked hyperemia of the meninges from the sinus transversus over the upper surface, and near the basis gradually decreasing.

Rabbit No. 819, blood extravasate in the cerebral tentorium alone..

Rabbit No. 975, marked diffuse meningeal hyperemia with edema. Marked increase of clear spinal fluid.

The above mentioned cases concern animals which acutely perished due to anthrax infection. By simultaneous inoculation of culture and immune serum, the course of disease can be long drawn out, and the postmortem findings of the brains can be compared in more chronic cases with the findings in the acute forms. Although in general it can be stated that, according to the curation of the sickness the hyperemia of the cerebral meninges is decreasing, this is still not the rule since after six days of disease the congestion of the vessels can still be marked. As to the amount of cerebrospinal fluid, no steady rule can be lined out either. In a few animals, in acute cases, the amount is sometimes strongly increased; in other animals this is the case only in a long duration of the disease. The spinal fluid never contains leukocytes, while lymphocytes can be sporadically found in it. In cases of turbidity of the spinal fluid, this is the result of an admixture of cellular detritus, mostly derived from necrosis of ependyma cells and from occasional erthrocytes.

The amount of anthrax bacteria found in the cerebrospinal fluid and cerebral parench varies markedly. In general, its concentration is more marked in acute cases, yet it is under that found in the blood and in the spleen. Nevertheless, sometimes in the blood only sporadic bacteria can be found microscopically, but an enormous thriving of them can be found in the subdural fluid. Long threads with well developed capsules let us suspect in the beginning that this fluid could be considered as a predilectioned site for the bacterial growth. Repeated tests have showed however that these cases are exceptions, and the CNS seems to be rather an environment in which the anthrax bacilli are being destroed than being able to exist and to develop.

HISTOLOGICAL RESEARCH OF THE PATHOLOGICAL ORGANS

The histological research of the organs in anthrax was chiefly directed upon the organs of the nervous system. Concerning the other organs, namely the heart, kidney and liver, we find more data in the literature and the below given results are meant as a supplement to the already known facts, whose corroboration they form only with the difference that the observed structural changes in the kidney and liver which were seen in our research seem to be of much more destructive type than it could be derived from the publications available to us.

The material of the research is derived from different stages of the pathological course, mostly in rabbits. After experimental infection with anthrax bacteria in different doses, there were killed at definite time intervals, so as to be able to follow the degenerative processes in their development. Besides, material was also taken from acute to very chronic cases of the disease, and comparative investigation was also carried out in other animal species. The effect of the dosage of the contagion in case of experimental infections, the occasional sequelae of vaccination and infection of experimentally or naturally resistant animals on the pathological histological picture were studied, partly on paraffin sections, partly as a supplement in frozen sections. For the first method the material of

frozen sections. For the first method the material of parenchymatous organs was fixed in 10% formaline and Bouin solution (formaline-picric acid-glacial acetic acid) and stained with haemaluin-cosine, Van GIESON and GIEMSA. For the organ sections, made with the freezing microtome, mostly the fat-staining with Sudan III was adapted.

LIVER.

In a series of rabbits subcutaneously infect with 100 M.L.D. of the Poerwakarta strain of anthrax, a dose calculated for them, the livers were examined 20, 28, 44, 52, and 68 hours after the infection. By reinoculation of blood and emulsions of spleen and brain on guinea-pigs, it could be determined, according to the negative results of the tests at the first mentioned two periods, that the septicemia stage in rabbits occurs only later than 28 hours after the infection. Thus, in the results of the investigation the remarkable feature is that the found pathological changes developed in the two first mentioned periods before a bacteriemia existed, and thus they are the result of a localized stage of anthrax.

Twenty hours after the infection already, liver degeneration can be observed. The organ is very hyperemic, and capillary haemorrhages are scattered. The nuclei of the hepatic cells vary in size, and many of them are phknotic, or happen to be swollen and in lysis, and can be recognized only as ghosts. The cellular boundary lines disappear and the protoplasma is disintegrated in large granules, and is vacuolized at many places. With Sudan staining, it seems that a fatty degeneration occurred, yet this is not evenly spread over the entire tissue, and in addition to the fatty vacuoles there are also others, larger ones which have no definite contents, and they are surely not of lipoid nature. Together with a slight fatty degeneration, there is thus another kind of degeneration present which gives the picture of much larger granualtion, vacuolization and cytolysis. It gives the picture of rapid devastation of the hepatic cells with the character of liquefaction or lysis, and not in accordance with the picture of an ordinary albuminoid or fatty degeneration. The intensity of this process may vary according to the site, and it is not evenly marked everywhere in the field of vision. At a later stage the hyperemia increases in such a way that the tissue acquires a porous aspect by the markedly dilated capillaries. Twenty eight hours after the infection, the vacuolization and the lysis of cells became so intensive that only crude granular residues seem to be left over from many cells. Although the fatty degeneration also increased, the lipoid granules seem to be too fine to explain the gross vacuolization on the paraffin sections. These are not stained with Sudan in frozen preparations so that it seems from this that both forms of protoplasma destruction have increased, of which however, the cytolysis is the dominant one. The trabecules are not disturbed in their course, except somewhat driven apart by the marked capillary congestion. Small-cellular lymphocytic infiltration does not occur, and only in a few cases are there scattered leukocytes observed in the liver.

To investigate the effect of the infective dose upon the intensity of tissue destruction, a rabbit was also inoculated with only 1 M.L.D. of the same anthrax strain, and killed after 20 hours. It is surprising that the degree of cellular lesions seemed to be not less than after the 100 M.L.D. in the same time. The hyperemia is even more marked with the small dose; here also the cellular boundary lines disappear, and the nuclei vary greatly in size and stainability. The cell protoplasma is vacuoliged withouth the occurrence of a fatty degeneration, from which it seems the most likely that in addition to the fatty degeneration, another form of cytonecrosis also occurs in anthrax.

A very significant point is that this intensive cell devastation occurs at a stage in which no bacteria are yet circulating and thus it must be the sequela of the action of a strong poison (toxin) or enzyme.

Long after an anthrax infection has been passed through and no bacteria can be demonstrated any longer in the organs and in the blood, the liver does not seem to have recovered from the sequelae of the possible toxic action, for six weeks after the infection the hepatic cells can be still markedly vacuolated, so that in many of them the protoplasm seems to be completely dissolved. The hyperemia of the organ is however again diminished, and a normal blood supply takes place throughout the organ.

The histological changes in the livers of rabbits were found to be of the same kind, and of the same intensity in the sheep and in the goat. Here also, acute hyperemia and cellular destruction with vacuolination occurred.

That a normally running vaccination against anthrax is not harmless to the liver, it appears from the examination of a rabbit which had well tolerated an injection of 1 cc of B.R.C. vaccine. Thirteen days after the vaccination the above described cellular lesions and circulatory disorders were found; they were of less marked degree than in the above mentioned cases.

Sheep No. 7, which previously was immunized by vaccination with 0.25 cc of a B.R.C. vaccine, was infected 3 weeks later with 1000 M.L.D. of the Poerwakarta strain. Apparently, it tolerated the infection well. Three weeks later it was killed. The liver showed the known picture of hyperemia, parenchymatous and fatty degeneration, and scattered occurrence of cytolysis.

Castle No. 354, having been used for years for the production of immune sera, had worked up an enormous dose of fully virulent anthrax bacillus cultures without difficulty. At its slaughter, its nutritional state seemed to be very good, and yet a parenchymatous and fatty degeneration was actually found in the liver. Although in the latter cases with the animals of active immunity the hepatic destruction was of a much milder degree than in the acute forms of anthrax, nevertheless it seems that this form of immunization does not represent a particular disadvantage for the body and a later infection cannot be of a harmful action or at the most only in a limited degree.

KIDNEYS.

In all the above mentioned cases the kidneys were also histologically examined.

Here also, it could be corroborated that already before the septicemic stage the kidneys can undergo intensive degeneration which, just as the liver degeneration, can be only the sequels of an agent of strong action which attacks the body from the site of the infection.

Already 20 hours after the infection of a rabbit with 100 M.L.D. of the Poerwakarta strain, marked hyperemia of the kidneys is striking; it can lead to scattered capillary hemorrhages in the cortical layer. In many cases, although still blood-containing, the glomeruli can be shrunk in a peculiar manner, and the syncytium shows the picture of liquefaction. Striking is the marked variation in the caliber of the tubuli. In the cortex, areas appear where the epithelium is swollen to an amorphus mass which completely fills the lumen of the tubuli. According to the result of Sudan staining, there is a regional slight fatty degeneration. In other areas the epithelial cells can be liquefied to a fibrous, vacuolized mass which entirely obstructs, or not, the tubular lumina. In accordance with this, the tubuli are markedly dilated as a result of urinary stasis. The cell nuclei also show signs of necrosis which is chiefly manifested in karyolysis.

At a later stage in the pathological process, the microscopic picture is dominated by the scattered occurrence of urinary cysts which are mostly found in the cortical zone. The renal congestion can diminish and change

into a condition of anemia where the glomeruli are shrunk in a large number. The shrinkage space within the glomerular capsule is filled out with a homogenous coagulated colloidal mass. Beside this, also apparently fully intact glomerule can be found.

In addition to the regionally occurring fatty parenchymatous degeneration, the epithelial cells have undergone a very intensive destruction along the way of vacuolization and liquefaction. Their internal wall is maredly fibrotic, and the cells apparently dissolve in the direction; with their necrotic products they fill up the tubuli entirely, and obstruct the urinary drainage.

Towards the medullary layer, this cytolysis decreases in the straight renal ducts, and the fatty degeneration becomes somewhat stronger. Even here, a variation can be observed in the width of the lumen, but not to such a dwgree as in the cortical zone.

It is true for the kidneys and for the liver that a more advanced stage of the disease does not necessarily indicate also identical developmental phase in the degenerative process of these organs. This is effected by more factors than time alone, and it is thus also possible that the cellular lesions in these organs can be more intensive at a yourngor stage than in a more chronic form of sickness.

In spite of an existing marked renal congestion, the glomeruli can be somewhat anemic, from which it seems that the organ hyperemia is not functional but it has a connection with the tissue destruction. The parts where the cell necrosis is the most marked have the most blood.

The infective dose, as it was also noted in the case of the liver, is not in a proportionate relation with the provoked pathological organic changes. Compared with nephritis due to infection with 100 M.L.D. of the Poerwakarta strain, the same animal species (rabbit) showeved an intensive form of cellular devastation of the same degree, except the hyperemia was less expressed.

In chronic cases, when, at simultaneous inoculation of virulent cultures and immune serum, the infection could be tolerated for longer periods of time, the kidneys seemed still less able to excape the devastating effect of the agent.

Even six weeks after such kind of infection, when the body is free of bacteria according to the negative results of guinea-pig inoculations with blood and organ emulsions, a picture of liquefaction and vacuolization of the epithelial cells is found, on their interior side toward the lumen, the cells can be still somewhat fibrotic; parenchymatous and fatty degeneration is definitely present; it is at a lesser degree than in the acute cases. The glomeruli have recovered their normal appearance; the variances in the width of the lumina of the tubuli are more levelled off, yet the total picture points out that the tissue is recovering slowly and with difficulty from the devastating action of the agent.

