A CYTOLOGICAL STUDY OF STIMULATION
OF THE LIVER

by

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Introduction.

The definition of stimulation.-Before entering into any discussion about stimulation of the liver it will be proper to define at first the terms "stimulation" and "stimulus". The latter, according to Verworn (Irritability, p.36) is defined as follows: "Stimulus is every alteration in the external vital conditions". "If a stimulus comes in contact with a body that possesses the property of irritability, i.e., the capability of reacting to stimuli, the result is 'stimulation'" (Verworn, General Physiology, p.348). A composite definition of the above mentioned terms is the following modification of Verworn's statements: "Irritability, stimulus, stimulation; the property, the agent, the process; the action of the stimulus on cells possessing irritability results in the process of stimulation" (Dolley, Chapter 3, unpublished work). These definitions bring out with clearness that besides "stimulus" and "stimulation" there is involved a third factor which is of primary importance, namely, the factor of irritability. It is the relationship of these three agents that forms the unity for stimulation. It is also quite evident from the above cited modification that "stimulus" and "stimulation" can be discussed only then when there is irritability in existence, since irritability is the alpha and omega of the entire physiological process. Without irritability there is no reaction, for no changes will be produced, and no equilibrium of matter will be disturbed, since "irritability is the primary basis of all dynamic reactions of the body in health and disease" (Dolley--last lecture).

As already stated above, a "stimulus is every alteration in the external vital conditions", in other words, the reactions of irritability are the changes produced in cells and organisms under the influence of changed conditions in their external environment. It is the irritability of the living protoplasm which is responsible for all changes occurring in the cell under the influence of changed external conditions, in other words, irritability is the potential and dynamic force of the cell. Furthermore, all reactions of stimulation can only be explained in terms of "conditions" and not in terms of "cause" and "effect", as stated by Verworn: "A state or process is solely determined by the sum total of its conditions. A state or process is identical with all of its conditions in totality" (Irritability, p. 29).

This physiological concept, namely, ^{of} the reaction of stimulation or better, the reaction of irritability, is applied not only to the organism as a whole, but primarily to the cell, since it is the aggregation of cells that makes up the organ or the organism as a whole.

The reactions of irritability.-Now, the question arises what are the effects, what are the results when the irritability of the cell is called into action? There is only one answer to this question, namely, that in any cell the reaction of irritability to the stimulus is expressed in two processes: excitation and depression, or a combination of the two.

The reaction of irritability according to Verworn can be either quantitative or qualitative. By a quantitative process is meant the change in rapidity, by a qualitative process is meant the alterations in nature (Irritability, p. 73). As a rule the major part of all temporary responses to stimuli consists in "alteration

in rapidity of the vital processes". These changes may produce either a quickening, or a retardation in the physiological processes. "If there is quickening in the process then there will be an increase or a strengthening of the specific action of the living organism; if, on the other hand, there is a retardation in the process then it will manifest itself in a decrease or repression of the same, namely, the specific action of the living organism". According to physiology, an increase in response means excitation, whereas a decrease in vital processes causes depression. Consequently, there are only two possibilities, and the only two of the reaction of irritability on the quantitative side. These two possibilities are: excitation and depression.

These two factors are not only deduced by physiology, but they are also confirmed by cytology, and demonstrated by Dolley and his co-workers in their work on the nerve cell. This work consists of a series of original investigations performed in this laboratory during the last ten years. The general results of this work have been to classify the effects of stimulation on an anatomical basis as either excitation or depression. A wide range of experimental factors has been employed, such as the mechanical stimuli of traumatic injury, different chemical stimuli - drugs, poisons, and bacterial toxins - thermal stimuli, and trophic stimuli of disturbed metabolism. As the primary basis of this analysis, the function of the cell was identified as a process of excitation by comparing animals artificially exercised with the various states of everyday life.

Thus, regarding the function of the nerve cells, there are two diametrically opposite possibilities of change in response to stimulation - one of functional activity, and the other of a de-

pression of such activity. By functional activity is understood the work of the cell, while by depression is meant the blocking or inhibition of the very same work. These two terms being so opposed to each other have, however, one point in common, namely, the end result of either process is a cessation of function of the cell.

