BOTULISM.

STUDIES ON THE MANNER IN WHICH THE TOXIN OF CLOSTRIDIUM BOTULINUM ACTS UPON THE BODY.

II. THE EFFECT UPON THE VOLUNTARY NERVOUS SYSTEM.*

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PLATE 24.

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In a previous report (1) it was shown that the botulinus toxin produces a peculiar blocking of nerve impulses in the parasympathetic fibers which have been described by Gaskell (2) as the prosomatic and bulbosacral outflows of connector fibers of the involuntary nervous system, but that the true sympathetic fibers, the thoracolumbar outflow, are not affected. As will be shown later in this report this blocking of nerve impulses adequately explains many of the clinical manifestations of botulism but there are certain other symptoms and signs which cannot be so explained.

Preliminary experiments by one of us (3) had shown that there is no apparent damage to the cell protoplasm when various bacteria, strips of frog pharynges, frog gastrocnemius muscles, or guinea pig muscles are immersed into the filtrate of a broth culture of Clostridium botulinum which contains a virulent toxin, and that if corresponding excised thigh muscles of normal guinea pigs and guinea pigs which have been poisoned with botulinus toxin are stimulated directly by repeated tetanizing stimulations, no difference can be demonstrated in the sen-

* These experiments are a part of an investigation of botulism which was made in California by the United States Public Health Service, Stanford University, and the University of California under a grant from the National Canners' Association, the Canners' League of California, and the California Olive Association.
sitiveness of the muscles to the stimulation or in their resistance to fatigue (Fig. 1).

In connection with the study of the effect of vagus stimulation upon intestinal movements (1) it was found that the direct application of barium chloride to the intestines of botulism cats results in as active response as is obtained in normal animals, that cut strips of the intestines of animals which are in the last stages of botulinus intoxication react as normal strips when placed in warm oxygenated Ringer's solution, and that immediately after death the intestinal movements of botulism animals are the same as are observed in normal animals.

From these observations it was concluded that the disturbances in function of the muscles are not dependent upon direct damage to the muscle cell but must lie somewhere in the nerve tract by which nerve impulses are conducted to it. A series of experiments was therefore undertaken to ascertain whether there is any obstruction to the passage of nerve impulses in the nerves which supply the skeletal muscles which is analogous to that observed in the parasympathetic fibers of the autonomic nervous system.

EXPERIMENTAL.

I. Experiments to Ascertain Whether There Is Any Blocking of Impulses from the Motor Area of the Brain.

Four normal animals, two rabbits and two cats, and six botulism animals, four rabbits and two cats, were used in these experiments. All observations were made when the animals were under ether anesthesia.

Trephine openings were made in the skull and the cerebral motor areas were stimulated by the unipolar method of stimulation. The stimulating current was obtained from a DuBois-Rémy induction coil with the secondary coil kept constantly at 10 cm. Care was taken to maintain the conditions of the experiment as nearly uniform as possible in all instances.

It was found that movements of the extremities, of the muscles of the neck and trunk, and of the upper eyelids were obtained as readily in botulism animals as in normal animals.

II. Experiments to Ascertain the Threshold of Stimulation in a Skeletal Motor Nerve.

Porter (4) applied Martin's method of determining the intensity of nerve stimulus (5) to a study of the threshold of stimulation in the radial nerve for extension of the wrist. His technique was closely followed.
Decerebrated cats were used in these experiments. The dorsal interosseous nerve was exposed, ligated, and cut, and a Sherrington electrode was applied distal to the point of section. Movements of the wrist were recorded by a light lever which was attached to the toes by a thread. The threshold readings were obtained in the manner described previously (1).

The results of the experiments are shown in Table I. The values obtained for normal animals and for botulism animals show little difference and both fall within the limits of normal variation recorded in Porter's series.

<table>
<thead>
<tr>
<th>Table I.</th>
<th>Threshold of Stimulation in a Motor Nerve (Dorsal Interosseous Branch of Radial) for Extension of the Wrist.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal animals.</td>
</tr>
<tr>
<td>Animal No.</td>
<td>Threshold in terms of Z units.</td>
</tr>
<tr>
<td>Cat N22</td>
<td>2.1</td>
</tr>
<tr>
<td>&quot; N23</td>
<td>1.8</td>
</tr>
<tr>
<td>&quot; N25</td>
<td>1.8</td>
</tr>
<tr>
<td>&quot; N26</td>
<td>3.9</td>
</tr>
<tr>
<td>Average</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Limits of variation in normal cats as established by Porter in observations upon 52 animals.

