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AN ANATOMICAL ANALYSIS OF THE
EFFECTS OF ETHER ANESTHESIA ON THE NERVE CELL

by

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INTRODUCTION

Stimuli are either excitant or depressant. It is pointed out by Verworn, to quote from his General Physiology, that "the same stimuli which with slight intensity or short duration produce excitation, with increased intensity or long duration can produce entirely the opposite effect, namely, depression." As a well known example he cites morphine, heat stimulation, and the anesthetics, although it has been shown that their essential effect is depression. A considerable amount of original experimental research has been carried on in this laboratory during the last five years on the changes in the nerve cells resulting from many forms and kinds of stimulation, both normal and abnormal excitant and depressant. The changes in the nerve cell produced by morphine and heat stimulation as well as other depressants have already been studied in this laboratory but no experiments have been made up to this time as regards the effects of the anesthetics. The experiments on morphine and heat stimulation proved that the statement of Verworn was correct as regards nerve cells. It would also be expected from the physiological action of the anesthetics that they would act in a similar way.

In this investigation the writer has attempted to ascertain whether or not the anatomical changes produced by ether are similar to those produced by morphine and heat stimulation, namely slight excitation followed by depression.

The present experimental work has been devoted to the anatomical changes produced in the Purkinje cell, a most highly differentiated type of nerve cell. It is this type of nerve cell upon which most of the previous work in this laboratory has been done as it is the most suitable of nerve cells for general study. However, the lower primitive cell of spinal or sympathetic ganglia goes through the same sequence of changes as the higher and more differentiated cell of the cerebellum (Dolley, 1912). The only difference is that the higher cell is more easily and quickly exhausted. Therefore, deductions from any single nerve cell may be applied to all nerve cells.

A REVIEW OF THE ANATOMICAL CHANGES
IN THE NERVE CELL WHICH ARE PRODUCED BY
FUNCTIONAL ACTIVITY AND BY FUNCTIONAL DEPRESSION.

The two possibilities, activity and depression, are the only functional possibilities of the nerve cell. The cell does one of two things--it does work or it is inhibited from doing work.

There have been demonstrated certain definite anatomical changes produced in the nerve cell which correspond to these physiological conditions of the cell. It is necessary at this time to review the changes which occur during these conditions. This is done because of the fact that the correlation of the anatomical changes with physiological states of function is of recent origin and it is this interpretation of the changes which is used in the material examined by the writer.

It is necessarily important to review the anatomical changes due to functional activity before a clear conception of the changes due to depression can be obtained and for this reason they will be first considered.

The process of activity leading to exhaustion of the nerve cell has been analyzed from the evidence of a number of investigators (Hodge, 1892; Guerrini, 1899; Holmgren, 1900; Lugaro, 1895; Mann, 1895; and Vas, 1892). The work of Dolley (1909) established a sequence of stages and showed that

there is no break in the continuity of the process, and that the structural evidences of transition from stage to stage and the orderly shifts in the chromatin distribution of the cell, from an excessive amount to a very lessened amount, are distinct and definite.

It does not come within the scope of the present work to discuss the extent and nature of this evidence. The present discussion relates mainly to morphology, with a brief reference to the biological theories which were the working hypotheses for an interpretation.

The present classification, which divides the process into thirteen stages, is based fundamentally on the shifts of chromatin in the cell and on the size changes of the cell. Briefly stated, in terms of the chromatin distribution, the thirteen stages are as follows (Dolley, 1910) (Figures 1 to 13, pages 44 and 45).

1. The resting cell. It is lacking in intranuclear chromatin except within the karyosome (nucleolus) and the amount of extranuclear chromatin varies with the individual.

2. The stage of progressive hyperchromatin, in which, in the pure type, the initial enlargement of the whole cell reaches its maximum.

3. The stage of maximum hyperchromatism, which is associated with the beginning of shrinkage.

4 and 5. The stages of regressive hyperchromatism together with the maximum of shrinkage. Coincident in

place but separated originally to denote the differences in shape, Stage 4 being more attenuated and spindle. Both Stages 4 and 5 are to be further divided into an early, the pure Hodge type, and a late division, characterized by the sharp beginning of the nuclear edema.

6. The return of the cytoplasmic chromatin in its continued reduction to the average normal level. This stage is principally distinguished morphologically by the maximum disproportion in the size of the nucleus owing to its much greater edema.

7 and 8. The intermediate stages leading to the primary disappearance of the cytoplasmic chromatin.

9 and 10. The stages of secondary restoration of cytoplasmic chromatin. The chromatin is first piled about the nuclear membrane and then passes out.

11. The stage of secondary disappearance of cytoplasmic chromatin. With the complete using up of the previous supply, the karyosome is left containing the only vestige of basic chromatin in a much more exhausted looking cell.