The anatomical changes in functional activity were divided by Dolley into thirteen states. The fundamental basis for this classification was the shift in chromatin in the cell and in the size changes in the cell. The thirteen stages are as follows (Dolley, 1910):

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

2. The stage of progressive hyperchromatism, in which 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 difference 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 (4' and 5'), and a late division, characterized by the sharp beginning of nuclear edema (4" and 5"). (Since 4 and 5 are identical in significance, stage 5' and 5" represent the group).

6. The return of the cytoplasmic chromatin, 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 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 nervous 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."

These thirteen stages were interpreted in terms of R. Herd~~wig~~'s theories: first, the nucleus-plasma relation theory, which postulates that under normal conditions there is a constant mass relationship between nucleus and cytoplasm; second, that the formation of extranuclear chromatic substance - the so-called Nissl substance in the nerve cell - is produced by the activity of both nucleus and cytoplasm, being a product of intracellular coordination. The initial part is done by the cytoplasm which is absorbing certain materials from its surroundings, as blood and lymph, and preparing this material for the nucleus. This prepared substance is then taken into the nucleus where it is synthesized into chromatin, or chromatin-yielding substance. This synthesized product is then absorbed back by the cytoplasm where it is stored in order to be used by the cell during activity. The genetic relationship of this extranuclear chromatic substance; or chromidial apparatus as it was named by Goldschmidt (1904), is evidenced by the size changes, the mass relations, and the morphology of its intra- and extra-nuclear material.

The conception of the chromidial apparatus is that the chromatic substance is not stored in the nucleus, except the karyosome, but that it is stored in the cytoplasm which makes it available for quick use in time of activity.

The process as a whole may be divided into three parts:

(1) the stage of hyperchromatism. Since the cell is under continuous stimulation, the metabolism of the cell is slowed down and the hyperchromatism diminishes. (2) The cytoplasm being under the strain of work increases its demand upon the nucleus which in turn attempts to compensate and to supply the cytoplasm with more chromatic material for use. The continued drain on both cytoplasm and nucleus causes a still slower metabolism, and a hypochromatism. (3) Finally, the nucleus makes its last attempt by giving up the chromatin from the karyosome - the end result being a complete exhaustion of cell and nucleus.

To summarize, the mechanics of functional activity consist of the shift of the nucleus-plasma relation from an initial advantage of the nucleus, characterized by hyperchromatism, to the end advantage of the cytoplasm, with dechromatinization of the nucleus and disappearance of the chromidial apparatus.

In the process of depression of function the anatomical changes are entirely different. Since depression of function is merely a stoppage of the functional activity, therefore, any cell in any stage is capable of being affected by conditions of depression. The fundamental characteristics of cells in depression are as follows. First, a diminution of chromidial apparatus in the cytoplasm with a great increase of the chromatin in the nucleus. The cytoplasm shows thereby a great affinity for the acid stain, whereas the nucleus stains very deeply with the basic stains. The appearance of the cytoplasm is granular while the nucleus may

represent either a picture of a homogeneous, formless mass stained very dark with the basic stain, or it may have the appearance of an aggregation of basic granules scattered densely over a very deeply stained matrix, according to the stage of depression. The nucleus-plasma relation is the exact opposite of activity being in favor of the nucleus. Second, karyorrhexis is another distinct feature of depression. This is accompanied by a degeneration of the cell body which has in severe depression a hyaline appearance.

The nucleus-plasma relation is expressed by the nucleus-plasma coefficient which is the resultant figure representing the relationship of the nuclear volume to the cell volume. Alterations of the normal coefficient are the index of the states of excitation and depression. The relative volumes of the cell, nucleus and plasma, and the relationship of the two latter were calculated by Dolley in his work for the nerve cell, and the resultant nucleus-plasma coefficient established as a fact for these states. He proved that in states of excitation the increase of the cytoplasm is relatively much greater than that of the nucleus, whereas in a state of depression the contrary holds true, namely, the nuclear volume is more increased as compared with the relative plasma volume. To express it more briefly as it is usually stated by Dolley (1917, Journal of Comp. Neurology, Vol. 28, p.468): "In functional activity the upset of the nucleus-plasma relation is in favor of the cytoplasm. In functional depression the upset of the nucleus-plasma relation is in favor of the nucleus."