Maximum ....................................................... 6.0 Z
Minimum ........................................................ 0.6 "
Average ......................................................... 2.3 "

III. Experiments to Ascertain the Threshold of Stimulation in a Spinal Reflex.

Porter (6) also applied Martin's method to a study of the threshold of stimulation in the posterior tibial nerve for reflex flexion of the hind leg and recorded observations upon 66 animals.

Decerebrated cats were used in the experiments and the technique of Porter was closely followed. The posterior tibial nerve was exposed, isolated, ligated, and cut distal to the ligature. The proximal end was passed through a Sherrington electrode. The femur was fixed in a clamp and movements of the leg were recorded by a lever which was attached to the heel by a thread. The threshold of stimulation was obtained as in the other experiments.

As in the experiments described in a previous report all operative procedures were performed under deep anesthesia.
The results of the experiments are shown in Table II. Here again, there is little difference in the values obtained for normal animals and for botulism animals, and all the values lie within the limits of normal variation in Porter's series.

**TABLE II.**

*Threshold of Stimulation in a Motor Nerve (Posterior Tibial) for Reflex Flexion of the Posterior Extremity.*

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Threshold in terms of Z units.</th>
<th>Animal No.</th>
<th>Threshold in terms of Z units.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat N22</td>
<td>3.5</td>
<td>Cat B14</td>
<td>3.0</td>
</tr>
<tr>
<td>&quot; N23</td>
<td>4.5</td>
<td>&quot; B15</td>
<td>4.1</td>
</tr>
<tr>
<td>&quot; N25</td>
<td>2.8</td>
<td>&quot; B16</td>
<td>3.0</td>
</tr>
<tr>
<td>&quot; N26</td>
<td>4.8</td>
<td>&quot; B19</td>
<td>3.4</td>
</tr>
<tr>
<td>Average</td>
<td>3.9</td>
<td>Average</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Limits of variation in normal cats as established by Porter in observations upon 66 animals.
- Maximum ...................................................... 21.6 Z
- Minimum ....................................................... 0.7 "
- Average ........................................................ 5.2 "

**IV. Experiments to Ascertain the Threshold of Vasomotor Reflexes from Stimulation of Afferent Nerves.**

Martin and Lacey (7) have shown that:

"Reflex drop of blood pressure is the typical response in cats to sensory stimulation when the intensity of the stimulation is of the order of magnitude represented by the threshold for a spinal reflex of skeletal muscle. No difference in effect on blood-pressure was observed when different sensory nerves were stimulated. Radial, ulnar, median, sciatic, and saphenous nerves all gave pressure-drop under stimulation near the threshold."

Two series of observations were run in these experiments, one in which the animals were decerebrated and one in which they were under urethane anesthesia. Thresholds of stimulation were recorded on the sciatic, ulnar, radial, and saphenous nerves in the manner described by Martin and Lacey.

The results of the experiments are shown in Tables III and IV. In each series the average threshold of effective stimulation was approximately the same in normal and in botulism animals, and in each the values were well within the limits of normal variation which were recorded by Martin and Lacey.
TABLE III.

Threshold of Stimulation of Afferent Sensory Fibers for Depressor Effect upon the Blood Pressure. Decerebrated Cats.

<table>
<thead>
<tr>
<th>Nerve tested</th>
<th>Threshold in terms of Z units</th>
<th>Nerve tested</th>
<th>Threshold in terms of Z units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sciatic</td>
<td>4.9</td>
<td>Sciatic</td>
<td>8.5</td>
</tr>
<tr>
<td>Radial</td>
<td>6.4</td>
<td>Radial</td>
<td>1.6</td>
</tr>
<tr>
<td>&quot;</td>
<td>9.0</td>
<td>Saphenous</td>
<td>23.5</td>
</tr>
<tr>
<td>Saphenous</td>
<td>10.0</td>
<td>Ulnar</td>
<td>2.0</td>
</tr>
<tr>
<td>Ulnar</td>
<td>10.0</td>
<td>&quot;</td>
<td>13.2</td>
</tr>
<tr>
<td>&quot;</td>
<td>19.0</td>
<td>&quot;</td>
<td>16.0</td>
</tr>
<tr>
<td>Average</td>
<td>9.9</td>
<td>Average</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Parallel observations upon decerebrated normal cats recorded by Martin and Lacey.