12. The disintegration and passing out of the ultimate content contained within the karyosome.

13. The exhausted cell.

The interpretation of these stages has been made in terms of Hertwig's nucleus-plasma relation theory and his theory as to the origin of the chromatin, which is closely dependant (1903). This nucleus-plasma theory of Hertwig's,

briefly stated, is that for every cell there is a certain definite size relation between the nuclear mass and the cell mass. So far as this relation is affected by function there are metabolic increases or decreases in the size of both elements. He explains chromatin formation specifically in terms of this theory as based on a mutual interchange of materials. This conception, as applied to the nerve cell, is that the so-called Nissl substance, that is, extra-nuclear chromatin, is obtained through the activity of the nucleus.

First the cytoplasm must absorb certain materials from its surroundings, the blood and lymph, and prepare this material for the nucleus. From the cytoplasm the material is taken into the nucleus, where it is synthesized into chromatin, or chromatin yielding substance. This chromatin substance is then resorbed by the cytoplasm and is thus stored for quick use by the cell during activity. This extranuclear chromatin is then a chromidial apparatus in the sense of R. Goldschmidt (1904), an extranuclear functioning nuclear material. Taking this as a basis, the whole process may be simply separated into three main divisions. First, the stage of hyperchromatism is a result of the stimulus to work. The fact that the process of metabolism is slower than the cell demands under continuous stimulation causes the hyperchromatism to become less marked. The second division is the attempt of the nucleus

to compensate and to supply the cytoplasm with further material. This necessitates a relinquishing of some of the reserve material of the nucleus, which while it serves to supply temporarily demand for more chromatin, eventually drains the nucleus. After this second supply of chromatin is used up, the nucleus makes its third attempt to furnish material by giving the chromatin stored in the karyosome. This is the last attempt of the nucleus to furnish material. When this last supply is gone the cell is left in a state of exhaustion. Such a condition is marked by a dechromatinized nucleus and plasma. Further function is inconceivable. In accordance with Hertwig's nucleus-plasma theory, the progressive enlargement of the cell in the stages of hypochromatism is necessarily a purposeful one, a functional hypertrophy. With an undiminished demand for chromatin during functional activity of the cell, the cell body is forced to take in an increased amount of material from the outside, and the nucleus, in turn, makes an increased demand on the cytoplasm. This enlargement of the cell furnishes a valuable index as to the stage of activity of a cell at any given time.

Briefly summarized, there are two factors upon which the anatomical diagnosis of conditions of functional activity is based. They are the shift in amount of chromatin within the cell from hyperchromatism to hypochromatism and on to complete loss of chromatin in exhaustion, and the shift

in the nucleus-plasma relation. In the hyperchromatic stage, this is necessarily a shift in favor of the nucleus; later, however, the shift is in favor of the cytoplasm and remains so until exhaustion.

The morphology of the process of depression of function is very different from that of functional activity just described (Figures 14-16). Depression of function, as the name implies, is merely a stoppage or inhibition of the physiological function of the nerve cell at any stage of activity. In studying the nerve cell in depression, there are found depressed cells of all stages of activity from the resting cell to the late stages of exhaustion. It is not considered necessary that the anatomical changes of depression be considered in detail for the stages of activity and only the more general effects upon the cell will be noted.

The microscopical appearance of a cell in depression and of the same cell in a certain stage of functional activity is different in that in depression the nucleus is found to contain varying increased amounts of chromatin, corresponding to the degree of depression, while the cytoplasm is deficient in chromatin to a corresponding degree. In the resting cell, which normally shows an abundance of extranuclear chromatin, this extranuclear deficiency varies from an appreciable lessening in amount to an absolute disappearance. The same is also true for the hyperchromatic cells, which normally have an excessive amount of extranuclear chromatin. Sharply defined

granules gradually become less distinct and the acid staining elements of the cytoplasm become more distinct, until finally there is little or no basic staining substance left. In the intermediate stages, just before the final loss of basic staining substance, the stained cytoplasm may appear murky and look as if it were poorly stained. The cytoplasm sometimes has a turbulent, floccular appearance or the remaining basi-chromatin may appear as fine dust-like particles.

Depression produces the same changes in the hypochromatic cells as those just described for the hyperchromatic cells. However, these changes are not so obvious due to the normally lessened amount of chromatin in the cytoplasm of the hypochromatic cells. The marked edema present in the more advanced stages of hypochromatism also changes the appearance of the cytoplasm from a deep acid staining, hyaline mass to a much lighter staining and more reticular mass.

The changes in the nucleus due to depression are as well marked as those in the cytoplasm. There is an upset of the nucleus-plasma relation in favor of the nucleus in the early stages. This increase of the intranuclear chromatin in depression is most characteristic, since for the most part the normal nucleus of the nerve cell contains no basic chromatin except in the karyosome. The deposition of the chromatin may be in the form of well defined granules or it may be sometimes found in a more diffuse form, causing the nucleus to appear as a homogeneous basic staining substance. The

nucleus may also show accessory karyosomes which are more numerous in the more advanced stages. In the final stages, karyorrhexis, or a disintegration of the karyosome may appear, leaving the true, acid staining nucleolus. At the time of complete depression, the nucleus appears as a homogeneous, formless mass, taking predominantly the basic stain, as opposed to the more granular and acid-staining appearance in the cytoplasm.