The problem of cloudy swelling in respect to stimulation.-- It is a well known fact in pathology that the most common morbid change seen at autopsies is that of "cloudy swelling", which is especially marked in the liver and kidney. According to the text

books of pathology it is usually an accompaniment of inflammation, fever, and circulatory, metabolic, and nutritive disturbances. The most frequent condition, however, is intoxication, either by bacterial toxins, as in the various infectious diseases, or by numerous organic and inorganic substances. In its gross appearance the organ which is in a state of cloudy swelling shows on the cut surface a dullness of grayish color which looks as if it had been dipped in boiling water (Adami, Text book of Pathology).

The definition of cloudy swelling is almost the same in every one of the text books. According to Stengel (General Pathology, p.70) it reads as follows: "cloudy swelling, also termed albuminous infiltration and parenchymatous degeneration, may be defined as an edema of the cellular protoplasm with granular alteration in the protoplasmic proteid and the production of opacity". The author thinks that the opacity is due to a coagulation, or precipitation of the protoplasmic proteid.

According to Adami (Text book of Pathology, p.268) the characteristics of cloudy swelling are expressed in the lost transparency of the individual cells, and the granular material is a product of changed cytoplasm which looks like Altmann's granules. There is a difference, however, in that in cloudy swelling the granules are aggregated into larger masses, and also in that there is none of the linear arrangement seen in the normal cell. He thinks that this granular material is a result of a conversion of certain colloids of the cytoplasm which are transformed from the soluble into the solid or "gell" state. He looks upon it as a result of disintegrated cytoplasm or of absorbed material which has not been completely "handled" by the cell, or it may be the result of both. The increase in size of the cells he ascribes either to

the increase of these paraplasmic materials, or to a hydropic condition.

Wells, after a long discussion about cloudy swelling gives the following summary: "Putting all these facts together, we may look upon the term cloudy swelling as applying to many different factors, the common factor being the precipitation or the coagulation of part of the dissolved cell proteids often with the separation of the intracellular fat and the imbibition of water" (Wells, Chemical Pathology, p. 33).

After all this discussion of cloudy swelling, its definition, origin, and character, the question arises can cloudy swelling be analyzed and interpreted in terms of stimulation? Cloudy swelling is listed among the degenerative changes, and "degeneration at bottom is not an objective pathological state but a physiological process" (Dolley, 1913, p. 120). Consequently, if cloudy swelling is not such a state in accordance with the old conception, but is a physiological process, it will be produced by the same conditions as any of the physiological processes.

The basis for this assumption is that irritability is not an exclusive property of the nerve cell alone. It is a primordial property possessed even by undifferentiated cells. The nerve cell simply has the property specialized to the highest degree, so that its specific function is limited to irritability. An anatomical basis for this property can now be ascribed to the discharge of nuclear substances into the cytoplasm and the formation of the so-called Nissl substance or chromidial apparatus. The latter may be considered as the energy-giving material of the nerve cell and as responsible for the function of the nerve cell, for which there is much evidence. As soon however as this material diminishes there

is associated a decline in its function which finally leads to a complete loss of function. But every differentiated functioning cell has its specific irritability through which its specific function takes place (Verworn). For instance, in terms of cytology the function of gland cells or secretory cells consists in the formation of a chemical product. This can be assumed to be the result of a combination taking place between the discharged nuclear substances and the cytoplasmic substances, thus constituting the functioning capacity of the secretory cell. Therefore, there is an homology between the formation of the Nissl substance in the nerve cell on one hand and of the zymogen in the secretory cell on the other hand. Both are the result of the same origin, the same nucleo-cytoplasmic mechanism, and both are responsible for the functional capacity of the cell. There is only one difference between them, namely, that the chromatin as a type of substance involved in the nerve cell and that in the secretory cell is of a different chemical make up. In both cases the irritability can be referred to the nuclear chromatin.