Maximum ...................................................... 31.5 Z
Minimum ....................................................... 1.28 "
Average ......................................................... 8.7 "

TABLE IV.

Threshold of Stimulation of Afferent Sensory Fibers for Reflex Depressor Effect upon the Blood Pressure. Animals under Urethane Anesthesia.

<table>
<thead>
<tr>
<th>Nerve tested</th>
<th>Threshold in terms of Z units</th>
<th>Nerve tested</th>
<th>Threshold in terms of Z units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sciatic</td>
<td>16.0</td>
<td>Sciatic</td>
<td>16.0</td>
</tr>
<tr>
<td>&quot;</td>
<td>17.0</td>
<td>Ulnar</td>
<td>19.2</td>
</tr>
<tr>
<td>Ulnar</td>
<td>17.0</td>
<td>&quot;</td>
<td>22.0</td>
</tr>
<tr>
<td>&quot;</td>
<td>30.0</td>
<td>Radial</td>
<td>23.5</td>
</tr>
<tr>
<td>Radial</td>
<td>22.2</td>
<td>&quot;</td>
<td>21.1</td>
</tr>
<tr>
<td>&quot;</td>
<td>22.8</td>
<td>Saphenous</td>
<td>29.0</td>
</tr>
<tr>
<td>Saphenous</td>
<td>30.6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Average</td>
<td>22.2</td>
<td>Average</td>
<td>23.2</td>
</tr>
</tbody>
</table>

Parallel observations upon normal cats under urethane anesthesia recorded by Martin and Lacey.

Maximum ...................................................... 37.5 Z
Minimum ....................................................... 2.3 "
Average ......................................................... 15.3 "
V. Experiments to Ascertain the Threshold of Stimulation of the Somatic Motor Portions of the Third, Seventh, and Eleventh Cranial Nerves in Animals Whose Parasympathetic Fibers from the Same Nerves Showed a Marked Blocking of Impulse.

In the course of the experiments to ascertain the threshold of stimulation for contraction of the pupil by stimulation of the oculomotor nerve (1) observations were made to test the intensity of stimulus necessary in normal and in botulism animals to induce initial contraction of the extrinsic muscles of the eye to rotate the eyeball. The results of the experiments are shown in Table V.

**TABLE V.**

**Threshold of Stimulation of the Motor Fibers of the Oculomotor Nerve for Initial Contraction of the Extrinsic Muscles of the Eye (Rotation of the Eyeball).**

<table>
<thead>
<tr>
<th>Normal animals.</th>
<th>Animals with botulism intoxication.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal No.</td>
<td>Threshold in terms of Z units.</td>
</tr>
<tr>
<td>Cat N62</td>
<td>8.7</td>
</tr>
<tr>
<td>&quot; N58</td>
<td>11.6</td>
</tr>
<tr>
<td>&quot; N61</td>
<td>12.6</td>
</tr>
<tr>
<td>&quot; N54</td>
<td>14.3</td>
</tr>
<tr>
<td>&quot; N56</td>
<td>18.2</td>
</tr>
<tr>
<td>&quot; N52</td>
<td>20.0</td>
</tr>
<tr>
<td>&quot; N60</td>
<td>30.0</td>
</tr>
<tr>
<td>&quot; N50</td>
<td>32.6</td>
</tr>
<tr>
<td></td>
<td>Average...................</td>
</tr>
<tr>
<td></td>
<td>18.5</td>
</tr>
</tbody>
</table>

* For comparative readings of the thresholds of the parasympathetic fibers of the oculomotor nerve in these animals see Table VI in the previous report (1).

It was found that although there is a marked increase in the threshold of stimulation of the parasympathetic fibers of the third nerve in botulism animals (1) the intensity of stimulus necessary to rotate the eyeball in botulism animals is no greater than in normal animals.