Dolley (1913), by special stains and methods, has found that associated with profound depression there appears in the cytoplasm a deposition of yolk material and of glycogen. The yolk material was noted as appearing not only in distinct globules but also in more diffuse form, causing the cytoplasm to appear somewhat opaque as if the tissue were improperly fixed. This deposition of yolk material in depression has also been demonstrated to occur in the sex cells and other body cells. It has a marked significance for it demonstrates the fact that the cytoplasm is incapacitated for work to such a degree that the raw material taken in is not synthesized but is deposited in the cytoplasm unchanged. This same significance is also attached to the deposition of glycogen in the cytoplasm. Tests for glycogen absorption in the normal nerve cell have been made with negative results, though it does occur to excess in depression. It appears that this absorption of glycogen in depression may be due to some chemical change in the cytoplasm. However this has not been shown as yet.

Depression of function as shown by the changes in the nerve cell then may be briefly summarized as follows:

(A). A lessening in the amount of chromatin in the cytoplasm and an increase in the amount of chromatin within the nucleus, which signifies a shift of the nucleus-plasma relation in favor of the nucleus.

(B). A deposition of yolk material in excessive amounts in the cytoplasm.

(C). A deposition of glycogen.

(D). At its maximum, a breaking up of the chromatin of the nucleus into a homogeneous mass, together with karyorrhexis. The process here becomes a condition of degeneration.

METHODS OF ANESTHESIA EMPLOYED

Dogs were used in this series of experiments as they appeared more resistant to the after-effects of anesthesia than guinea pigs and rabbits. Only healthy young animals were used, the most of them being less than three years old.

Ether was the anesthetic employed and the time length of the anesthesia was varied in the different experiments. Because of the fact that it was deemed necessary to produce anesthesia for considerable periods of time, an apparatus was constructed for its administration which would decrease the liability of producing pneumonia.

This apparatus (Text-Figure 1, page 14a), is a simple device which, however, was found to be very useful and efficient. It consists simply of an ether bottle (G), with a valve (F) to supply outside air; a bottle (D) through which the ether vapor from G is passed to be warmed; a metal container for D (E), in which water at 34° C circulates to and from a metal coil (H) surrounding an electric light bulb, the whole imbedded in an asbestos and plaster of Paris cast; and a throat tube (A) running from the warming bottle D.

In order to use the apparatus the animal is first anesthetized and the throat tube inserted. This throat tube is made of glass tubing and is so shaped and curved that it may be passed through the mouth and will fit snugly into the trachea. At inspiration outside air is bubbled

ETHER WARMING APPARATUS

- A. Throat tube.
- B. Valve to allow the escape of expired ether vapor.
- C. Thermometer.
- D. Bottle through which ether vapor is passed to be warmed.
- E. Metal container in which warm water circulates.
- F. Valve to supply pure air.
- G. Ether bottle.
- H. Asbestos cast containing metal coil surrounding electric light bulb.
- I. Electric light connection.

through the ether in the ether bottle G and into the warming bottle D and to the lungs of the dog. At expiration most of the expired air escapes at valve B.

With this apparatus anesthesia can be kept at a uniform degree of depth for considerable periods of time without danger to the animal. It has quite a number of advantages over the open mask method.

First, it provides warmed ether vapor. In the experiments in which this apparatus was not used microscopical examination of the lung tissue showed well developed and marked pneumonia. In reviewing the literature on anesthetics, only two publications were found which attempted to prove the uselessness of warmed anesthetics, while numerous investigators, Gatch (1910), Coburn (1912), Boyle (1912), and others, have made experiments which prove the value of warmed anesthetics. These investigators report that not only is the "value of the anesthetic increased as regards life but the after-effects are reduced to a minimum."

One of the publications referred to above, "The Fallacy of Warmed Ether Vapor," by Seelig (1911), was objected to by Gwarthmey (1912) in a later paper. He says that Seelig's experiments were evidently imperfect; that ether can be heated easily and inexpensively. The present experiments have shown that there is decidedly a value in warmed anesthetics, especially in ether anesthesia of many hours duration.

Second, in further enumerating the advantages of the anesthesia apparatus over the open mask method, it is noted that with it anesthesia can be kept at a uniform degree of depth for any desired length of time.

Third, the apparatus requires far less attention of the anesthetist. This fact, although not of a great deal of importance, was of considerable convenience in the present experiments, as the apparatus could be regulated and the anesthetist could then go about other work, sometimes for as long as an hour. It is entirely feasible to keep two sets of apparatus going at the same time as it requires but little more attention to watch the two than one, and in this way quicker results were obtained.

Fourth, the apparatus provides a uniformity in all experiments.

Fifth, it requires a less amount of ether.

In the review of the literature of anesthesia, it was noted that there were similar yet much more complicated and elaborate forms of apparatus now in use in some of the best hospitals. For animal work, in the writer's experience, this simple apparatus is entirely satisfactory.