Of course, this conception can only be put to work provided that a dynamic morphological theory of function is accepted. This theory postulates that structure and function are inseparable and that instead of function being dependent on structure, the reverse holds true, namely, that structure is dependent on function. This theory has already been developed by Dolley in the case of the nerve cell, as discussed in the introduction of this paper. It has already been set forth how as a result of continuous excitation the nerve cell changes in size, size relations, form, distribution of substance, and above all in the disappearance of nuclear materials and organelles, and also in the reconstitution of cytoplasmic formed

elements, so that the dependence of structure on function goes far indeed.

"The dynamic conception has come in with the great recent development of the experimental method. No better examples of its results are to be found than the enormous shift and play of the processes of stimulation. No one could follow such processes at all deeply, and not be convinced of an impermanence and conditionism involving even the foundation of the cell, though the latter withal is relatively stable and is only affected by mass effects or very prolonged factors" (Dolley, Chapter 2, unpublished work).

A priori, this dynamic conception can be applied to cloudy swelling, for it is a well known fact that cloudy swelling is a phenomenon of functioning cells. The most susceptible cells to cloudy swelling are the highly specialized cells, such as those of glands, muscle, and nerve. The conditions of cloudy swelling are in accordance with the definition of the stimulus, since they are nothing else than changes or alterations in normal vital conditions external to the cell. Therefore, this would lead to the assumption that the diverse changes which are usually classified as cloudy swelling are nothing else than the results of different stimuli which are working through irritability to simple or more complex processes of excitation and depression.

This deduction is based upon the support of the following sources: first, the nerve cells are frequently described as the seat of cloudy swelling. As it is, however, known from the work of Dolley and his associates there is not such a specific state as cloudy swelling in the nerve cells. It was proved experimentally by Simmons and Martin who worked in this laboratory that agents which are said to produce cloudy swelling, respectively diphtheria

toxin and heat exhaustion, give results of processes of excitation and depression, and also a combination of the two, namely, initial excitation followed by later depression. These variations depend upon the force and frequency of administration. Special features of cloudy swelling may belong to excitation alone, as for instance the vacuolation and swelling. On the other hand, granulation is mostly a characteristic feature of depression alone. As a matter of fact however, it is the combination of the initial excitation with later depression that conforms to the usual description of cloudy swelling. This is also in agreement with the well known fact that the greater part of pathological stimuli are initial excitants and later depressants. Therefore, a conclusion could be drawn that the so-called cloudy swelling of the nerve cell is nothing else than a process of cell stimulation conditioned by abnormal stimuli. Consequently, it would be only reasonable to assume that the same processes take place in cloudy swelling in other functioning cells in accordance with the irritability that they possess.

Another anatomical homology between cloudy swelling and the processes of stimulation is provided by Adami (Principles of Pathology, Vol. I, p.816). He states that there are three stages of cloudy swelling: first, the increase of the nuclear chromatin; second, the accumulation in clumps at the periphery of the nucleus, with the achromatic substance in the center (chromatolysis); finally, complete chromotolysis and karyorrhexis.

It may be added that the latter - karyorrhexis - is the characteristic feature of depression, while hyperchromatism of the nucleus, and chromotolysis are phenomena of both excitation and depression.

A still further connection of cloudy swelling with stimulation is furnished by the identity of its phases with those of overwork. For instance, Schilling ('94) found that after ligation of the renal vein of one kidney in the rabbit, bringing it thus to a state of no function, the other kidney after forty-eight hours showed changes of cloudy swelling, which he interpreted as a result of compensatory overwork. Adami is of the opinion that all indications are those of stimulation.

In correlation with the above said the work for this paper was undertaken to demonstrate that the changes taking place in the secretory cells of the liver are identical with those in the nerve cells under both normal and abnormal stimuli and to prove that cloudy swelling is nothing else than a product of stimulation.

Experimental Data.