Similar observations were made of the somatic motor portion of the spinal accessory nerve whose parasympathetic fibers are carried
over to the vagus nerve, and of the facial nerve whose parasympathetic fibers constitute the chorda tympani nerve. It was found that in botulism animals whose parasympathetic fibers show a marked increase in the threshold of stimulation (1) the intensity of stimulus necessary to induce movements of the muscles of the face upon stimulation of the facial nerve, and to draw the head towards the stimulated side upon stimulation of the branch of the spinal accessory nerve which supplies the trapezius muscle, is no greater than is required to produce the same effects in normal animals.

A survey of the results of these experiments shows that the somatic motor fibers of the cranial and skeletal nerves are not affected in the manner that has been demonstrated in the parasympathetic fibers of the prosomatic and bulbosacral outflows of connector fibers in the autonomic nervous system (1) but that impulses are transmitted as readily and initial muscle response to stimulation is as active in botulism animals as in normal animals under the conditions of the experiments. In fact, nothing was found in the experiments up to this point which indicated that the nerve supply of the skeletal muscles was in any way affected by the action of the botulinus toxin.

When, however, an attempt was made to correlate the results of these experiments with the clinical manifestations of botulism in human beings and in animals in which the poisoning had been experimentally produced, it was found that it was still impossible to explain all the signs and symptoms of the intoxication from the data which had been collected.

For example, it had been shown that the parasympathetic fibers of the oculomotor nerve are so damaged that there is a blocking of impulse to the intrinsic muscles of the eye which would fully explain the mydriasis and loss of pupillary reflex to light, but it was also shown that there is no interference to the passage of stimuli along the somatic fibers of the oculomotor nerve in botulism animals notwithstanding the fact that in botulism there are blepharoptosis, loss of ability to accommodate for near vision, and diplopia, all signs which have been attributed to paralysis of the oculomotor nerve. Again, the experiments also showed that there is no interference to the passage of stimuli along the somatic fibers of the spinal accessory nerve, whereas in botulism it is an exceedingly characteristic manifestation that victims of the poisoning, whether human, animal, or fowl, are unable to support the head.
It was apparent that although the experiments had shown that there is no true paralysis or blocking of impulse for initial contraction of the skeletal muscles in botulinus intoxication, they had not furnished any explanation for the marked muscular weakness, drooping of the eyelids in human victims and limber-neck in chickens, etc., which is characteristic of botulism. Further investigation was therefore indicated, and since it had been noted clinically that sometimes a botulism victim is able to raise the eyelids or an extremity once or twice but cannot repeat the act, it was decided to investigate whether fatigue might play a part in determining the symptom-complex of botulinus intoxication.

VI. Experiments to Determine Whether Fatigue Is an Essential Characteristic in botulinus Intoxication.

Decerebrated cats and rabbits were used in the experiments but only the results obtained in cats are included in this report. Identical results were, however, obtained with rabbits.

The method of procedure was similar to that described by Gruber (8) although minor modifications of his technique were introduced.

After the animals had been decerebrated a slit was made in the skin of the leg over the sciatic nerve and the peroneus communis nerve was exposed and separated from the tibialis nerve. The distal end of the cut peroneus communis nerve was passed through a Sherrington shielded electrode in which were two pairs of platinum wire electrodes, the points nearest the muscle being used for determining the threshold of stimulation at intervals, and those which were distal being used to convey the fatiguing stimulations.

The tendon of the tibialis anticus muscle was then severed from its insertion and was connected to a muscle lever by means of a strong thread which passed over a pulley so placed that the pull when the muscle contracted was in the normal direction. The foot and the upper part of the leg were firmly fixed to the animal board.

The muscle lever consisted of a pivoted metal bar which carried a writing point at one end and was provided with a spring support at the other, and the thread from the muscle tendon was attached to the lever immediately below the spring so that each contraction of the muscle would pull directly against it. The spring was adjusted so that the initial tension was approximately 100 gm., and the tension when the muscle contracted was from 120 to 150 gm.

The contractions of the muscle were recorded upon a slowly moving drum.

The fatiguing stimulations were obtained from a DuBois-Rémy induction coil with the secondary coil placed at a distance of 10 cm. from the closed position. The interruptions were obtained by a vibrating reed interrupter which was...
attached to a separate cell and inserted in the primary circuit. The rate of interruption was 6 per second. The terminals from the secondary coil were attached to the distal pair of points in the Sherrington electrode.