MICROSCOPIC TECHNIC

Following the experimental work of Mann (1894), Fleming (1895), and V. Lenhossek (1897), sublimate was constantly used for the fixation of brain tissue. This fixative, which is the adopted one of this laboratory for brain tissue, gives very satisfactory results. It produces no undue distortion of shape of the nerve cells, and, in view of the fact that much depends on this feature in the anatomical diagnosis of nerve cell activity, it is much superior to the ordinarily used fixatives, particularly strong alcohol.

However, Dolley (1911), has compared the results obtained from the more commonly used types of fixatives and has noted that no matter what fixative is used the findings in the nerve cell are constant.

The aqueous sublimate was combined with formalin according to the following proportions.

Saturated corrosive sublimate -----	95 cc.
40% formaldehyde -----	5 cc.

From twelve to twenty-four hours were generally allowed for fixation, and then the tissue was run through the graded alcohols up to 80% alcohol, in which it was iodized for six days before it was placed, for one day each, in 95% and absolute alcohols. From that stage the tissue

was run through as follows:

Absolute alcohol and xylol (equal parts) one hour.

Xylol, one to four hours.

Paraffin dissolved in xylol (room temperature) 3 to 5 hours.

Paraffin dissolved in xylol (oven temperature) 3 to 5 hours.

Melted paraffin (in oven), six hours.

Imbedding in paraffin.

Sections were cut of five micra thickness and mounted on thin slides.

The technic used in staining is very simple.

Following the routine of this laboratory, erythrosin-toluidin blue was used. The toluidin blue is a saturated aqueous solution. Erythrosin, which is employed as a counterstain, is that in the solution of Held, i.e., one gram to one hundred and fifty cubic centimeters of distilled water, to which are added two drops of strong acetic acid.

The staining of the sections was carried out according to the following procedure: After the paraffin was dissolved from the sections they were passed through the graded alcohols to water. They were then stained one and one-half minutes in erythrosin solution heated to 40 degrees C.

After thoroughly washing in water, they were stained in toluidin-blue solution for about seven minutes, again washed in water, and then differentiated by passing through 80% and 95% alcohols. The process of differentiation was followed under the low power of the microscope and stopped when the internal markings of the cells became clear. After the sections were placed in absolute alcohol for a few minutes they were cleared in xylol and mounted in Canada balsam.

In looking over this microscopic technic, the noticeable fact is that only the ordinary cytological methods were employed and that no unusual stains were needed.

DATA OF EXPERIMENTS

Experiment Anesthetic 2. (numbered in laboratory series). Large male dog, probably two or three years of age. Weight about 12 Kg. Anesthesia by the open mask method. Time length of the anesthesia 13 hrs. and 40 min.

Remarks:-- The animal was hard to keep anesthetized, requiring a considerable amount of ether. A noticeable fact was that after about 8 hours more ether was required to keep deep anesthesia, as judged by the absence of eye reflexes, than was needed during the previous 5 hours. For several hours previous to the time of death of the dog ether was almost continuously poured down the mask without any apparent change in the depth of the anesthesia and an eye reflex was present from then until the time of death.

Post-mortem findings:-- Marked hypostatic congestion of the lungs. On microscopical examination, a marked pneumonia was noted.

Experiment Anesthetic 3. Apparently an old male dog. Weight 6 Kg. Anesthesia with the ether warming apparatus. Time length of the anesthesia for the first day, 6 hours; for the second day, 6 hours. Total time of anesthesia 12 hours.

Remarks:-- This animal was easily kept anesthetized and required only a small amount of ether to keep deep anesthesia.

Post-mortem findings were negative as far as influencing any factor of this experiment was concerned. Tubercles were found throughout one lobe of the left lung.

Experiment Anesthetic 4. A medium sized female dog, three years of age. Weight 8 Kg. Kept under deep anesthesia 3 hours the first day, 4 hours the second day, and 6 hours the third day, at which time it was killed. It was noted during the 4 hours previous to its death that even in very deep anesthesia an eye reflex was present. There were negative post-mortem findings.

Experiment Anesthetic 5. A three-fourths grown female dog. Weight 8 Kg. Time of anesthesia, 2 hours.

Remarks:-- The animal was very easily kept under the anesthetic, requiring only a very small amount of ether in comparison with the other dogs in Experiments 2 and 4. At no time during the anesthesia was an eye reflex present except for a minute or two at a time. A post-mortem showed nothing abnormal.

Experiment Anesthetic 6. A four-fifths grown female dog. Weight 8 Kg. Time of anesthesia 4 hours. The animal was difficult to keep anesthetized.

Experiment Anesthetic 7. A four-fifths grown female dog. Weight 7 Kg. Time of anesthesia 6 hours. The dog was hard to keep under the anesthetic.

Experiment Anesthetic 8. A small bull dog of less than two years old. Weight 6 Kg. Time of anesthesia 5 hours.