The experimental material for this investigation consisted of bull frogs and rats. The work on the frogs was rather undertaken as a preliminary part. The interest to study the frog's liver was incited by an article written in German by Eugenie Koiransky ('04).

The author of this article made an extensive study of the liver of the frog, salamander, and triton. Her aim was to study the question of the extranuclear basic material from the point of view of its origin, whether it is of protoplasmic or of nuclear origin. If of nuclear origin, it would be correlated with the idea of Garnier's ergastoplasm theory. She demonstrated the presence of basic chromatic substance in the form of rods, flakes, and masses in the inner capillary zone of the frog's liver. She came to the conclusion that this extranuclear basic material or ergostoplasm was of nuclear origin primarily, adding that "it is in no way proved that there is a localized qualitatively peculiar part of the cell body's architecture concerned". After reading this article the question came up whether there is not an identity between this ergastoplasm and the extranuclear chromatin in the nerve cell worked out by Dolley on the basis of Hertwig's and Goldschmid's theories.

Source of material.- Frogs. The frogs were caught in the beginning of the fall about the fifth of October and were stored in the animal house. Out of that batch of frogs seven were used as experimental material for the purpose of this paper. Out of these seven frogs, two were used as controls, and the rest were subjected to the following experimental agents: pilocarpine, secretin, heat, and room temperature. A more detailed description of the experimental procedures is given in the accompanying table I.

A remark ought to be made in advance that this experimental work was complicated by the fact that the frogs were under abnormal conditions for five months. They refused to eat, and even in the fall, the room temperature was above that of their natural habitat. These conditions of starvation and temperature had an effect on them before and during administration of the drugs. That this is true is confirmed by the data of measurements in the accompanying table. So definite, however, are the processes of excitation and depression, that it has been possible to discount the known effect of these complicating factors.

Rats. - The experimental material for the major part of this work consisted of twenty-seven rats, albinos and half-breeds. The measurements were taken only from seventeen, but the microscopic examination was performed over all the material in possession. Out of these twenty-seven rats four were normals used as controls. The rest were subjected to the following experimental conditions.

1. Bile salts: sodium glycocholate and sodium taurocholate.
2. Hydrogen gas inhalation.
3. a. Hemolytic streptococcus in growth emulsion.
b. Diphtheria toxin.
c. Heat exhaustion.
d. Antityphoid bacterin and B. typhosus in growth emulsion.

These experimental agents were undertaken with the following theoretical plan in view: namely, the bile-salts were expected to work as pure excitants; the hydrogen gas inhalation as a pure depressant by its replacing oxygen; and the others, hemolytic streptococcus, diphtheria toxin, B. typhosus, and heat exhaustion, as initial excitants and later depressants.

The results, however, obtained did not justify in some details the theoretical expectations made beforehand. For instance, the

bile salts instead of furnishing controls of the excitation side, since they are stated as the best excitants of liver function in all of the pharmacology text-books, turned out to belong in most doses to the group of initial excitants and later depressants. The solutions used were of a strength which ranged from five per cent to five tenths of one per cent. By varying the doses and also the duration of time, the results showed stages which varied from an almost pure excitation to some degree of depression, the latter being in accordance with the greater strength or frequency of the dose administered.

Such was also the case with the hydrogen gas inhalation. A number of rats were subjected to this gas inhalation in the laboratory by W. D. Collier who kindly handed over the liver material to me. This gas inhalation varied from two days duration to almost two weeks, the inhalation being repeated about every other hour and still no state of pure depression was observed. The inhalation of such a gas sets up in the organism a very complicated series of processes. In every one of the prepared slides there were observed stages of initial excitation which were associated with a greater or less stage of depression.

The hemolytic streptococcus which was administered in a solution of growth emulsion with saline furnished the best possible results of pure excitation instead of initial excitation and later depression as was expected.