Although it is externally without difficulty, the vaccinationalso seems to be not of a harmless nature for the kidneys. Renal hyperemia and parenchymatous degeneration point to a nephritis as a result of an anthrax vaccination applied to a rabbit. Just as it was seen at the examination of the liver, a well-tolerated active immunization does not protect the kidneys against the fatal effect of an afterward following infection with virulent anthrax strain. Sheep No. 7, without any apparent difficulty after the vaccination, had tolerated an infection with 1000 M.L.D. of the Poerwakarta strain. When three weeks later it was killed, intensive degeneration, vacuolization, and liquefaction of the epithelial cells of the cortical layer was found. In addition there were also areas where the tissue remained more intact, yet the general aspect

was that of a grave nephritis. Even the glomeruli were not free of vacuolization, while in the medullary layer, where the degeneration was less expressed, small diapedetic haemorrhages were found at scattered sites.

Characteristic for the organ degeneration in anthrax is that no small-cellular lymphocytic infiltration can be found. It is not improbable that the slow recovery of the liver and kidney diseases in this pathological entity is due to the fact that leukocytes do not cooperate in the process of transporting the degenerative products and in tissue purification.

The process of gradual hyperimmunization in serum animals, as it seems in the liver examinations, is not without effect upon the kidneys. Parenchymatous nephritis in serum cattle No. 354, associated with hepatitis, shows that an antitoxic(?) immunity is a doubtful question in hyperimmune animals.

The findings in hepatic and renal examinations of acute anthrax cases in rabbits are corroborated as to character and intensity by the histological examination of these organs in sheep and goats. In these animals, too, the pathological process is characterized by the vehemence of cell destruction, which is accompanied by fatty degeneration, vacuolization and liquefaction.

HEART.

In a few rabbits and a sheep the heart was histologically examined in the cases in which death came suddenly as a result of anthrax.

In case of positive myocarditis, the muscular tissue is hyperemic, edematous, and the fibrils are driven apart. Fatty and parenchymatous degeneration is here the usual picture, a degeneration in which the muscular cells can disintegrate into gross granuels, and the very thin sarcolema changes over into an almost empty sheath. Local proliferation of the muscular nuclei occurs. Typicalfor such inflammations is again the absence of leukocytes in spite of the tissue destruction. Yet, it is a rule that any serious symptom of myocarditis is absent, and the tissue can have a normal appearance over large distances. Only at scattered sites are the muscular cells show suggestions of a slight parenchymatous degeneration. The heart of the sheep shows not the smallest histological involvement. The more fulminantly the death arrives, the smaller the myocardium is attacked.

The BRANDSBURG tests have indicated that we must be very cautious in searching for the cause of myocarditis in an agent which would act directly upon the cardiace muscle. In rabbits and dogs if their cervical sympathetic nerve or the vago-sympathetic is cut out, there will be some edema, round-cell infiltration, degenerative structural changes in the myocardium's cells, which show resemblance to the histological findings described in anthrax. The probability that in anthrax the myocardial degenerations thus arise secondarily to a neural disorder, i.e., a lesion of the sympathicus and parasympathicus, this probability, in connection with the later histological findings became larger.

In connection with the above described histological changes in the parenchymatous organs, it is pertinent to bring up briefly the opinion of SINGER. His publications on the histological examination of organs in anthrax announce among others that death may come so rapidly that demonstrable cellular lesions can be absent. The liver cells are subjected to a fatty degeneration, which can again disappear near death. Glycogen disappears from the liver. The gravest form of renal degeneration is due to the fatty degeneration of the epithelial cells, nevertheless in more cases of fatally running anthrax in the small experimental animals no other affection could be found but hyperemia.

The most known textbooks, among others those of FRIEDBERGER and FROHNER, and that of HUTYRA and MARECK, recall only the existence of swelling, parenchymatous degeneration and marked hyperemia of the kidney and liver. Nowhere are the enormous cellular devastations mentioned which have been regularly

found in these organs of our experimental animals. Even in connection with the later to be discussed pathological changes in the neural cells, here again the markedly destructive action of the anthrax agent should be pointed out which makes itself active already before the septicemic stage. First of all, the character of the cellular lesions, vacuolization and lysis, which is also seen in the CNS, call attention to themselves, and can be perhaps of significane for the identification of the presently only hypothetical anthrax toxin.

HISTOLOGICAL INVESTIGATION OF THE CENTRAL NERVOUS SYSTEM(C.N.S.)

In the examination of such a fine tissue as the nervous system, we have to exclude possibly everything which would lead to the formation of artefacts at fixation, further tissue treatment and staining. The chief requirement is that the tissue pieces should be fixed, while warm, immediately after the arrival of death. For the making of paraffin sections, the best is the fixation in 80% ethyl alcohol for only a few hours, followed by a longer stay, e.g., overnight stay, in 90% alcohol. In anthrax it seems that is the nervous system a softening process occurs so that in a 70% alcohol, probably as a result of imperfect fixation, often a white sediment develops which will not occur with the use of an at least 80% alcohol through several steps of tissue hardening.

The dehydration can be made in acetone, where the material should remain not more than 2 hours to be put into melted paraffine for a similar time.

Among the other usual fixation agents for use with the common stainings, the Bouin solution is to be recommended. This solution gives better shrinkage pictures, yet after this fixation the staining in the finer differentiation stands behind the one after the use of alcohol. For comparative examination, in a few animals silver impregnation of the neural tissue was used after formalin fixation.

Since in the tropics we have to use a paraffine of high melting point, of 60°C, the material should stay in it as briefly as possible. The use of a freezing microtome is therefore recommended for comparative studies.

In the course of examination the line was followed essentially which was in the examination of the liver and kidney. In a comparative way thehistological examination of the brain in rabbits is supplemented with examination of the brain in sheep, goats, cattle, horse, dove and hen.

RABBIT

BRAIN.

The pathological histological changes were traced at different parts of the cortex at successive stages of experimental anthrax. Cases of chronic anthrax were studied in animals which by the administration of immune serum have withstood the fatal infection for several days, or even survived it.

In a series of rabbits, some have already died before the septicemic stage which, by means of guinea-pig inoculation of blood and organ emulsion, could be put at 30 hours after the subcutaneous infection. Thereby it could be determined that already 20 hours after the infection with a virulent anthrax stain definite cellular reactions have developed.

One of the most complicated problems in the study of pathological processes in the CNS is the exact evaluation of the importance of the glial elements. Their multiformity, origin, mutual task distribution have not yet been uniformly evaluated in the literature. HISSL distinguished two forms in the ectodermal neuroglia cells: - one with small dark nuclei the size of lymphocytes, and another with larger less chromatin-containg nuclei. Both possess only a little protoplasma. Aside from these with brightly staining nuclei, other cells also occur with bizarr protoplasma, where the nuclear form

is modified, and it can be hooked, lobular, or stab-formed. NISSL thinks that for the cell determination the classification according to the form of the nucleu is of the greatest importance.

SPIELMEYER made an effort to come to a better insight in the glial tissue by the study of the tissue's behavior under the pathological circumstances. Here, according to him, two types of changes occur: - the so-called progressive and the regressive changes. The latter are characterized by shrinkage pictures in the more slowly occurring forms of degeneration and karyorrhexis in the acute processes. Karyolysis should develop less often. In case of shrinkage, the cell types with the small darker staining nuclei will predominate, and the bright, chromatin-poor nuclei will decrease. According to SPIELMEYER, hyperchromatosis of the entire nucleus is also a sign of disintegration, and then there occurring new formation of nuclear substance, which in chemical respect is related to the substance of the nucleolus, must be considered as a sign of regression. Although karyorrhectic glial types may occur under normal condtions (young rabbits), nevertheless these are otherwise to be understood as manifestations of regression.

The progressive glial changes lead to a large diversity of neculear and cellular metamorphoses. This progression is manifested both in hypertrophy and in hyperplasia. In the first form, the enlargement of the cell's body is combined with increased chromophilia. The round or oval nucleus undergoes an increase and has a white (pale) appearance, whereby the markedly stained nucleolus is sharply outstanding. Hyperplasia under pathological conditions leads to the origin of multiformity of cells and nuclei. The different types vary at the same time in size. Among the small cellular types the stab-cells are striking which are characterized by their long extended nucleus and cellular body. Under pathological condtions, the glial cells are able to form fibrils, and according to SPIELMEYER all types are supposed to have this ability to a smaller or larger degree. Generally, the fibril formation occurs when the disintegration process is still going on, or had been already finished. Under the new formationof the supporting tissue, the nervous system tries to reestablish the disturbed tension which results from the destruction of the cells and nerves.

In addition to these types which NISSL, SPIELMEYER et al., distinguish as ectodermal neuroglia cells, there are also dermal cells which, in addition to that they do not show any difference morphologically from the previous ones, may also have the same function. Of other cells which occur as phagocytes we know surely that they have mesodermal origin and they can be also morphologically differentiated from the glial cells. The so-called mast cells with their basophil granulation and the adventitial cells changed to plasma cells leave no doubt in this regard.

From the here briefly described opinions concerning the type and function of glial cells, the opinion of GALLEGO is basically different. In a much more recent publication, this author cautions against the view announced by many to arrange the different cellular types under glial tissue, such types which do not belong to glia in the proper sense. Indeed, different cellular types were described and, in addition to the glial cells, the so-called amoeboid microcytes (DEXLER) were established, nevertheless many people do not accept any essential differentiation.

GALLEGO distinguished the glial element proper in two varieties: - one with a granular protoplasma and pyknotic nucleus, and another with homogenous cellular body and chromatine-poor nucleus at which these show sometimes such a slight affinity that they appear as ghosts. In addition to these ectodermal forms, he sharply distinguishes the cells of mesodermal origin, the so-called microglia or the cells of Hortega. These are actually macrophages of the nervous system, real interstitital cells which occur independently from the vascular infiltration. GALLEGO considers them related to the cells of the reticulo-endothelial system, and therefore they should play a great role in diseases. In this groups of cells provided with polymorph chromatin-rich nuclei he distinguishes three types: star-shaped, longitudinal, so called

stab-cells, and round cells. Among these, there are scattered also very small forms which are still smaller than lymphocytes, with point-shaped pyknotic nuclei, and they should be considered as the juvenile forms of the microglia. First of all, the round type which has no steady size, is the phagocytic form. Their pyknotic and also rather deformed nucleus is situated in a granular protoplasma. They can exceed in size the glia cells proper, sometimes even the neural cells. The announced view that they are changed glial forms, is wrong according to GALLEGO, even already on the ground of their totally different embryonal origin.

Where marked proliferation of small cells is found in the CNS, these should be microglia, for the neuroglia undergoes more regressive changes in the cerebral diseases. The microglia plays an important role in the inflammations of the CNS.