Experiment Anesthetic 9. A female dog of less than three years old. Time length of anesthesia the first day, 3 hours, the second day 1 hour.

Experiment Anesthetic 10. A female dog of apparently about 2 or 3 years old. Weight 10 Kg. Time of anesthesia 8 hours. Heart rate 170 per minute, respiratory rate 102 per minute at the time the anesthetic was removed. After one-half hour the respiratory rate had become very rapid, 280 per minute. Heart rate could not be ascertained. At two hours after the anesthetic was removed the respiration and heart rate had returned almost to normal, but the animal could not even raise its head so great was the collapse. The following morning the dog was found dead, 15 hours after the anesthetic was stopped.

Post-mortem findings negative.

Experiment Anesthetic 11. A female dog of good vitality and apparently less than one year old. Weight 6 Kg. Time of anesthesia the first day was 4 hours. On the second day, the animal was apparently recovered and showed no effects of the previous day's anesthesia. On the third day the time of the anesthesia was 7 hours. One-half hour after the removal of the anesthetic there was noted a very shallow, fast respiration, a heart rate of 260 per minute, and the animal vomited repeatedly. At one hour later the respiratory rate had decreased but was still 146 per minute. The dog had cutaneous reflexes, but otherwise

was apparently lifeless. It could not raise its head. Four hours later the dog had recovered to a slight extent and could raise its head. Fifteen hours later, the heart rate was 170 and the respiratory rate was 56. The dog howled at times and would try to move but merely went around in a circle, as if partially paralyzed. It was very excitable as it would try to move whenever a noise, such as clapping the hands, was made in the room. Thirty hours later there was no noticeable change from what has been described. At forty hours after the anesthetic was stopped the dog was found dead.

Post-mortem findings:--abdominal organs congested with blood. An intussusception was found in the small intestine.

Experiment Anesthetic 12. A female dog of about two years old. Weight 8 Kg. Time of anesthesia 8 hours. Ten minutes after removal of the anesthetic the respiratory rate was 216 per minute. The heart rate could not be ascertained. One half hour later the respiratory rate had increased to 330 per min. Two hours later the respiratory and heart rates had returned almost to normal but the animal appeared almost lifeless. Four hours after the removal of the anesthetic the dog was found dead.

Post-mortem findings were negative.

DESCRIPTION OF THE CHANGES
PRODUCED BY ETHER AND THEIR CORRELATION WITH DEPRESSION

Before a thorough microscopical examination and study of the material obtained in this series of experiments was begun, a careful study was made of the Purkinje cells of the cerebella of normal dogs, and of dogs in a state of profound depression which had been produced by a known depressant. This was done in order to become familiar with the microscopical appearance of these cells in the various stages of normal functional activity and in the various grades of depression.

On making the microscopical examination of the cerebellar tissue in the first of this series of experiments, Experiment Anesthetic 2, it was noted for the first time that ether anesthesia produces depression of the nerve cells. The changes of depression which had been produced by the thirteen hours and forty minutes of anesthesia were very marked, in fact, all of the Purkinje cells showed some degree of depression. The essential changes were also noted to be similar to those produced by the known depressants. There was a loss of basic-staining substance in the protoplasm causing it to have a murky appearance. Some of the cells showed varying amounts of chromatin in the nucleus in the form of well defined granules, while in some the nucleus appeared as a formless, homogeneous, basic-staining mass. The karyosome showed in some of the cells complete

karyorrhexis, in others only the beginning of disintegration.

Depression was again noted in the next two experiments, Anesthetics 3 and 4. In these experiments anesthesia of several hours duration daily for several successive days was shown to produce an almost as marked degree of depression in the nerve cells as a continuous anesthesia for the same number of hours. For example, an anesthesia of 4 hours daily for three successive days produced almost the same degree of depression as a continuous one for 12 hours.

Having found that ether anesthesia produces the changes of depression, it was decided to ascertain, if possible, the shortest time in which these changes would appear. For this reason experiments 5, 6, 7, 8, and 9 were performed. As a matter of convenience to the reader the lengths of anesthesia of these experiments will again be stated. They are as follows: Anesthetic 5, 2 hours; Anesthetic 6, 4 hours; Anesthetic 7, 6 hours; Anesthetic 8, 5 hours; Anesthetic 9, 4 hours.

In each of these experiments depression of the nerve cells was noted in the material examined. However, there was only a mild degree of depression in the four experiments, 5, 6, 7, and 8. The depression involved only a portion of the cells, the most of them showing no apparent change. The cells involved showed a diminution or an absence of extranuclear chromatin in the protoplasm, the protoplasm having a diffuse basic-staining appearance. There was very little change in the nuclei and karyosomes.

Apparently the depression had just made its appearance.