The threshold of stimulation was obtained at the beginning of the experiment and at stated intervals during the course by discontinuing the fatiguing stimulations and determining the intensity of stimulus necessary to induce initial contraction of the muscle with the calibrated inductorium as in the previous experiments, the terminals from the secondary coil of the calibrated inductorium being attached to the pair of points in the electrode which were proximal to the muscle. In this way the initial threshold estimation in each experiment served as the control for the experiment as it was obviously impossible to determine the normal threshold for each animal before it was injected with the toxin.

The results of the experiments are shown in Text-figs. 1 to 4. It was found that in normal cats it is possible to apply continuous fatiguing stimulations at the rate of 6 per second for 3 hours without...
TEXT-Fig. 2. Rate of onset of fatigue in a botulism animal as shown by the thresholds of stimulation for muscular contraction taken at regular intervals during the course of continuous fatiguing stimulations.

BOTULISM ANIMAL, CAT B 113
increasing the threshold of stimulation for muscular contraction (Text-fig. 1) but that in botulism animals, although the initial threshold is always within the limit of variation for normal animals, the thresholds for contractions of the muscle at intervals during the course of the fatiguing stimulations soon increase in value (Text-fig. 2). It was also found that when fatigue has developed in botulism animals, as indicated by the upward trend of the fatigue threshold curve, a

rest of considerable duration will cause the initial threshold after the rest to approach the normal but that the rise in threshold values is much more rapid when the fatiguing stimulations are renewed (Text-fig. 3).

An attempt was then made to ascertain whether the rapidity of onset of fatigue bears any relation to the stage or intensity of the \textit{botulinus} intoxication.
TEXT-FIG. 4. Comparison of the fatigue threshold curves obtained in a normal animal and in animals at varying intervals after the administration of equivalent amounts of botulinus toxin. a, normal animal, Cat N103; b, botulism animal, Cat B105, 24 hours after administration of toxin; c, botulism animal, Cat B106, 30 hours after administration of toxin; d, botulism animal, Cat B110, 40 hours after administration of toxin; e, botulism animal, Cat B113, 46 hours after administration of toxin.
Animals of approximately the same weight were selected and the fatigue threshold observations were made 24, 30, 40, and 46 hours, respectively, after the administration of an amount of toxin which was estimated to be sufficient to cause the death of the animals in about 48 hours. It was found that after an interval of 24 hours Cat B105 showed no signs of illness and the fatigue threshold curve showed no variation from normal, that after 30 hours Cat B106, which was weak in the hind legs but could still move about and eat, showed a gradual rise in the fatigue threshold curve, and that Cats B110 and B113, which were prostrate after 40 and 46 hours, respectively, showed a marked and rapid rise in the fatigue threshold curves (Text-fig. 4). There was little difference in the rate of the onset of fatigue in the last two animals.

DISCUSSION.

The results of the experiments which have been recorded in this and in our previous report (1) may be summarized as follows:

The action of the toxin of *Clostridium botulinum*, Type A or B, upon the nervous system is peripheral and not central. It affects the peripheral endings of the motor fibers of portions of the autonomic or involuntary nervous system and of the voluntary nervous system. It has not been ascertained whether the damage is located in the terminal nerve endings or in the myoneural junction, and the type of damage is unknown save that it is not of the nature of an organic destruction of tissue. There is no demonstrable change in the muscle cells of striated or smooth muscle.

The effect of the toxin upon the autonomic nervous system is confined to the motor and secretory fibers which constitute the parasympathetic system, described by Gaskell (2) as the prosomatic and bulbosacral outflows of connector fibers, and results in a relatively unstable blocking of nerve impulses which is manifested by disturbed function but not true paralysis of the muscles which they supply. The fibers of the sympathetic system, the thoracicolumbar outflow of Gaskell, are not affected.

The effect upon the voluntary nervous system is apparently less severe since the initial response to stimulation of the motor nerve fibers of this type is as active as is observed in normal animals, but when repeated stimulations are applied to these nerves there is a rapid and progressive fatigue which is manifested by the progressive rise in the values of the threshold of stimulation for muscular contraction.
which is proportional to the intensity of the intoxication. The sensory fibers of the peripheral nerves and the reflex arcs are not affected.