It was not the purpose of this examination make a decision in the scientific viewpoints under discussion concerning the problem of the type of the supporting tissue. Although according to the opinion of GALLEGO the use of the word "glia" does not seem to be justified in many cases, in the following investigation of the nervous system this will be done nevertheless. The main thing is that we give an account of the behavior and the occurring differentiations of the small types of cells, which is the most important goal for the practical pathology, where there is any doubt about the existence of a pathological change, it is recommended to compare the histological sections with preparations of the normal tissue.

In the examined earliest initial stage of the disease, i.e., 20 hours after the experimental infection, in its gross structure the brain appears to be almost normal. Hyperemia or other forms of circulatory disturbances could not yet be found. It is only surprising that form and number of glial cells and nuclei in the different areas may vary, even in a single section. Mostly in the superior parts of the cortical layer, a slight multiplication can be found in the number of these cells. Even in the size and appearance of the glial nuclei, varieties occur. In addition to a predominant number of round forms, at scattered sites we also find stab cells and polymorph types which have chromatin-rich nuclei and a more or less vaculoized protoplasma. Among the round-nuclear glial cells we can observe two types which differ in size and in the chromophilia of the nuclei. The smaller ones are darker stained than the larger ones, and both have only a small edge of protoplasma. Among the round-nuclear types, several show already regressive symptoms, manifested in hyperchromatosis of the nuclear wall, so that in a certain optical position such nuclei appear almost centrally vacuolated. These nuclear changes occur exclusively in the large round forms. Besides, there are areas where the behavior of the glial cells does not show any alteration from the normal picture. Where progressive activity of the glial cells can be obsdrved, it can be noticed that they arrange themselves around the pyramidal cells. These areasalways uninjured, well stainable round-nuclear cells with small granulated edge of protoplasma which as satellites besiege a large number of neural cells (pseudoneuronophagy). One or more of them is not only pressed toward the upper level of the ganglion cells, but also situated in their cavities so that they give the impression that they have already eaten themselves into the cellular body, and in this way they imitate the picture of neuronophagy. We have to be only very cautious with the finding of the latter; for, proliferation of satellites often gives the impression of the existence of a phagocytic process. Furthermore, satellitism occurs normally, so that its pathological form can be found only by comparison with sections derived from healthy animals; when moreover the affected pyramidal cells show degenerative symptoms, for neuronophagy of intact neural cells is impossible to imagine.

In the examined histological section of the brain the presence of neuronophagy cannot be denied in some cases; for, in the differently injured pyramidal cells satellites have already eaten their way in, and thus they can be considered as macrophages. A peculiar lysis which can begin unilaterally and in which a part of the pyramidal cell is transformed into a finely granular, fibrous or vacuolated mass, and appears to be apparently normal for the

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other part, is alternating with a total dissolution of the protoplasma which is characterized by decreasing stainability of nucleus and cellular body, total loss of cellular differentiation and fine vacuolated mass, and seems to be apparently normal for the other part, is alternating with a total dissolution of the protoplasma which is characterized by decreasing stainability of nucleus and cellular body, total loss of cellular differentiation and fine vacuolization.

At a stage older by 8 hours, i.e., 20 hours after the infection, and increasing capillary hyperemia of the pia mater can be observed, and the lymphatic capillaries are somewhat dilated. Around the superficial capillaries, a slight concentration of lymphocytes occurs which decreases toward the deeper cortical layers so that here only isolated lymphocytes complicate the overall cellular picture. Such a lymphocytic emigration occurs only in a few preparations, and it is not typical for the tissue reaction whic otherwise is just characterized by the complete absence of any lymphocytic and leukocytic infiltration.

Regionally, the progressive reaction of glial cells is mostly directly under the pia mater. It is predominately composed of round-nuclear cells which proliferate among which those with the slightly stained large nuclei predominate in the superficial layers.

The pyramidal cells show increasing disintegration which can vary locally as to its intensity. Many of them are destroyed under lysis and vacuolization, and neuronophagy is undoubtedly present at scattered sites. The cell nuclei frequently undergo swelling, in which decreasing chromophilia is associated with sharp differentiation of the often deformed, eosinophil nucleoli.

That many ganglion cells are already destroed at the initial stage of the disease can be observed in Ammon's horn. Vacuolization and lysis have reduced the number of intact cells in this part.

In the septicemic stage, 48 hours after the infection, an increase in hyperemia cannot be found so much as rather a dilation of the lymphatic pathways, mostly in the white substance. Nothing can be observed of a small-cellular infiltration.

The ground tissue in the cortical layers is fine spongiose, which shows tissue liquefaction according to SPIELMEYER. In this acute state of spongiosity, the tissue areas do not participate all to the same degree, and the glial cells behave here passibely. Their number did not increase in a convincing manner, nevertheless there is greater variety in the cell types, which is partly due to regressive change. Among the round-nuclear glial cells, situated at scattered sites in the tissue, chiefly those with the larger lightly nuclear wall and central dissolution of the chromatine, karyorrhexis, and the arising of nuclear ghosts. Now, this latter form is already visible under normal conditions as a result of a slight chromophilia of some glial nuclei. As a pathological symptom it can be only noticed if the other regressive symptoms occur which have been here described.

It is remarkable that where satellitism occurs, predominantly the round-nuclear, intact, well-stained cell types enter into action. Their protoplasma can vary in volume, and it is finely granulated or almost homogenous. The satellites are divided by size and staining affinity of the nuclei again in two types which during the entire developmental process of the disease remain as such in the CNS. Scattered in the tissue, there are also glial forms, with bizarr nuclear shapes such as lobulated, stab-formed, star-formed, and point-shaped. According to GALLEGO, the latter extremely small type, which are even smaller than the lymphocytes, are supposed to be considered as the juvenile stages of glial cells and their presence can well be explained in proliferation.

By an increasing destruction of the pyramidal cells, their number is diminished. The already described forms of degeneration, lysis, vacuolization, loss of cellular differentiation, karyolysis, are present at an increased degree in this stage. The nuclei can either shrunk and become hooked pyknotic forms, or they can undergo swelling in which the markedly stained nucleoli sharply contrast with the reduced chromophilia of the nuclei. The majority of the pyramidal cells is apparently still intact although an increasing number of satellites still indicates a reactive action. In the white substance, there is a noticed slight proliferation of round nuclear glial cells in which as likewise described in the cortex for the satellites, two types can be distinguised.

In a study 56 hours after the infection, together with an increasing moisture content in the tissue, we see that the progressive glial reaction is reduced, and the regressive reaction takes the upper hand. The status spongiosus is more marked. Glial proliferation is absent, and it is surprising that the round-nuclear satellites are always perfectly and well stained, while these same forms, loose from any cellular connection in the tissue, occurring at scattered sites, are showing rhexis and lysis of the nuclei and hyperchromatosis of the nuclear wall. The symptoms of destruction have regionally somewhat increased in the pyramidal cells. The white substance is edematous and it is also remarkable that a hydrops of the vascular walls is manifested, and sometimes strongly dilated lymphatic spaces originated around these which are not the result of a tissue shrinkage. In the edema of the white substance, the glial cells are regressively changed and the overwhelmingly round-nuclear cells are regressively changed and to a large part the overwhelmingly round-nuclear cells have swollen, vacuolated or pyknotic nuclei.

If we follow the pathological process in the brain in cases which stretch out for days (7-12), than a somewhat increasing capillary hyperemia, but first of all edema of the tissue can be found. The lymphatic capillaries can become sometimes enormously dilated. This change in the circulation of the cerebrum indicates that the acute congestion has changed into a more chronic form of circulatory disturbance, in which small-cellular infiltration never occurs. Mostly the greater vascular plexus of the lateral ventricles and the pia mater show edematous swelling.

The status spongiosus of the cortex is very marked, and also the dilation of the perivascular lymphatic spaces is striking. Regionally, where the stasis phenomena are less intensive, a slight multiplication of glial cells can be seen, but the degenerative symptoms on these have increased. Neuronophagy occurs scattered, and the here occurring satellites are always the round-nuclear type which are completely intact and well stained, somewhat well contrasted with the symptoms of glial destruction in the ground tissue. In the white substance, also the round-nuclear cells domeinate which are here undergoing a more marked proliferation than in the cortical layer. The glial disintegration is much less in the white substance than at the center of the ganglion cells.

As the course of disease assumes a more chronic character, the number of intactly staying ganglion cells in the cortex and Ammon's horn appears to be larger. Indeed we observe all kinds of cellurlar pictures which indicate regression, such as loss of cellular designs, liquefaction, karyolysis, as well as the neural cells may transform into undifferntiated hyaline forms, in which all or no nuclei are found, yet numbderically the degeneration pictures are reduced in chronic cases. According to the chronicity of the process, the neuronophagy isalso reduced, and there are smaller groups of satellites which beseige the ganglion cells. It seems as if,with the reduction of the active hyperemia and the progressive hydrops,their phagocytic ability or irritability would also become weaker, at least in view of the certainly degenerated ganglion cells which are left in peace by the macrophages.

If the infection was successfully passed, then a slight serious infiltration of the tissue, or scattered dilation of the lymphastic capillaries can be the sign of a still not fully recovered circulatory disturbance. The glial elements are brought back to their normal proportions, but the round nuclear forms dominate to the last. The regressive symptoms at at all cells slowly disappear. Nevertheless, six weeks after the infection, the tissue regeneration is till not complete, the pyramidal cells still reveal unmistakable lesions, and the significance of neuronophagy in the rest of cases of satellitism also shows a longlasting after-reaction of the ganglion cells. Indeed, their stainability has increased, and the protoplasma and cellular differentiations appear sharper. The passage of the disease seems certain with the better condition of the neural cells, the returning function of the glial elements and the recovery of the circulation of blood and lymph.

CEREBELLUM.

In the further description of the microscopic pathological picture of the CNS in rabbits the same sequence was taken in the stages if disease whhat was followed for the cerebrum as the line of investigation.

It is remarkable that even the cerebellum can show definite lesions already before the occurrence of a septicemia, which must be thus the sequela of a toxic effect at a distance, starting from the site of infection. As the first symptom, a slight hyperemia appears in the pia mater. Indication of a slight serious infiltration starts in the white substance, and 28 hours after the infection it can be found. A slight lymphocytic infiltration which was seen only in two experimental animals, and in all other cases it was absent, lets us assume that here we had to do with accidental forms.