It was further noted that there was very slight difference in the degree of depression in these four experiments although the time lengths of the anesthesia varied. A noticeable fact was that the dog which was easily kept anesthetized showed almost as marked depression after two hours anesthesia as the dogs which were hard to keep anesthetized but which were kept in that condition 4, 5 and 6 hours. It was the observation in these four experiments, as well as in the others, that the animals which were easy to keep anesthetized showed the changes of depression earlier than the animals which were hard to keep anesthetized. In three of these experiments, 5, 6, and 7, there was also a uniformity, as far as possible; the dogs were practically the same age and weight, and the ether warming apparatus was used.

It appears from this that the changes of depression produced by ether anesthesia vary with the animal as well as with the time length of the anesthesia, and that these changes first appear microscopically after about one and one-half to two hours, through they may be delayed several hours longer. In the previous study of nerve cells of animals kept under ether anesthesia for less than one and one-half hours during numerous operations, no depression had been noted (Dolley 1914).

In Experiment 9, an anesthesia of three hours on the first day and one hour on the second day, there was noted

a higher degree of activity than normally found and only a few of the cells showed depression. This would then indicate that there are produced by the ether anesthesia first the changes of excitation on which are superimposed the changes of depression. It may be interpreted from the description of Cavalie and Rolland (1903) that anesthesia primarily stimulates the cells to activity.

In the last three experiments, 10, 11 and 12, a most marked and profound depression was found on making the microscopical examination of the material. This marked depression was seen in practically all of the cells. Not only did they show marked depression but large numbers of them showed degeneration and beginning necrosis. Especially was this noted in cells of Experiment 12, in which the animal lived forty hours after the anesthetic was stopped. In each of these three experiments a symptomatic condition, which at first was very difficult to properly diagnose, accompanied these changes in structure. This condition, which will be discussed in detail in the next chapter, is regarded as probably the outward constitutional effect of profound depression. It made its appearance only in the experiments in which practically all of the nerve cells showed marked depression and in which large numbers had begun to degenerate and appeared incapable of function.

To summarize briefly: Depression was noted in all of the experiments performed. The degree of depression produced was in proportion to the time of anesthesia, with allowance for the individual variations of animals. An

anesthesia of two to six hours produces a moderate depression, one up to eight hours a marked depression, and one of more than eight hours a profound depression, with the beginning of necrobiosis.

DISCUSSION OF CERTAIN
CONSTITUTIONAL EFFECTS OF THE ANESTHETICS

The symptoms of the constitutional effect referred to in the last section will now be discussed. It was the observation in Experiment Anesthetic 2 that after about eight hours anesthesia a larger amount of ether was borne indifferently by the animal. At least this appeared to be the case, for it seemed to make very little difference how much ether was given as the eye reflex remained present and the respiration was shallow until the death of the animal. This was also the observation in Experiments 3 and 4, beginning each time after eight to ten hours anesthesia. However, very little attention was paid to this condition until several recovery experiments were performed. In these, Experiments 10, 11 and 12, anesthetics of approximately eight hours each, it was decided instead of continuing the anesthesia until the death of the animal, as in the other experiments, to stop after it was thought depression had been produced in order to study recovery changes. The condition described as appearing after eight to ten hours in Experiments 2, 3 and 4 had also begun in the recovery Experiments 10, 11 and 12 before the removal of the ether. In the latter experiments, however, not ended by intentionally killing the dogs, the condition developed to its full extent.

It was too serious to permit recovery, as all the dogs died within two days, but for itself it was a fortunate turn which permitted its study.

This condition, which appeared to be the outward symptomatic effect of depression, was as follows: On the removal of the anesthetic the already rapid and shallow respiration of the animal gradually increased until it became a violent pant, in one case becoming as rapid as 330 per minute at half an hour after the removal of the ether. This respiratory rate could be counted only with difficulty and was estimated at 330 per minute by repeated counts. The heart rate could not be ascertained because of the marked respiration. At one hour after the removal of the anesthetic the respiratory and heart rates were back to normal and the dog had reflexes but lay upon the floor more or less unconscious, with a lowering of temperature and probably blood pressure, and partial paralysis. It appeared to be in a condition of very marked collapse. The animals remained in this condition until death, in one case 40 hours after the removal of the anesthetic, never recovering muscular control.

In the review of the literature on anesthesia there were found several reports of the occurrence of a similar condition. These investigators have explained it as a post-anesthetic intoxication (Brown, 1911 and Inman, 1911) or as a delayed post-anesthetic poisoning associated with

sepsis (Rees, 1912). Turck (1903) calls the condition shock. He produced this "shock" with ether anesthesia as he says in the absence of trauma, hemorrhage, fright, or manipulation of the visceral organs. He also says that shock is intimately associated with the nervous system. The description of the animals in the condition he terms shock was exactly the same as that noticed in the animals of these three experiments. He noted also that some animals would show the evidences of this condition more readily than others of the same species. This fact bears out what was noted in these experiments, namely, that the degree of depression varies with different dogs. White (1899) echoes the universal clinical observation that anesthesia always adds to shock. Hewett (1857) claims that surgical shock will occur more readily under ether than chloroform.