In discussing the symptoms and signs of *botulinus* intoxication with reference to these findings it must be remembered that the manifestations which are typically those of botulism do not, as a rule, appear until after 18 to 24 hours have elapsed after the ingestion of the poison. The early nausea and vomiting, sometimes with diarrhea, which are observed in about one-third of the cases, are probably caused by the local action of the spoiled food in the gastrointestinal tract and not by the action of the toxin itself. This conclusion is based upon the fact that the majority of the human victims of botulism and practically all animals in which the poisoning is produced by feeding do not show signs of acute gastrointestinal disturbance, and that invariably these symptoms disappear with the onset of the true symptoms of the poisoning.

We believe that all the characteristic signs and symptoms of *botulinus* intoxication may be explained on the basis of the observations made in our experiments although it must be repeated that the actual cause has not been determined because the nature of the interference with conduction of nerve impulses has not been ascertained. In discussing them the course of a typical case of botulism will be followed and the probable cause described.

Among the earliest, and often the first indications of *botulinus* intoxication in human beings are disturbances of vision which include dimness of vision, mydriasis, loss of accommodation for near vision, diplopia, loss of pupillary reflex to light, nystagmus which is sometimes unilateral, photophobia, blepharoptosis, and vertigo.

Mydriasis, loss of accommodation, and loss of the pupillary reflex to light may all be caused by the blocking of impulses in the parasympathetic fibers of the oculomotor nerves and the photophobia is due to the persistent dilatation of the pupils as long as they are not covered by the drooping upper lid. Mydriasis is more marked because of the persisting function of the sympathetic fibers.

Vertigo is probably caused by the attempts to accommodate.

Dimness of vision may be partly due to the disturbance of accommodation but is more probably the early result of imbalance of the extrinsic muscles of the eyeball which is caused by susceptibility to fatigue in the endings of the somatic fibers.

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Throughout this discussion where the phrase "in the nerve endings" is employed, no differentiation is implied between the anatomical terminal endings of the nerve fibers and the myoneural junction.
fibers of the third, fourth, and sixth cranial nerves which ultimately leads to diplopia and occasionally immobility of the eyeball. Blepharoptosis may be caused by susceptibility to fatigue in the somatic nerve supply of the branch of the oculomotor nerve which supplies the upper lid, and nystagmus is caused by the imbalance of the extrinsic muscles.

Closely following the disturbances of vision there is usually difficulty in talking and in swallowing, the tongue movements are sluggish, the mouth is dry, and the patient suffers from the accumulation of thick mucus in the pharynx.

Dryness of the mouth is due to an inhibition of the serous portions of the saliva caused by the blocking of impulses in the parasympathetic secretory fibers of the chorda tympani and glossopharyngeal nerves, and the accumulation of thick mucus is due to the persistent function of the sympathetic fibers which supply the salivary mucus glands.

The sluggish movements of the tongue may be due to susceptibility to fatigue in the endings of the somatic motor fibers of the glossopharyngeal and hypoglossal nerves and the sensation of enlargement of the tongue is due to the relaxed, atonic condition of its muscle fibers.

Difficulty in swallowing is partly due to the dryness of the mouth and pharynx but impaired function of the muscles of the pharynx must also play a part. This may be due to susceptibility to fatigue in the nerve endings of the somatic motor fibers of the ninth and tenth cranial nerves. That there is no true paralysis is indicated by the fact that the accumulation of mucus or attempts to swallow may induce severe strangling spells.

The earlier stages of difficulty in talking are undoubtedly due to the impaired movements of the tongue since at first the voice sounds remain but the patient cannot pronounce certain words; eventually, however, the voice sounds disappear and the patient can neither articulate nor phonate. At this stage susceptibility to fatigue in the endings of the somatic motor fibers of the vagus and possibly also of the hypoglossal nerves would explain the loss of function in the larynx. The fact that in milder cases of botulism the patient becomes progressively more husky and less easily understood if he continues to talk indicates that it is fatigue and not paralysis which is responsible for the disturbance in function.

Botulism differs from the usual types of food poisoning in that, instead of the occurrence of acute gastrointestinal disturbances, there is inhibition in the movements of the stomach and intestines so that retention of food materials in the stomach and persistent constipation are characteristic of the intoxication. It is probable that the absence of moisture and the presence of thick mucus in the bowel may play some part in causing the constipation but there is no doubt that the most important factor is the blocking of motor impulses in the parasympathetic fibers of the vagus and pelvic nerves which respectively supply the upper and lower portions of the gastrointestinal tract.