The glial cells have undergone reactive multiplication which cannot be found in all cases with the same great certainty. Compared with normal tissue sections, a variation comes up in the type of glial nuclei, similar to the one described in the brain. Where proliferation occurs in the glial tissue all types are represented. In the stratum ganglionum often stabformed, starformed and round types are found. From this zone, cellular infiltrations are formed in the molecular layer. Regressive nuclear symptoms such as rhexis, pyknosis shrinkage in all kinds of bizarr forms, occur everywhere. Different cells of Purkinje are situated as if buried under the glial cells. In the molecular layer, small groups with round nuclei occur at scattered sites which probably clean up the neural fibrils. Hereby, the opinion of SPIELMEYER is also corroborated that this can already happen early. All sorts of glial forms complicate the cellular picture in the molecular layer. The protoplasm is mostly finely granulated or vacuolized. Hypertrophic types with large cellular bodies provided with dendrits, and round-oval nuclei and in between large monstrous forms, in addition to round and bizarr nuclear types, make a great variety of glial types in the gray substance. Proliferation of glia is the most expressed in the stratum ganglionum.. Different capillar loops give chance to see the exuberant growth of endothelial cells which perivascularly swarm out as loose cells, separating themselves from their basic connection below, having oval nuclei and spongious protoplasma. In the white substance the glial reaction is much less, and the round-nuclear types of cell predominate, although stab-cells also occur sparsely. Among the former types of cells, one can again distinguish the same two types according to size and chromophilia of the nuclei as it was mentioned for the cerebral cortex. In addition to the ptoliferation, one can also observe regressive glial reactions appearing in the form of shrinkage, lysis and vaculolization of the nuclei. The large Purkinje cells give interesting objects for the study of neural cellular degeneration. One of the first symptoms is the loss of cellular differentiation. Then, a fine vacuolization develops in the protoplasma, at which, in accordance with the negative results of the Sudan staining, no fatty degeneration is found. Tigrolysis, karyolysis, and even dissolution of the entire cell alternate with the pictures of cellular necrosis. The nuclei are reduced somewhat in stainability; the membrane can disappear without any trace; the chromatin is free in the cell as a small heap of fine substance. Whether the eccentric position of the nuclei

which is found here in many cases could be considered a pathological symptom still remains a question. The Purkinje ganglion cells are not all in the the very same stage of destruction. In addition to such cells which have already reached an advanced stage of disintegration there are also visible some which are completely normal. Here and there, the row of neural cells is interrupted by gaps. These can be places where earlier cells were situated which have now disappeared due to degeneration, but the gaps can also occur normally and they are by no means an indication of cell disintegration. Similarly, sometimes at these places in the molecular layer we see that the dendrits of the Purkinje cells survive still for a long time, and only an amorphous residue of the cell can be found. In such a case, we can speak of a hiatus (gap). There are now such gaps which can already develop after 30 hours, while the rests of the Purkinje cells amidst macrophages are indication of a rapid destruction which takes several of the neural cells in the row as victims. Pseudoneuronophagy is already present at this initial stage of the disease, yet at different places there is also a great probability of neuronophagy. The glial cells here lack any indication of fibril formation. In the layer of granular cells no lesion can be found, and the eosine bodies seem to be also completely intact.

In the septicemic stage, the microscopic lesions become more distinct. The hyperemia is more marked, and mostly in the white substance scattered strongly dilated lymphatic capillaries are filled with a homogenous acellular fluid. In the molecular layer, a status spongiosus develops in many cases. Proliferating vascular endothelial cells, which swarm out perivascularly as isolated cells, can be found also at first, but later, then the necrotic process becomes more intensive, this symptom will be absent.

In the stratum gangliosum, the glial cells are somewhat increased in number regionally, and the round-nuclear types predominate, which we also encounter mostly in the white substance. It is remarkable that the hyperchromatosis of the nuclear membrane -- which is especially found in anthrax --, and nuclear swelling in the glial cells occur almost exclusively in the stratum gangliosum in the cerebellum, and this symptom decreases toward the molecular and granular layers. As a sign of regression, the herewith corresponding reduction of glial proliferation is comprehensible. The hiatuses in the row of neural cells become larger, and cellular residues and ghosts are situated in the spaces as evidence of an intensive destruction. This goes on with loss of the normal protoplasm diffentiation, with tigrolysis, unilateral or total liquefaction. In many cases this starts on the base of the neurite. The protoplasma becomes less stainable and its characteristic structure is dissolved into a fine or crude fibrillary mass where the cellular picture is reduced by vacuolization and shrinkage to an almost unrecognizable residue or ghost. The nuclei can show the already previously described changes, and a siries of shrinkage, loss of membrane, lysis breaks up the normal cytological image. Already before it has gone so far, these cells are besieged by satellites which in the beginning are distinguished by polymorph, well stainable nuclei. Neuronophagy definitely occurs, which does not exclude that the Purkinje cell can also be destroyed without being phagocytized. Lymphocytes and leukocytes are completely absent. In the layer of the granualr cells, the small eosine bodies also show lesions with fibrillary disintegration and vacuolization, which indicates that even this zone does not excape the harmful action of the pathological agent.

Here we have still to point out the typical reaction of the Purkinje cells. Already at the initial stage, most distinctly however still on the second day after the infection, several Purkinje cells become rounded off, when it comes to a separation between the cell body proper and the dendrit. Here, the glial cells play an important role, for not only is a fine fibrillary substance formed between the cell body and the dendrit, at which the latter is separated off, but we also see distinctly a few glial cells lying upon the place of separation. The mostly intact neural nucleus with a residue of protoplasma is rouneded off to a completely globularly shaped body directly surrounded by a fine fibrillary substance in which a circular arrangement can be noticed so that the cell is surrounded by a sort of fine capsule which at the same time separates it from the dendrit. Several glial cells are constantly found in the direct neighborhood of these reaction products. Here, the impression is not confirmed

that this process means death of the cell, for nucleus and protoplasma seem to be mostly completely intact. Sometimes however, the dendrites appear to externally survive, and they can separate from the degenerated cell, while they will still keep their normal character for a while. Small series of glial cells with round nuclei are situated along the dendrits, and reveal their phagocytic activity in their cleaning up. It seems that dendrits can become atrophic in such a manner that the spaces in the molecular layer, which they have occupied before, will remain as channels, without being filled up directly by the surrounding tissue. Generally, it can be said that the longer tha animal is surviving the infection, or the longer it tolerates the infection, the smaller is the cellular destruction, the smaller are the hiatuses in the row of Purkinje cells. Nevertheless, sometimes it can be concluded from the microscopic picture that a vehement cellular destruction first cleaned off a large portion of the tissue, after which an improvement followed, which terminated the process of destruction. But then almost all Purkinje cells can undergo more or less marked lesions. Not only atrophy of the cells, but also of the dendrits and even of the entire molecular layer occurs as the result of this. In such older cases, another function of the glial cells becomes apparent, i.e., the formation of fibrils which not only surround the neural cells as capsules, but they also occupy the place of the destroyed cells. Therefore, at the end of the destructive process we notice the reappearance of bizarr, stab-formed and star-shaped glial cells which, through the formation of fibrillary substance, render their most important collaboration to the regenerative process.

In the stage of disintegration, the glial cells, parallel with the advancing infection, show regressive symptoms such as swelling and hyperchromatosis of the nuclear walls. According to the active hyperemia which passes into stasis, all progressive symptoms decrease, and with the restitution of the blood circulation after the passage of the infection, the signs of glial disintegration disappear. In the white substance, all sorts of glial cells are indeed represented, but the round-nuclear variety predominates and the variation in their number is surely connected with the neural destruction. This tells of dilatation of the neural sheaths which can be already found at the acute stage, swelling, or marked tortuous course of the axis cylinder.

After the passage through the disease, the tissue recovers its normal stainability. The tigroid bodies and nuclear structures again are seen, whereby the dull and even staining in the period of disintegration makes place for a sharp detailed design. This sequence of destruction and regeneration is also recognizable in the granular layer. The first is characterized by vacuolization and lysis of the nuclei, and degeneration of the eosin bodies which is expressed in reduction of chromophilia and of sharpness of contours, together with a fibrous viscoe structural change. Very gradually this zone will be reconstructed, but six weeks after the infection, all symptoms have not yet been fully overcome.

MEDULLA OBLONGATA.

Following the same line of research as described above, this section of the CNS makes a very interesting object of study. As the first symptom in the initial stage, a slight hyperemia can be observed. Following this, the symptoms of increased lymph secretion will soon occur. Regionally, the tissue can be somewhat edematous, and dilated lymphatic capillaries can be found scattered. The primarily occurring active hyperemia soon changes into a circulatory disorder which, in addition to the edema of the neural tissue, finds its expression also in the hydrops of the perivascular lymphatic space. With the progress of the infection, the fluid infiltration (imbibition) becomes more intensive, and the lymphatic capillaries can be found enormously filled with a homogenous acellular fluid. Especially directly around the ventricle, the edema is spread the most. Apparently simultaneously with the occurring active hyperemia, proliferation of the glial cells begins which varies regionally in intensity. In the stage of glial proliferation all types of cells occur, although the two already previously distinguished round-nuclear cell types predominate. These two forms occur almost exclusively as satellites, and they are characterized always by their intact nuclei, and slightly vacuolized pro-

toplasma which is of different width. As the infection proceeds, the regressive symptoms increase simultaneiously with a numerical regression, but the number (of cells) still remains above the normal. Nuclear wall hyperchromatosis again becomes more evident, in addition to rhexis, pyknosis, and lysis of the nuclei. These are chiefly the round-nuclear type of cells which occur sparsely and do not function as satellites; they can be seen with central nuclear vacuolization. But in addition, it must be mentioned that they are again the round-nuclear cells which remain the longest available chiefly as group of satellites. The more bizarr glial types come and go more rapidly. Probably by their task as macrophages, the presence of the round-nuclear cells is longer required. An activity toward fibril formation, to fill gaps resulting from the destruction of ganglion cells, comes less distinctly to expression in the medulla oblongata than in the cerebellum. This is supposed to be caused by the fact that in the medulla oblongata the small neural cells are exclusively cleaned up by the macrophages, and thus the hiatuses are noticeably smaller as well as the restitution of the broken tissue tension is less necessary.

As satellites, the round-nuclear types occur already 20 hours after the infection, and, scattered all over in the tissue, we find small groups of glial cells with the remarkable feature that they besiege exclusively the small ganglion cells. The large neural cells never show pseudoneuronophagy. With all reservation which we have in the determination of neuronophagy, in many cases we must take notice of its existence, for even in the initial stage it is not an exception that we find macrophages which have eaten themselves into the degenerated body of ganglion cells. Regardless how much the larger ganglion cells could be destroyed, they will never be phagocytized in this manner. To which neural nuclei (motor vago-glossopharyngeus; large-cell terminal nucleus of the No. 8 vestibular root?) the large ganglion cells belong, cannot be here recognized, yet the reaction of the ganglion cells is typical against the different neural elements. Leukocytes play nowhere a role in the phagocytosis of the ganglion cells.

Tigrolysis, karyolysis, eccentric nuclei, swelling of nucleus and nucleolus, disappearance of nuclear membrane and the disintegration of the chromatine into a heap of fine substance, also circular arrangement of the tigroid bodies at the periphery of the cell -- these are the well-known first appearing symptoms of a degeneration of the ganglion cells. As to their significanc in this connection, we are still not in agreement in regard to all the facts. They can be well considered as reaction symptoms, although not every reaction must lead to cellular death. Nuclear shrinkage, or also diffusion of the chromaffine nuclear substance into the protoplasma, where the latter acquires basophilia and the nucleus appears as a big vacuole, are also reaction pictures which occur. From the nucleus, the nucleolus remains the longest, and sometimes it can be somewhat swollen, while the rest of the nucleus is on the way of lysis.