This condition of collapse just described appeared to be the outward physiological symptomatic effect of a profound depression. While it is not possible at present to explain each individual symptom on the basis of cytology--that being a question of physiological relations--a fundamental understanding of the origin of the condition as a whole is afforded. As stated, the symptoms appeared only in the experiments in which practically all of the nerve cells examined showed marked depression, and in which large numbers had begun to degenerate. In other words,

their capacity for function was minimal, and the physiological reaction must be connected with this changed anatomical structure.

The condition was not one of shock, as Turck names it, ^{neither} according to the usual restriction of the term, nor as cytologically interpreted. As more commonly used, shock is surgical or traumatic. Mechanical stimulation is the physiological factor, and this traumatic stimulation excites the nerve cells affected to activity, then fatigue results and finally exhaustion. All symptoms are referable to the results of stimulation (Dolley 1910). In a more general sense the principle can be extended to any form of stimulation such as the shock of pain or emotional disturbance.

There is no positive evidence that mechanical stimulation ever produces depression, though there is much negative evidence (Verworn, 1899). The ether collapse then is not shock. As to its origin it is the exact opposite of shock. Instead of overfunction, there is inhibition of function of the nerve cells.

Depression explains entirely the most marked and characteristic symptom, the partial paralysis of the animals. This corresponds with the results of Simmons from this laboratory (1914). He noted that the paralysis after diphtheria toxin was coincident in time with marked depression in which there was degeneration and beginning necrosis of the Purkinje cells.

Depression also explains by itself the fall in temperature and in blood pressure. It does not alone, however, explain the over-activity of the heart and respiratory mechanisms. It can be suggested that depression removes the inhibition of the higher centers, so that these organs are no longer under the usual restraint. The very rapid respiratory rate and heart rate had stopped many hours before the death of the animals.

It is also clear why Turck diagnosed the condition as shock. The end of shock is organic exhaustion. Complete exhaustion must be accompanied by loss of function. Depression is primarily a loss of function. From opposite causes the same functional incapacity is reached (Dolley 1914). In its extreme, therefore, complete ether depression must give many symptoms in common with shock exhaustion.

REVIEW OF THE LITERATURE

In a review of the literature since 1895 it was strikingly demonstrated that very little investigation has been made on the nerve cell and especially on the effects of anesthetics on the nerve cell. In fact, after carefully searching the literature as reported in the Index Medicus, only six publications were found in which the effect of the anesthetics on the nerve cell has been studied. There were however, to be found numerous publications on the effect of various anesthetics on the nerve fiber but these were of no value on this investigation.

The investigators, a review of whose publications will be stated later, have given different interpretations or no interpretations at all of the various changes in the nerve cell which they considered to be produced by anesthesia. However, none of these investigators regarded their findings from the point of view of this paper, that is, of a functional analysis.

Such interpretations as are given incline to the idea of toxemia or degeneration, rather than to a natural process of stimulation in its broad sense. Consequently, only their objective findings will be examined in this review in respect to agreement or possible disagreement with the present results. Changes which are now known to belong only to normal function are usually considered to be artefacts

or degenerations.

Cavalié and Rolland (1903) studied the action of a mixture of ethyl chloride, ethyl bromide, and methyl chloride on the Purkinje cells of the cerebellum of the cat, guinea pig, and rabbit. Their methods were as follows: Anesthesia of five minutes, anesthesia of fifteen or twenty minutes, anesthesia of one hour or more, and anesthesia of one hour followed by one hour of rest. The results briefly summarized were: After five to ten minutes of anesthesia there was no apparent change in the pyramidal cells or Purkinje cells, although there were changes in the axones which, however, are of no interest in this investigation, and for this reason will not be stated. After one hour or more of anesthesia, the modified structure of both Purkinje and pyramidal cells was fairly well marked, and "the nuclei which were more or less visible were colored about the same as the protoplasm." These results are interpreted by the writer as simply the changes due to primary excitation. Their conclusions briefly stated are: That the effect of a general anesthetic ought to be considered as that of a substance more or less toxic; that a general anesthetic produces a certain number of important changes in the Purkinje and pyramidal cells; that at the beginning of anesthesia the Purkinje cells are stimulated while the pyramidal cells remain intact; that there is ^a sort of an elective affinity of the anesthesia for cellular elements of Purkinje cells, and that anesthesia

acts first by its affinity on the cerebellum and next on the cerebrum; that with chloroform anesthesia for periods of one-half to one and one-half hours there was no apparent change microscopically in the pyramidal cells of the cerebrum or the Purkinje cells of the cerebellum.

Tedeschi (1897) studied the acute poisoning of chloroform and noted that there was an abating of the swelling of the protoplasm with diffusion of the chromatic substance of the nerve cell.

Feischi (1898) noted that besides the diffuse coloring of the protoplasm of the nerve cells of the anterior grey horn there existed between the cells a diversity of coloring.

Schmidt (1898), with repeated anesthesia, observed in the nerve cells of the ganglia of the heart fragmentation, disappearance, and lumping of the chromatin, enlargement of the cell and vacuolation of the protoplasm.