A sensation of fatigue and of general muscular weakness is an early manifestation of botulism and progressive weakness which is especially noticeable in the neck and in the extremities is characteristic of the intoxication. In cases
of mild intoxication the victims complain that they are unable to masticate their food because of weakness of the jaws and not infrequently the face has an expressionless appearance because of the relaxed tone of the facial muscles. In the typical severe case the patient lies helpless in the bed with the muscles relaxed in a manner not unlike that seen when under deep general anesthesia, but although the condition may be so severe as to simulate paralysis, it is characteristic that the deep reflexes are intact and that the patient may be able to initiate effective muscular contraction to open the eyes or raise the head or an extremity once or twice although he cannot repeat the act.

All these phenomena may be explained on the basis of susceptibility to fatigue in the nerve endings of the motor fibers which supply the skeletal muscles, and it is significant that in those portions of the body where sustained muscular action is necessary to maintain the normal position of the part—the upper eyelid in man and the head and neck in fowl and quadruped animals—failure of function in these parts occurs early in the course of the intoxication.

Inhibition of many of the secretions is also characteristic of botulism and reference has already been made to the absence of the serous portion of the saliva. It has been reported (9) that, especially in animals, there may be a salivation instead of an inhibition of saliva, but this has not been observed in any of our human cases or in our experimental animals. It has been noted in our experiments that the animals may continue to champ the jaws, apparently in the attempt to free the mouth from thick mucus, and it is our opinion that it was this and not a true salivation which was the cause of the apparent dribbling in the cases which have been reported.

It has been reported that inhibition of the secretion of urine is characteristic of botulism but we believe that this is not strictly correct. It is true that because the patient is unable to swallow the water intake is greatly restricted and the urine output is correspondingly decreased, but there is no evidence that there is cessation of kidney function. There may be retention of urine in the bladder, however, and the reason for this is suggested by the failure to induce contraction of the wall of the bladder by stimulation of the parasympathetic fibers of the pelvic nerve.

There is lack of uniformity in the reports of human victims of botulism in as far as the secretion of the sweat glands is concerned. In the earlier literature it was stated that there is inhibition of sweat secretion and that the skin becomes hard and dry but in our series of cases there have been a few instances in which the patients were bathed in perspiration late in the course of the intoxication. It is impossible to correlate these observations with the results of the experiments since, anatomically, the sweat glands obtain their nerve supply from the sympathetic system and our experiments show no effect of botulinus toxin upon the sympathetic fibers. However, it is of interest that in the experiments with acetyl choline Dale (10) observed that the effect upon the sweat glands was one of the chief exceptions to the general parasympathetic action of the drug.
The initial slow pulse rate in botulism and the rapid pulse which is characteristic of the later stages of the intoxication are fully explained by the experiments upon the cats in various stages of the poisoning. The experiments showed that in the first 24 hours of the intoxication there is no disturbance of the transmission of inhibiting impulses through the vagus nerves but that after that time the threshold of stimulation for inhibition of the heart rate is greatly increased.

When death occurs from cardiac failure the heart muscle is found to be relaxed and flabby and it is probable that it ceased its action because of fatigue.

In the early stages of botulism there is no disturbance of respiration beyond what may be explained by the psychic response of the victim who is often excited and apprehensive as to the outcome of his illness, but in the later stages of the intoxication breathing becomes labored and all the accessory muscles of respiration are brought into play. Toward the end in fatal cases there may be indications of asphyxia and sometimes there is Cheyne-Stokes respiration, both dependent upon the combination of disturbed respiration and impaired heart action.

The respiratory distress may be explained by a loss of the controlling influence of the vagus nerves upon respiratory movements, and when death occurs from respiratory failure it is undoubtedly due to the fact that because of a susceptibility to fatigue in the nerve endings which supply them, the accessory muscles of respiration are unable to maintain their function. Fischer (11) has shown that the diaphragm ceases to function before the accessory muscles of the chest.