But still in the initial stage of the disease, before bacteriemia develops, the ganglia can already show signs of a fatal effect of the agent. Chiefly on the larger cells can this be well studied. Many lose all cellular differentiation, and, under the intensive swelling, the protoplasma often becomes an amorphous mass with reduced stainability. In itself, the latter symptom still does not indicate a cell destruction, for the Nissl bodies are considered by many as reserve material which are used up in trophic disorders and can be later again replenished. In several cases, a definite nuclear disintegration can be observed, and moreover cell processes (dendrits) can be here severed off with collaboration of the glia cells, as it was described in the Purkinje cells. Then, the loss of cellular differentiation is indeed to be considered as a symptom of degeneration.

A cellular picture very frequently found in anthrax is following: - The cell body can be swollen; the surface is wrinkled, and it goes over into a vacuolized or fibrillary zone which at the fixation sometimes will leave open a pericellular space due to shrinkage, as it is also found in normal cells.

Originally it was thought that here we have to do with edematous cells which at fixation lose their fluid, that then the shrinkage hole is filled up and it coagulates into a fibrous or viscose substance. Against this opinion it is true that the cell surface is certainly eroded; that the fibrils continue into the protoplasma from the pericellular zone, and that finally transitions can be found from cells with such a space around them to such where the whole cell is changed into the substance. It seems from this that we have to do with forms which have come into a condition of liquefaction which, beginning at their periphery, attacks them always further until the whole cell is transformed into a viscose fluid. At the fixation a pericellular coat arises with a gradual transition to the central protoplasma residue which spreads always further at the expense of the latter. Even the nucleus is involved in this process.

The liquefaction of the ganglion cells in acute swelling likes to begin sometimes at the periphery of the cell. This is well-known to several authors, and they contrast this form of destruction with the perinuclear lesions. That there is no basic difference, appears from the findings in anthrax, where both forms occur close to each other as result of the effect of the very same agent. In another way we can also study the peculiar marginal liquefaction, i.e. on smears. We press a clean cover glass upon the cross section of a freshly removed piece of medulla oblongata, or rub the latter carefully on the glass, fix it by the flame, and in methl alcohol, and then stain it with Giemsa. Thus we get convincing pictures of an intensive cellular devastation with the formation of liquefaction vacuoles (Fig. 1). These are places where the protoplasma has changed into a homogenous, light-blue stained substance which, when we fix the preparation with chromium-osmium acid instead of with methyl alcohol, does not stain black, and thus cannot be of a lipoid nature. This is fully confirmed by the negative result of Sudan staining of frozen sections. The vacuole formation is the result of a cytolysis, as this was also found in the kidney and liver, and is the manifestation of a vehement cell destruction which however does not attack all cells to the same degree. In addition to such which are in fargoing condition of destruction, there can be also others situated in the direct neighborhood which are either only in its initial stage, or have not undergone any visible morpholegical changes. Cell destruction may also occur regionally, and the same contrasts exist then in regard to the different areas.

If we compare the peiture of the acute form with that of the chronic disease e.g., varying at from 1 to 4 weeks, then, in addition to the reduced satellitism, a slower tempo can be observed in the course of cell degeneration. As the type of cell destruction, only the lysis dominates. In case of more chronic course, the progressive cellular activity decreases simultaneously with the active hyperemia. Satellitism enters on the background, while the haematogenous and lymphogenous stasis increases. These circulatory disorders recover gradually in 6 weeks, yet the ganglion cells still keep on having certain microscopic lesions whose volume and intensity have however markedly decreased, and the rest of the ganglion cells are entirely normal. The swelling of the ganglion cells, which can be considerable, is only an acute symptom. Later the enormous differences in the size of these cells can be more balanced.

Another point of importance in the microscopic examination is the everywhere occurring degeneration of the axis cylinders and the enlargement of the neural sheaths. Soon after the infection already, in the neural pathways we see axis cylinders which are striking by their enormous swelling. They can surely increase to four times their normal width, either very locally as a button-like thickening or over a longer distance, sometimes so far as they can be followed in the field of vision. Their substance is homogenous, hyaline, and very frequently vacuolized. The markedly tortuous course of the axis cylinders, too, mostly in widened neural sheaths, is a well-known symptom of degeneration. In the later stages, this dilatation is a less often occurring symptom. They are never whole neural bundles which come so to destruction, rather these pictures are scattered, and it is not improbable that they correspond to destroyed ganglion cells.

LUMBAR SPINAL CORD.

As far as we can judge according to the external form, the condition of the ganglion cells in the lumbar spinal cord is better than in the proximal portion of the nervous system. Although degenerative forms can also occur, the tigroid bodies are still intact for a longer time, and neuronophagy and liquefaction are in their developmental stage always behind that in the brain. Hyperemia and edema can be very intensive, nevertheless, and in the acute stage they may lead to diffuse capillary haemorrhages. Local bloody infiltrations can spread into the central canal. It seems that the haemorrhages occur more in the ventral half of the cross section of the lumbar cord and therefore the motor horns are also more affected in the process than the sensory horns. Now it is well known that in haematogenous degeneration of the spinal cord resulting from toxins, mostly the ganglion cells of the ventral horns are more attacked, which is supposed to be explained so that these are supposed to have a separate special blood supply (ZIEGLER).

Edema and lymph stasis occur in the spinal cord more intensively when the course of the disease is more chronic. The behavior of the glial cells agrees with that described in the medulla oblongata. Their phagocytic character is again marked exclusively against the smaller ganglion cells, whil the larger motor cells show the already described forms of degeneration of the large cells in the medulla oblongata.

Prior to this, the changes in the C.N.S. were provoked by subcutaneous inoculation of 100 M.L.D. of virulent anthrax. For sake of comparison, the cell lesions were also studied in the initial stage after infection of a rabbit with 1 M.L.D. of the same anthrax strain. Twenty four hours after this inoculation the animal was killed and the nervous system was examined.

Compared with the same stage after administration of the 100 M.L.D. the brain still seems to be intact. In the white substance, however, the lymph capillaries are already dilated. The hyperemia is not expressed; the glial proliferation is questionable, although satellitism in the form of pseudoneuronophagy is definitely present. The round-nuclear cells are again dominating here. Some ganglion cells are in a condition of degeneration, even though it is still only at the beginning. Tigrolysis in various stages, fine-granular disintegration of nucleus and protoplasma, even vacuolization and liquefaction are represented as reactions forms.

In the cerebellum, the progressive reaction of the glial elements is limited to the places where the Purkinje cells are on the way of disappearance. It is again the round-nuclear types of cell with little protoplasma which have their function in the stratum gangliosum, and can be found up to the pia mater. The neural cells are in a better condition than in case of an infection with larger doses. In addition to the externally nomal cells, there are still a few already whose nucleus is eccentrically situated, disintegrated to a heap of fine substance, or perhaps appears to be vaculoized. The cell bodies here give the image of lysis which is seen in different stages which starts as an unilateral liquefaction with vacuolization, or the cell is completely affected, and it surface seems to be wrinkled. Here and there, a cell ghost can interrupt the row of ganglion cells. Although still in a less advanced stage, the cerebellum undoubtedly has already been attacked.

The medulla oblongata shows questionable signs of glial proliferation, tigrolysis, karyolysis, circular arrangment of the tigroid bodies on the periphery of the cell and satellitism. The latter reaction is less intensive in case of smaller infective does, yet the destruction of the large ganglion cells shows less differences in degree with the earlier described cases. It is again the small ganglion cells exclusively which attract the round-nuclear glial cells. As a whole the cellular destruction is not in any proprotionate relation to the infective dose, as we have thus found by the degree of cell changes which were caused in such a short time by a small amount of contagion, still indeed before

bacteria are present in the circulation. If we compare this picture with that of a 4-day old stage after infection with the same dose of contagion, then in the latter it seems that a more marked glial reaction exists; the hiatuses in the zone of the Purkinje cells are somewhat larger, and the degenerative symptoms have increased on all ganglion cells.

In addition to the effect of the infective dose, the effect of the degree of virulence was also examined. For this purpose, the C.N.S. of a rabbit was examined 13 days after subcutaneous inoculation with B.R.S. vaccine in a dose of 1 cc, which was said to be harmless for this experimental animal. Compared with preparations which were derived from rabbits inoculated with 1 M.L.D. of fully virulent culture, the glial reaction is less, yet the lesions of the neural cells are of a superficial type at the very least. Glial proliferation is questionable, and even the satellitism is thereby doubtful. The round-nuclear types of cell dominate and only at the places where Purkinje cells are destroyed in the cerebellum does one find a slight polymorphism; there is no sign of glial destruction. Indeed, we can see fibril forming glial cells in the stratum gangliosum of the cerebellum in the hiatuses of the ganglion cells; morever, we get the impression that they themselves are destroyed during function; nevertheless this is no pathological symptom.

In the row of Purkinje cells, definite degenerative phenomena are demonstrated in the form of vacuolization, beginning liquefaction, severance of the cell processes, rounding off of the residue of the body, and loss of protoplasma characteristics. It is remarkable that the isolated dendrits in the molecular layer are not attacked by any glial cells, which indicates atrophy without marked chemical destruction. In the white substance, at all cerebral portions, slight serous infiltration is present. The medulla oblongata shows slight progressive glial reaction, and somewhat increased satellitism. It is again the small round-nuclear types which can be seen concentrated slightly also along the neural fibrils. In addition to these, mostly much larger hypertrophic forms occur in dissemination, with large well-staining round-oval nuclei within an abundant and granulated body of protoplasma. Normal ganglion cells alterate with definitely degenerative forms in all stages of tigrolysis, karyolysis, vacuolization, among which the latter symptom is prevailing. Neural disintegration is expressed in slight swelling of the axis cylinders and myelin sheaths. Leukocytes or lymphocytes are not found anywhere.

In supplementing the findings concerning the renal and hepatic symptoms after vaccination, it seems from the cerebral examination that active immunization, even though it is apparently tolerated without any difficulty, does not take place without some damage to the body.

PERIPHERAL NERVES.

In several rabbits, the peripheral nerves were examined in various stages of the pathological process to see eventual degenerative changes. Immediately after the death, with all possible protection against stretching the nerves were quickly prepared from the foreleg and hindlegs and from the cervical tract, split up necessarily with a sharp scalpel, and liberated from the connective tissue. It is still better to look for the thinner branches, to cut them off, and to fix them in chromium-osmic acid for 24 hours. Thereafter with a sharp needle the finer bundels can be searched and isolated from each other, clarified in glycerine, and examined between a coverglass and a slide. Here it seems to be an advantage that before the embedding in glycerine the nerve is freed of the superfluous chromium stain in a 70% alcohol, after which the placement of glycerine is better.