Camia observed with acute poisoning a thinning and diffusing of the lumped chromatin in the protoplasm of the cells of the grey substance in the cortex of the pons, bulb, and medulla.

It appears that Schmidt and Camia very probably produced the changes of depression although they did not interpret them as such.

Wright (1900) studied the action of ether and chloroform on the neurons of rabbits and dogs. Some of his conclusions,

which are of value in this investigation, are as follows: "In rabbits both ether and chloroform anesthesia cause certain changes in the nerve cells of both brain and spinal cord. These are slight at first, but become more pronounced as the anesthesia is continued. By the methylene blue method, the principal change is rarefaction (or lessening) in amount of the Nissl bodies, in the most marked cases of all, a pseudo-degenerative change." The rarefaction must refer chiefly to the hypochromatism of activity and from the plates which he presented, the Hodge stage of activity is included in his pseudo-degenerative change. He also noted that in dogs there are practically no changes up to two hours, but that between that time and four hours changes occur in the nerve cells similar in kind to those observed in the rabbit. The changes become more marked as the anesthesia is continued.

From this summary of the literature it appears that the anesthetics produce certain changes in the nerve cells. The changes after anesthetics of short duration appear to be only the changes of excitation while those of longer or repeated anesthesia can be identified as depression. The investigators noted that there were no marked changes produced by anesthesia up to one and one-half hours but that they made their appearance between that time and four hours, and that the changes produced depended upon the duration of the anesthesia. These two statements both agree with the results obtained in this investigation.

SUMMARY

Ether anesthesia produces certain definite anatomical changes in nerve cells of dogs. The changes are first those of mild activity and later there are superimposed changes of depression depending in severity upon the duration of the anesthesia. The changes first make their appearance microscopically in one and one-half to two hours. An anesthesia of two to six hours produces a moderate depression, one up to eight hours a marked depression, and one of more than eight hours a profound depression, with the beginning of necrobiosis.

The severity of the anatomical changes in the nerve cell appears to be in direct relation to the length of the anesthesia, allowance being made for individual variations.

The changes vary in degree in animals of the same species kept under the same form of anesthesia for the same length of time.

An anesthesia of several hours duration for several successive days produces almost the same degree of depression in the nerve cells as a continuous one of the same number of hours.

Animals which are easily kept anesthetized show more marked anatomical changes in the nerve cells than animals that are kept under the anesthesia with difficulty when the time length and the kind of anesthesia are the same.

A peculiar constitutional condition of collapse results from anesthesia of eight or more hours duration. This condition of collapse is coincident with profound depression, and the depression is considered to stand in causal relation to this condition.

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STAGES I to VII OF FUNCTIONAL ACTIVITY

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STAGES 8 to 13 OF FUNCTIONAL ACTIVITY

8

9

10

11

12

13

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DEPRESSION OF FUNCTIONAL ACTIVITY

14

15

16

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Figure 14. Stage 6 of functional activity in moderate depression.

Figure 15. Stage 8 of functional activity in marked depression.

Figure 16. Very marked depression with early necrobiosis.

May 15, 1915.

Professor E. R. Clark,
39 Medical Bldg.

My dear Professor Clark:

It is customary for the Graduate Committee to refer dissertations, submitted by candidates for the degree of Master of Arts, to some member of the Group who is not connected with the Department in which the candidate's work has been done. I am sending you herewith a dissertation which has been submitted by E. E. Butler. I shall be greatly obliged if you will kindly examine the same at your earliest convenience and report to us for the Graduate Committee whether in your opinion the dissertation meets the general standard which has been established in this University for the Master's dissertation.

Very truly yours,

A handwritten signature in cursive script, reading "Walter Miller".

Chairman, Graduate Committee.

UNIVERSITY OF MISSOURI
COLUMBIA

PREVENTIVE MEDICINE

May 14, 1915.

Dean Walter Miller,
Academic Hall,

Dear Sir,--

I beg to approve the thesis on "An Anatomical
Analysis of the Effects of Ether Anesthesia on the Nerve
Cell," which is submitted by Mr. E. E. Butler from the
Department of Pathology.

Very truly yours,

D. H. Dalley

UNIVERSITY OF MISSOURI
COLUMBIA

DEPARTMENT OF ANATOMY

May 22, 1915.

Prof. Walter Miller,
Chairman, Graduate Committee,
Academic Hall,

My dear Prof. Miller,-

I have read the dissertation
submitted by Mr. E. E. Butler from the Department
Pathology, entitled "An Anatomical Analysis
the Effects of Ether Anesthesia on the Nerve Cell" as
ent of the fulfillment of requirements for the degree
Master of Arts. As this is the first of such
dissertations I have seen, I am unable to
give an opinion as to its value as compared with
others. I can, however, say that if other theses
presented for the degree of M. A. are as excellent

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is this, the standard established in this University
or this degree is a very high one.

Very truly yours,

Eliot P. Clark.

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An anatomical analysis of
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