There is no indication that the subnormal temperature in botulism is in any way directly dependent upon disturbance of the nervous mechanism of temperature control since when patients who have shown the typical subnormal temperature throughout the course of the intoxication develop insufflation bronchopneumonia the temperature promptly rises. It is probable that the subnormal temperature is dependent upon the condition of general muscular relaxation and inactivity although it is possible that there may also be some underlying factor, perhaps some insufficiency of the ductless glands, which is the primary cause of the disturbance of function in the nerve endings as well as of the lowered body metabolism.

The maintenance of normal blood pressure, the persistence of secretion of the mucus portion of the saliva, and the extreme dilatation of the pupils suggest that, as in the experiments, the sympathetic system is not involved; and the absence of any demonstrable variations from normal in the cerebrospinal fluid may be construed as indicating that there is no gross change in the tissues of the central nervous system.

Clinically, as well as in the experiments, there is no disturbance of sensory function in botulism, and it is characteristic of the intoxication that the victims show no disturbance of mentality so long as the functions of circulation and respiration are maintained.
It is not the purpose of these reports to discuss the treatment of botulism, but there is one group of observations which should be mentioned in connection with the administration of botulinus antitoxin.

In a previous report (12) it was noted that when guinea pigs are injected with a sufficient amount of toxin to cause their death in about 48 hours, the administration of antitoxin within 24 hours after the toxin will enable them to survive, but that if the antitoxin is delayed beyond that interval they will succumb. The results of the experiments\(^1\) outlined in a previous report (1) and in Text-fig. 4 of this report are of interest in this connection because they show that there is no demonstrable interference with the conduction of impulses in the parasympathetic fibers and no increased susceptibility to fatigue in the somatic motor nerves within 24 hours in botulinus cats but that in 30 hours disturbances in function can be demonstrated and that after that time they are marked.

There can be no doubt that the peculiar relationship which exists between the results of these three sets of experiments is not merely coincidence. The indications are plain that up to a certain time, under the conditions of the experiments 24 hours, the botulinus toxin is not so bound to the tissues that disturbances in function can be demonstrated by the methods used in the experiments, and that during this interval it is possible to counteract its influence by the administration of antitoxin, but that after that interval has elapsed the toxin is so bound with the tissues that disturbances in function can be demonstrated and that when this is true the administration of antitoxin does not neutralize its effect. This corresponds with what was observed clinically because in the experiments the animals had not shown any definite indication of illness up to 24 hours after the administration of the toxin. It also suggests a reasonable explanation for the fact that in the treatment of human victims of botulism the administration of antitoxin after the onset of symptoms has not proved to be of any value.

The conception that botulinus toxin exerts its action peripherally and not directly upon the central nervous system was first expressed in 1877 by Pürcckhauer (13) who based his conclusions upon clinical observation. More recently Schübel (14) has advanced a similar conclusion, his preliminary report being made within a few days of our

\(^1\) Dickson and Shevky (1), Table II.
own (15). His experiments were performed upon frogs and certain invertebrate forms and he found that frog muscle does not undergo any change after a chronic intoxication of several weeks, and that there is a peripheral action upon the end-plates of the nerves which he describes as simulating that produced by curare. In addition to the peripheral action of the botulinus toxin Schübel describes degeneration in the spinal cord of frogs, a process which we have been unable to demonstrate in our experiments with warm-blooded animals.

CONCLUSIONS.

1. In addition to the effect upon the fibers of the parasympathetic nervous system which was described in a previous report (1), the toxin of Clostridium botulinum, Types A and B, exerts an influence upon the endings of the motor fibers of the voluntary nervous system which leads to a marked susceptibility to fatigue. It has not been determined whether the damage is in the anatomical nerve endings of the somatic motor nerve fibers or upon the myoneural junction, but it is not of the nature of an organic destruction of tissue.

2. There is no effect upon the sensory fibers of the peripheral nerves.

3. The muscle cells of the smooth and striated muscles are not affected.

4. The disturbances in function which have been demonstrated in the voluntary and involuntary nervous systems fully explain the characteristic signs and symptoms of botulinus intoxication.

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EXPLANATION OF PLATE 24.

Fig. 1. Tracings showing the rate of onset of fatigue in excised thigh muscles of two guinea pigs of equal weight, one of which was in the later stages of *botulinus* intoxication (Type A). Stimulations were applied directly to the muscles at the rate of 40 per minute. The break in the indicator record denotes a period of rest of 5 minutes. The muscles were suspended in aerated modified Locke’s solution which was maintained at body temperature.