Neural degenerations could be very easily found among the normal fibrils. The myelin sheath which normally stains evely dark with osmic acid, in case of degeneration of the neurofibrils shows the well-known picture of granular decay, at which the granual are first still stained black, later they remain

unstained due to continued chemical decomposition. The axis cylinders also do not look then evely wide along their whole length. The n.ischiadicus (sciatic nerve), the median, radial and vagus nerves were examined in this manner with the following results. Forty eight hours after the infection, the peripheral nerves already seem to show morphological changes, at which they are never affected throughout their whole cross section, but degenerated bundles occur always among intact bundles in an extension which varies according to individual cases and the examined nerves. In some, the sciatic nerve was more markedly attacked, in others again the vagus nerve or the median nerve. These incomplete neural degenerations explain at the same time why the muscular paralyses are not typical in anthrax. As far as it could be found in the literature, only BURKE mentions the occurrence of motor paralyses in horses of British India.

Domestic animals.

The observations made on rabbits were controlled and supplemented with observations on domestic animals. The material is from animals which all received subcutaneiously either a lethal dose of virulent anthrax culture, or an amount of anthrax vaccine followed, or not, by an injection of unattenuated contagious matter. One lethal dose of virulent anthrax strain of the Poerwakarta type was administered exclusively to: an Australian horse (no. 2, page 12)). two goats and a sheep which all died from acute anthrax. The small ruminants succumbed to an apoplectic form of the disease, while the agony of the horse lasted about half an hour. A sheep was used for testing the harmlessness of the anthrax culture, and it tolerated 20 cc of this vacine seeminly without difficulty. Another sheep, No. 7, was infected, after a preceding vaccination with 1 cc of anthrax vaccine, with a lethal dose of virulent culture which infection was also apparently well tolerated. Finally, for the histological investigation of the brain, material was used which was derived from cattle No. 35 which has been serving for years for the production of immune serum, and for this purpose it has elaborated enormous amounts of virulent contagion without any externally perceptible difficulty.

The histo-pathological findings on the brains of these animals completely corroborated what has been acquired by the same examination in the rabbits. Therefore, these can be discussed very concisely.

Fundamental differences could not be found in the pathological histological picture in the fatally running anthrax forms in the horse, goats and sheep. We see indeed that, in the brain of the horse, the stasis of blood and lymph and marked serous infiltration are coming more in the foreground as symptoms, while in the small ruminants the hyperemia of the tissue is not accompanied by circulatory disturbances, nevertheless this makes no basic difference. Small-cellular infiltrations were never found, and it is left to the glial cells, among which the round-nuclear types predominate, to fulfil the task of macrophages. Compared with the degenerative cell pictures which were exhaustively described for the rabbits, the found types of cellular decay in the brains of domestic animals do not offer any essential differences. It can be only remarked that the intensity of the tissue destruction in the goat is remarkably less than in the other animals. Probably, the high susceptibility of this animal for anthrax is demonstrated by its greater susceptibility for lesions in the C.N.S., so that the death will enter already in a condition of tissue degeneration which, histologically considered, could be still considered as a developmental stage.

The reaction of the C.N.S. at vaccination against anthrax is of great significance. Although it could be remarked that the sheep, whose brain was examined, has received a very large dose of the vaccine, yet no externally visible symptoms could be seen during the immunization process, which would show that the animal suffered from it in any respect. In addition to capillary hyperemia and a slight increase in the number of glial cells, definite regressive symptoms can be observed on ganglion cells and neurofibrils. Although a large portion of the ganglion cells remained externally intact,

we find cells in all parts of the brain and the medulla oblongata which show the presence of a serious degeneration manifested by nuclear and protoplasmic changes. In many cells, the pathological picture is in complete agreement with that of positive anthrax cases. In the cerebellum, a large number of the Purkinje cells disappeared, and among the remaining, shrinkage and atrophy occur as symptoms of degeneration. In the medulla oblongata, the nerves are more affected than the ganglion cells, which is expressed by the swelling of axis cylinders and myelin sheaths which occurs diffusely.

At an infection with a dose of virulent anthrax culture which follows the vaccination, the histological changes in the C.N.S. are considerably increased. Although Sheep No. 7 has tolerated this kind of treatment without any external difficulty, the reaction is very intensive on the side of the C.N.S. Disorders in blood and lymph circulations are absent, but the status spongiosus of the brain, the regressive changes on the pyramidal cells, the large number of Purkinje cells which perished under nuclear loss, vacuolization, liquefaction and neuronophagy, indicate a serious degeneration of the brain. In the medulla oblongata, certain degenerative forms among the ganglion cells call attention. Under tigrolysism around the cell body a coat of fibrillar substance is formed which surrounds the protoplasm as an evenly thick zone, or occurring unilaterally it can so strongly increase in width at the expense of the cell and even of the nucleus that a wide stripe of coating substance arises. The process presents itself as a variety of the already previously described picture of peripheral liquoraction, with the difference that here it does not make the impression of colliquation but of a transition into a more solid substance.

Even the process of hyperimmunization does not happen without damage to the C.N.S. In the brain and cerebellum of cattle No. 354, the number of pyramidal cells and Purkinje cells is reduced, while among the remaining ganglion cells in the cerebellum and medulla oblongata different cells occur which are on the way of regression, as shown by colliquation, vacuolization, severance of the dendrit processes.

BIRDS.

Finally the C.N.S. was histologically examined in hen and Indian doves ("perkutut" - Geopelia striata) after infection with virulent anthrax culture. Although it was not possible to produce anthrax in hens, after repeated infections a reaction of the C.N.S. could be found. In addition to a slight hyperemia of the cerebral cortex and a slight progressive glial reaction, definite degeneration of the ganglion cells occurs which is slight in the brain, yet much stronger seems to be in the cerebellum and the medulla oblongata. Among the Purkinje cells several are missing, while among the remaining cells nuclear loss, vacuolization and even colliquation is found. A large portion of the ganglion cells remained intact in the cerebellum and in the medulla oblongata.

Since the Indian dove, Geopelia striata, seems to be susceptible for anthrax, a number of these birds are experimentally infected. In these animals, death occurred in its apoplectic form, at which they remained apparently entirely normal until the last moment. The susceptibility for anthrax in diverse speciments of these birds seems the most clearly from the intensive cerebral reaction. In comparison with the hen, the cerebral and cerebellar symptoms are less clearly marked. In addition to a slight hyperemia and a little edema, a regressive reaction of the ganglion cells can be noted. On contrary, the medulla oblongata shows strong degeneration in the form of edema, neuronophagy of the small ganglion cells, and especially strong cellular destruction of the large type of cells. Chiefly, a marked vacuolization which by its way and intencity could be taken characteristic for the "perkutut", attacks the large ganglion cells almost without exception.

F[illegible] it seems that the lesions of the medulla oblongata are responsible f[illegible]ce of death, for -- in comparison with the hen which is not [illegible] anthrax, the brain and cerebellum are less affected, while in the hen the medulla oblongata remains exactly more intact.

HISTOLOGICAL EXAMINATION OF THE SYMPATHICUS

For practical reasons due to the danger of infection at the preparation of the different sympathetic ganglia, the examination of this subsection was limited only to one horse and three sheep.

From the horse the superior cervical ganglion was taken; in the sheep the excision of the superior cervical ganglion and of the coeliac ganglion was considered. Although the cervical ganglion is exactly determined in position, and at its removal no difficulty was expected, its finding seemed to meet unexpected difficulties. Finally therefore, the vagus nerve and sympathicus in the neck section were so far exposed as necessary, by an estimate to cut them out simultaneously with the search ganglion. The microscopic examination has later confirmed that for the horse this method of orientation is well indicated. In sheep, in the course of the taken nerves, no sympathetic ganglia were found. From this it seems that there was an atrophy of the superior cervical ganglion, for no other explanation can be accepted, at least for its absence at the macroscopic examination. The detection of the coeliac ganglion did not cause any difficulty. After fixation in alcohol, the tissue is stained in the usual manner.

COELIAC GANGLION.

The ganglion cells, scattered or grouped amidst neurofibrils, show signs of degeneration which are not identical in all the three sheep. In one, no convincing changes were found, for according to SPIELMEYER, the peripheral position of the nucleus which we found is not an abnormal symptom. In the ganglion of the other two sheep, diffuse marked globular swelling of the nucleus was found with hyperchromatosis of the wall and vacuolization, at which the nucleus can be also markedly enlarged. Furthermore, the nuclear membrane can become dissolved, and total karyolysis can occur. Most of the cells are however outwardly normal.

CERVICAL GANGLION.

The cervical ganglion of the horse shows more marked reaction. Many cells seem to be small and atrophic; the cell outlines are vague, and a fine vacuolization occurs in the protoplasma. The nuclei vary in size and stainability. Phimosis, lysis, and rhexis occurs at scattered sites. Around the sympathicus ganglia, marked proliferation of small cells is found, either in a crescent-shaped arrangement, or as an irregular grouping of well stainable uniform cell types with intact round nuclei. Locally the proliferation can be so marked that the ganglion cells are covered by it. These are the so-called capsule cells which can markedly increase in number under pathological conditions, at which according to SCHULZ the normally only weakly staining cells gain in chromophilia at the same time. The cervical ganglion thus shows more reaction to the infective stimulus than the coeliac ganglion, a matter which CHACHINA had also found in diseases of dogs, TERPLAN, ORMOS, MOGINICZKY, and MULLER in human disease.

Small-cellular infiltration is not found in case of anthrax. The description of histo-pathological changes in the cells in the sympathetic ganglions in infectious diseases of man and animals reported by the above mentioned investigators is briefly this. In acute disease, edema and hyperemia and swelling or shrinkage of the ganglia occur which later can become atrophic by connective tissue proliferation. The cells show here a whole gamut of degenerative pictures, beginning with loss of cellular structure, chromatolysis, nuclear swelling or pyknosis, dissolution of the nuclear membrane, vacuolization of the protoplasma, irregular cellular contours, ending in partial or total necrosis and atrophy of the ganglion cells. Not all cells can either markedly proliferate, or rather decrease in number. STAEMMLER and MOGILNICZKY point out also the vasimotor disorders which in the course of the sympathetic degenerations may occur, and which can complicate the pathological poiture.

HISTOLOGICAL CONSIDERATION

From the histological investigation of the C.N.S. in anthrax cases, the existence of an encephalo-myelitis diffusa non purulenta seems to be the most understandable. In many cases in which edemas or harmorrhages were found in the meninges, the process is supposed to be associated with meningitis.

The process of demolition and reconstruction is going on without the participation of lymphocytes and leukocytes, and their task will rest entirely upon the glial cells. Only in the beginning of the infection and mostly in the initial stage, when there is still no septicemia, did glial proliferation occur. The grade of it varies individually, regionally, and according to the size and virulence grade of the infective dose. Where proliferation was found, a polymorphism can be found in the cell types, at which the cells with round nuclei, according to size and chromophilia, can be divided into two types, and can occur as satellites or macrophages. Moreover, their granulated protoplasma can vary in size. The proliferation of the polymorph glial types has a brief existence. The tissue edema and glial degeneration are occurring very rapidly; the increase is often questionable, and the stab cells, the star formed and point-shaped types return to their normal behavior. At most, they occur at the severance of the cell processes (dendrits) and at the filling out of the hiatuses between cells.

In the septicemic stage, the round-nucleated cell types also predominate, and their increases go parallel with increased satellitism which is ever found in connection with the large ganglia in the medulla oblongata. In the white substance, and in the molecular layer of the cerebellum, they also form groups or rows which actively occur at the clean-up of disintegration products of degenerated nerves. The large hypertrophic glial types play here numerically a subordinate role. Why in one case more glial reaction can be observed than in another of the same infective dose, and why the reactions also vary regionally, is still unexplained.

In the stage of active hyperemia, proliferating endothelial cells are also found which leave their basic connection and swarm out. When in the passage of infection the demolition stage is finished, again a slight increase occurs in the number of polymorph glial cells. In addition to their bizarr shapes of cell and nucleus, they are mostly distinguished by pyknotic nuclei. That the latter symptom should be a regressive manifestation, as SPIELMEYER thinks, must be denied on the basis of the occurrence of proliferation in this stage, which is thus a stage of intensive activity. Moreover, they occur chiefly in the initial stage and after the passage of the tissue demolition proper, i.e., exactly in the periods in which the above symptoms of cellular disintegration are the least. SPIELMEYER correctly points out that the glial proliferation very rapidly appears but also again disappears under certain stimuli. In the C.N.S., where the polymorph types come and disappear quicker, and the round-cell types dominate, one has to assume therefore that the latter are better against a condition of toxic effect, and therefore they have their importance exactly in the stage of toxin circulation. By the often occurring degenerative symptoms on these cells it seems that they are partially destroyed during their eventual working up of the toxins. The polymorph types of cell have probably more the task to fill out again the hiatuses which developed from degeneration of cells and nerves by means of forming a fine fibrillary substance, and this way to restore the disturbed tension in the tissue. This function is not specific, for the round-nucleated cells can also participate therein. Thus, they have apparently an extended task, for theirs is also the protection and the phagocytosis of ganglion cells and nerves. It is peculiar in anthrax that sclerosis has not been found.

The finding of ALZHEIMER and ROSENTHAL, that at edematous conditions of the nervous system the amoeboid round-nucleated glial cells are many, could not be confirmed by experiences in the study of anthrax. Here, it seems rather that edema is a definite brake for the multiplication of glial cells. Indeed,

an edematous condition often coincides with that of tissue demolition, and then a predominance of the round-nucleated cells can be always proportionately noticed, without being able to speak of an absolute multiplication of these cells.

That in anthrax a marked tissue demolition exists, appears from the status spongiosus which occurs already soon in the acute stage of the disease. Softening and fusion (colliquation) of tissue and of ganglion cells, without the collaboration of leukocytes, is characteristic for anthrax. Among the ganglion cells, there are a large diversity of degenerative forms, among which those which occur with swelling and vacuolization and colliquation are the most characteristic in anthrax. Now, these are also at the same time the pictures which are known in neurohistology to occur the most often. There is nothing here of characteristic degenerative forms of ganglion cells, since under the very same agent the cellular reactions can run very much apart. The colliquation of the nervous system, however, completely corresponds to the liquefaction processes which are found on the renal and hepatic epithelial cells. As such, this general symptom gets a special meaning for anthrax, and it maybe perhaps valuable in the determination of an anthrax toxin. Because, that a bacterial product is at action, it appears not only from the degenerative cellular picture, but from the fact that this already occurs before the bacteria developed.

The question why one ganglion cell will be phagocytized by glial cells and the other is not, remains a puzzle for a while. There is evidently a preference in glial cells for the supervision of ganglion cells in various parts of the C.N.S. If the infection happened with virulent anthrax, then the satellitism happens to be the most marked in the small ganglion types of the medulla oblongata, which can be so intensive that the latter can be completely masked by these cells. Then come the Purkinje cells, while the pyramidal cells can be besieged only by a few satellities. Only the large ganglion cells in the medulla oblongata remain from from them. A connection with the size of the cells cannot be made from this, however, for the Purkinje cells are much larger than the pyramidal cells, we get the impression that the disintegration products of the large cells keep the satellites at a distance, since not only do not they attract any macrophages in the advanced state of disintegration, but, as they are completely destroyed, their places are not taken up by a fibrillar glial tissue. Should we look upon pseudoneuronophagy as a process of protection? In the course of the disease, the glial reaction does not represent any definite phase, and it can vary in intensity at infection with the same dose and with the same strain. It seems from the examination that the ganglion cells in the cerebellum are generally more intensively and earlier attacked than in the brain, and thus perhaps they are more in need for protection by the satellites. The unprotected large ganglion cells can show marked variations in reaction, even in the same neural nucleus. Some will disintegrate very soon, while others will remain completely sound for a long time. If we connect with satellitism the idea of protection against fatal irritations, then it is surprising why in anthrax in which the agent acts especially intensively we are always finding satellites in such a good condition. And yet, the process is related to the degree of virulence, for after vaccination the glial reaction is generally less intensive than after infection with virulent contagion, while the damage also has a definite effect.

In connection with this, it is important to quote the opinion of CRUVEILHIER, NICOLAU and KOPCIOWSKA. At rabies vaccination, they found an increased pseudoneuronophagy in addition to the ganglion reactions which according to the description must be also of regressive nature, although they assert that they never saw degenerated neurons. Therefore, they considered the symptoms as signs not of disintegration but of defense. According to them, the nervous system is suppose to intermingle in the defense system of the organism by paraspecific repression of the contagion. In this regard, their opinion is in agreement with that of METALNIKOFF which also assumes a connection between immunity and reaction of the nervous system. According to these authors, the cerebral reaction is supposed to mean nothing else but the recruiting of more intensified defense processes in the organism.

This opinion is the more acceptable, when we consider that the CNS is till the place by which the processes of life are regulated. The vegetative processes which undergo a thorough modification in infectious diseases adjust themselves to the changed organismic situation under the impulses which are issued from the sympathicus and parasympathicus. The activity of the endocrine glands, the combination of the chemical and cellular elements of the blood condition, the behavior of the red and white blood cells mutually, and their absolute number, the elimination of the poisons accumulated in the organism, the total metabolism and nutritional setup are all reactions upon stimuli which originate in the vegetative centers. Upon the harmonious and favorable course of all these processes, the defensive ability of the organism against the arising infections will depend. Nevertheless, the connection between the observed histological reactions and the effect upon the defense capacity against infections is still not clear. Why in anthrax motor paralyses of the skeletal muscles are not regularly found, in view of the changes of the C.N.S., is still not clear. It is also sure that the large vegetative cerebral centers are affected and the the anthrax appears predominantly as an affection of the autonomous system, and the clinical symptoms of the disease on the organs are the sequelae of the interrupted equilibrium between the sympathetic and parasympathetic systems, which bears the regulation of the unconscious functions of life.

CONCLUSION FOR THE PRACTICE

The examination of the nervous system in anthrax leads to the following considerations which give a better insight into some problems of the practice.

In anthrax, the degeneration of the neural elements does not proceed evenly in all parts, not even in the same neural nuclei, and the arrival of death should depend upon the localization, the tempo, the intensity and the extent of the appearance of the destructions. The respiratory center is histologically not represented by a group of ganglion cells, nevertheless there is no doubt that lesion of this center causes the sudden death. No other center comes in consideration, in connection with the blood findings, which could be responsible with its functional disorder for such a rapid appearance of death.

With tetanus as a neurotropic disease, anthrax has it common that no result is gained from a curative serum therapy, since the vital centers are already affected. That the results with specific anthrax serum can be so multiform and that the curative action is the better the earlier it is administered is completely explainable from this fact. Thus, 100 cc serum when administered in time can have a striking effect, while a dose of more than a liter, given too late, cannot save the life of the animals.

ANAPHYLAXIS.

It is not the purpose of the examination to give an explanation concerning the essence of true anaphylaxis, for no histological basis could explain what individual hypersensitivity can accomplish. The symptoms of anaphylactic shock alone, which PLESSOW describes, point out that this rests upon a stimulation of the C.N.S. Excitement, stamping, licking itself (itching), urticaria, swollen eyelids and face, salivation, cough, polypnea, cyanosis, dullness, weakness of heart and meteorism, which symptoms are supplemented by SCHELS with symptoms of choking and extensive edemas, are all the sequelae of stimulation or paralysis of those neural centers which at the start of the investigation (at the first part of this study) have been recapitulated.

POSTVACCINAL INOCULATION REACTION.

In anthrax vaccination, a series of unwanted inoculation reactions may occur which can very seriously harm the popular acceptance of this type of disease prevention. According to intensity and type, these are dependent upon the type species of animal and upon the individual. The goat is the most sensitive among the domestic animals, then comes the horse, while the sheep, cattle and buffalo show less susceptibility in this respect. In its most frequently occurring form, the inoculation reaction appears as a painless

swelling of the skin which can be demonstrated after a few days to a month either as a limited local edema, at which the temperature and the appetite remain normal, or associated with general symptoms such as fever, disturbed appetite, constipation. The large swellings should be somewhat later develop than the smaller ones. Not only can they start out from the site of inoculation, but they can occur also on extensive parts of the skin; at which then the swollen areas are separated by normal parts. Rabbits are supposed to illustrate this picture well. Horses after inoculation will sometimes suffer on the neck surface on extensive edemas which extend from the chest and forelegs to the throat, swollen eyelids, stasis, and quickened breathing. Definite dyspnea has not been described in India after anthrax vaccination. In buffaloes at Celebes, blue discoloration of the abdominal skin was seen.

The edemata can be sterile, and trials to demonstrated bacilli in them were unsuccessful. Serum injections also do not have any success in such cases.

Concerning the probability of the occurrence of postvaccinal inoculation reactions nothing can be said in advance. QUIN points out that in the laboratory the vaccine can look completely harmless, and yet in the practice it may give opportunity to complications. Sometimes, small or strongly diluted doses make much more serious symptoms than larger doses. QUIN has seen with the use of the same vaccine among horses in a certain herd that inoculation swellings occurred in a region, which were absent in another herd and at other land area. VILJOEN, CURSON, and FOURIE have found that sometimes after the first large dose of vaccine which the animals received they die on a subsequent injection of a small amount of contagion, while others are able to take a large amount of virulent bacilli without any difficulty after a small dose of vaccine. Here seems to be a paradoxically incomplete immunizing action as complication.

From the results of the examination of the whole nervous system, a logical united explanation can be drawn for all these findings. The histological findings have shown that neural lesions can occur both by the infection with a virulent strain and by vaccination; these lesions are the more intensive the larger is the virulence and administered dosage. The passage through an infection with very virulent strains will not necessarily create an increased defense against its repetition. Thus, according to SEKIER, the degree of virulence and the immunizing ability of an anthrax bacillus are wholly different qualities. MAZZUCHI also sees that very virulent strains will sometimes not kill the rabbits, yet the overcoming of the infection had not left the smallest immunity after itself.

These otherwise well and generally known facts were again tested at our laboratory. Although the below following results are supposed to be treated in a following later publication, for the sake of illustration here are given preliminary communications. From a series of rabbits, which were infected with the very virulent Poerwakarta anthrax strain, some remained alive, either with the help of specific serum, or in an unexplainable spontaneous manner, as MAZZUCHI has already also found. What is remarkable in this not very small number of cases is the fact that due to the passage through the infection the defensive ability is not increased, but rather it is diminished, for the second fatally acting infective dose is much smaller in some cases than the first, and is in itself harmless for the normal rabbits. They tolerate 1 cc B.A.S. vaccine, and certainly higher doses of the much weaker P.G.V.vaccine, without difficulty, while in the below following cases a small amount is lethal.

All these animals died from definite anthrax. Increased defense could never be found; up until the present the resistance against a repeated inoculation always seemed to be diminished. We should be able to quote that the simultaneous inoculation with serum did not let the infective dose come to its effect, but then it should be still remarked that the animals kept so alive are derived from a series in which, with the exception of these few, none did die with the same treatment. Moreover, with purpose the infective dose was taken so large that it could not be assumed that the elaboration of such a large amount of contagion could have been done without the active

collaboration of the organism. On the contrary, for the diminished defense a very plausible reason can be given. This is explainable with a cumulative action of the agent. Since a virulent anthrax strain is unable to provoke immunity, in the first infection the nervous system is surely attacked, but not sufficiently to result in death. By the imperfect immunization, a cumulation can take place indeed, and at the second much milder infection, even with an attenuated contagion, the destructive action of the first dosage of contagion is continued, whereby vital nerve centers can be so devastated that death comes.

Rabbit No.	Date of inoculation	Dosage of Poorvakarta strain	Died (date)
886	14 Dec. 35'	100 M.L.D.	
	28 Jan. 36'	100 M.L.D.	29 Jan. 36'
87	28 Jan. 36'	1 M.L.D.	
	10 Feb. 36'	1 M.L.D.	12 Feb. 36'
89	28 Jan. 36'	1 M.L.D.	
	10 Feb. 36'	1 M.L.D.	12 Feb. 36'
207	18 Feb. 36'	100 M.L.D. + 6 cc serum	
	31 Mar. 36'	0.5 M.L.D.	5 Apr. 36'
254	3 Mar. 36'	100 M.L.D. + 1 cc serum	26 Mar. 36'
	24 Mar. 36'	1 M.L.D.	
215	19 Feb. 36'	100 M.L.D. + 4 cc serum	
	24 Mar 36'	1 M.L.D.	27 Mar. 36'
208	18 Feb. 36'	100 M.L.D. + 2 cc serum	
	31 Mar. 36'	0.5 cc B.R.S. vaccine	8 Apr. 36'
212	18 Feb. 36'	100 M.L.D. + 5 cc serum	
	31 Mar 36'	0.5 cc B.R.S. vaccine	5 Apr. 36'
214	18 Feb. 36'	100 M.L.D. + 3 cc serum	
	31 Mar. 36'	1 cc P.G.V. vaccine	2 Apr. 36'
231	19 Feb. 36'	100 M.L.D.	
	24 Mar. 36'	1 cc B.R.S. vaccine	30 Mar 36'
172	10 Feb. 36'	100 M.L.D.	
	21 Feb. 36'	1 cc B.R.S. vaccine	25 Feb. 36'
341	13 May 36'	1 M.L.D.	
	9 June 36'	1 cc B.R.S. vaccine	14 June 36'

Since death itself can come in this manner, how much easier can then the many harmless inoculation reactions develop. In anthrax areas, some animals are supposed to have opportunity to pass through a not fatal infection which perhaps did not result in any serious clinically demonstrable symptoms, yet it could have produced a certain degree of neural lesions. Where pathological changes on the part of the sympathicus ganglia can be demonstrated in anthrax, a sympathicus disturbance due to a cumulative action can be easily explained in a subsequent infection or vaccination.

The vasoconstrictors which are under tonus, can lose this entirely or partially as the central or peripheral sympathicus centers lose their control over them. MULLER also points out that, at the tonus change of the sympathicus, not all symptoms of the pathological picture appear simultaneously. The lability in the system alternates strongly, and so in the various regions of the sympathetic the tonus can show varieties. In the ganglion cells which once were affected by degneration, a regeneration is not possible, although antagonistic cell groups can bring a certain rather high functional compensation. The lability of the vegetative innervation is thereby indeed increased so that equilibrium imbalances will occur much more easily. As to its expansion, it supposedly depends upon the extent of the functional paralysis, while retrograde nerual palsies can be hinted also by the increasing extent of the edemata. Just the fact that one cannot find any bacteria, points to a functional vasomotor disturbance. Thus the edemata at far remote skin areas can be also explained as a more centrally occurring cumulative paralysis. That the administration of specific serum in this stage does not help any longer, is obvious, for the disturbed function is the result of the fact that the neural elements have absorbed harmful circulating substances, and they underwent protoplasma changes which by a later administration of antibodies could not be undone any more. If disturbances have not yet advanced too much, then results can still be expected from such stimul which can again restore the t[illegible]as displacement, i.e., local application of could (douche, regrigerating substances) or injection of adrenaline.

Postvaccinal inoculation reactions rest very probably upon cumulative action of the mysterious anthrax toxin. Even where they occur after the first vaccination, let it be that it is an individual hypersensitivity or anaphylaxis, an earlier natural infection could have already prepared the neural centers. It depends however now upon how far the primary lesions have progressed, or the inoculation reactions are more or less extended or serious. The vaccine can appear completely harmless in the laboratory, and yet in the practice it can bring unexpected and unwanted symptoms. That even small and diluted doses of vaccine sometimes give more intensive reactions, depends upon the stage of preparation by the primary cause. The fact that in well-known anthrax areas the results can be the most fatal is thus quite understandable, and that a susceptibility is localized at certain areas and in certain herds, is explained not from the composition and strength of the vaccine but it is in connection with the cause which acts jointly in the area and/or in the herdn i.e., the degree of the preparation of the nervous system. They are then not necessarily limited to the vasomotor disorders, but the post vaccinal inoculation reactions can also cause, of course, other functional vegetative lesions, such as tachypnea and tachycardia, constipation, meteorism, ataxia, and so on.

Herewith, the observation of VILJOEN et al. is also explained who stated that a larger dose of vaccine sometimes does not protect against a subsequent weak infection. Rather, the large vaccine doses can harm the neural centra which may show intensive changes microscopically. What is perhaps gained on the one side by the provocation with a larger concentration of immune substances is destroyed on the other side by the destruction of vital neural elements. The bizarrness of the total reaction picture is the result of the fact that the tissue destruction takes place so unevenly in the nervous system, and moreover at the tonus changes in the sympathicus and parasympathicus not all symptoms of a disorder used to occur simultaneously.

COMPARATIVE HISTOPATHOLOGIC INVESTIGATION

TETANUS.

The material for the brain examination is obtained from two guines-pigs, one rabbit and a horse. The horse and the guinea-pigs were killed at the appearance of definitely observable symptoms of the disease. The rabbit, which was infected with a dose of tetanus culture whose amount corresponds to 1000 M.L.D. of the guinea-pih, was killed within 24 hours, to compare the pathological changes in this stage with thos of anthrax at the same period. In the horse and the guinea pig, the hyperemia and the edema of the whole CNS are striking. Glial proliferation is visible chiefly in the white substance and

and it is questionable in the area of the ganglion cells. Certainly, we find in the medulla oblongata satellitism in connection with the small ganglion cells. The degenerative processes of the neural cells show everywhere much agreement with those described in anthrax, among which the peripheral cellular colliquation and the severance of the dendrits attract attention.

The rabbit shows the histological picture of a beginning reaction, without any serious neural lesions having come to a full development. If we compare this stage in the pathological process with that in anthrax in the same period of infection, yet provoked with only a dose of 1 M.L.D. of the contagion, then the neurotropic nature of the anthrax process seems to be definite, at which its malignancy comes especially to expression. More than in other diseases, the pathological cell pictures are in agreement, at which the intensity of the lesions in the brain and the cerebellum in tetanus exceeds those in anthrax, nevertheless in the latter the ganglion destruction in the medulla oblongata is evidently stronger. Even from the much stronger regressive glial reactions in anthrax, the harmfulness of the agent is apparent for the organism.

RABIES.

To be able to compare the histo-pathological picture in the brain of this neurotropic disease with that of anthrax, three rabbits were infected intramuscularly with rabies material, and killed at the first appearance of the clinical symptoms, after three weeks.

A fundamental difference from anthrax is in the formation of perivascular lymphocytic concentration which speak definitely against the last mentioned disease. A slight glial multiplication is found mostly in the cerebral cortex, and a definite difference from anthrax is the almost total lack of satellitism in the medulla oblongata, and of regressive phenomena on the glial cells. Although convincing pictures of ganglion disintegration occur in all parts, yet there are found no forms of vehement cellular destruction, vacuolization and colliquation. Even in the cerebellum the loss of neural cells is visibly less. In general, the course of anthrax encephalitis is much more malignant than that of rabies.

RAUSCHBRAND.

From two guinea-pigs and a calf the CNS was fixed for examination immediately after the death of the animals. All have been infected intramuscularly and died within 24 hours on its consequences. The typical rauschbrand swellin in the guinea-pig spread over the whole rear half of the body, while in the calf it took the whole back portion. Although thus an enormous bacterial process permits to suspect an intensive reaction on the part of the nervous system, the histological picture did not agree with the expectation. Only in the guinea-pig is it possible to find a hint of a circulatory disorder as a slight dilation of the lymphatic capillaries. Small-cellular infiltrations are entirely absent. The glial reaction is much less than in anthrax, and a progressive multiplication is noticeable only in the medulla oblongata among the satellites of the small ganglion cells. The disintegration of the neural cells in the entire nervous system is much less than in anthrax. The cerebellum in this respect had somewhat more suffered than the cerebrum. The most intensive degeneration was found in the medulla oblongata, nevertheless nowhere are found vacuolization or colliquation of the ganglion cells, which can characterize the tissue picture of anthrax.

HAEMORRHAGIC SEPTICEMIA.

The material of examination in this disease was acquired exclusivelyfrom rabbits which died within 24 hours after the infection. The histo-pathological picture was dominated by the enormous symptons of stasis and edema of the entire CNS. Glial reactions are absent, while small-cellular infiltrations are not found at all. Without showing the variety of pathological cellular changes as described in anthrax, the disintegration of the ganglion cells is huge. Nevertheless, over the whole extension of the nervous system, the histological picture reminds us strongly of putrefaction. Shrinkage and swelling of the cells, with loss of protoplasm characteristics and of the staining ability in many cases give the tissue the appearance of an undefineable destruction without active cellular reaction, whereby the similarity with tissue

putrefaction becomes very large. Severe intoxications also bring on such tissue exhaustion or death, where reactions which point to resistance or defense are entirely missing. In no other respect is therefore the histological picture of the CNS in septicemia comparable with that of anthrax.

PICTURE APPENDIX

FIGURE 1: Vacuolized ganglion cells, medulla oblongata, rabbit. Smear preparation, Giemsa staining.

FIGURE 2: Large ganglion cells, medulla oblongata, Sheep No. 7. Severance of dendrits, fibrillary disintegration and formation of pericellular zone.

FIGURE 3: Marked vacuolization in five large ganglion cells, medulla oblongata, perkutut (dove). K = residue of necleus.