The diphtheria toxin was used in dilutions of 1:1000, 1:100, 1:10, and 1:5, and also in concentrated form. The dose and also the duration of time in administration ^{were} ~~was~~ varying and in accordance with that the results ranged from an almost pure excitation to a very deep depression. Consequently, diphtheria toxin works as an initial excitant followed by depression for the liver as it has

already been proved (by R. R. Simmons) for the nerve cell who worked in this laboratory several years ago. He worked on rabbits, animals that are very susceptible to this toxin. Rats, on the contrary, showed great resistance and insusceptibility to this bacterial toxin. As a matter of fact, it was a very difficult thing to work out the minimal lethal dose. The first experimental injection consisted of the M. L. D. for a guinea pig, which was one cubic centimeter of a dilution of 1:1000 per day. This dose was gradually and continuously increased up to two cubic centimeters of concentrated diphtheria toxin per day, and even that was not fatal to the rat.

Heat exhaustion was used as follows. The rats were placed in a hot air oven provided with a thermometer and a thermostat for regulating the temperature. A floor of asbestos was placed in the oven in order to make it more comfortable for the animals. The starting point of the temperature was from 40°C up to 50°C, the increase being made very gradually. Intensity of heat and duration of time were varying, namely, one of the animals was kept in the oven for a brief time under a high temperature while the other rat was subjected to a mild temperature for a long time. The results in both cases were a combination of initial excitation with a later depression as expected since this agent had been already used in this laboratory by F. A. Martin who worked on the rabbit's nerve cells.

A combination of initial excitation with depression was also obtained from these rats that were injected with antityphoid bacterin and *B. typhosus* - growth emulsion, as it was expected. A remark ought to be made that the rats showed great resistance in all experimental conditions to which they were subjected.

Microscopic technic. - The animals, frogs and rats, were chloroformed and blocks about three to five millimeters in thickness were removed from the liver. The tissue obtained was placed immediately in the fixatives that had already been prepared.

Fixatives used.— 1. The bichloride formalin method of fixation. This fixative consists of 95 cubic centimeters of saturated mercuric bichloride solution and five cubic centimeters of a 40 per cent formaldehyde. After twenty-four hours of fixation the tissues were carried through progressive grades of alcohol. The 80 per cent alcohol contained iodine to remove the excess of bichloride. The tissues were kept in the iodized alcohol for three days until the iodized alcohol was no longer decolorized. After absolute alcohol the sections were placed in cedar oil for from two to three hours, then passed to xylol for two hours, and finally to a saturated solution of paraffin and xylol, also for two hours. The final change was to 52°C paraffin for twelve to eighteen hours in the incubator. They were then imbedded in paraffin, cooled, and ribbons from four to five micra thick were cut and mounted.

2. Zenker's Fluid. This fixative consists of a solution of bichromate of potassium 2.5 Gm., corrosive sublimate 5 Gm., distilled water 100 cc, and glacial acetic acid 5 cc. The acetic acid is added to Zenker's fluid at the time of using. The tissue is kept in this fluid for twenty-four hours, and then washed in water for twenty-four hours. After this the procedure is the same as for the bichloride formalin method, with this difference that the tissue is kept only for twenty-four hours in the 80 per cent iodized alcohol.

Carnoy's Fixative. This fixative consists of a mixture of absolute alcohol six parts, glacial acetic acid one part, and

chloroform three parts. The tissue is fixed for twenty-four hours, transferred to absolute alcohol for twenty-four hours, and then it is carried through the cedar oil, xylol, and paraffin as the others.

Stains used. - 1. Dolley's modification of Held's erythrosin-toluidin blue method. This method consists as follows: The slides are carried through xylol to remove the paraffin, then through the graded alcohols to water. They are stained for one and one-half minutes in erythrosin which has been warmed to 45°C, washed thoroughly in water, and then placed in toluidin blue for seven minutes, again washed thoroughly in water, decolorized in 70 per cent and 80 per cent alcohols, differentiated in 95 per cent alcohol, dehydrated in absolute alcohol and cleared in two xylols, and mounted in Canada balsam. 2. Delafield's hemotoxylin with aqueous eosin as a counter stain. Sections were stained for half a minute in a concentrated solution of Delafield's, washed in water and placed in eosin for five minutes. 3. Grübler's eosin in 5 per cent solution followed by Unna's alkaline methylene blue. The sections were kept for ten minutes in each and then the same procedure as in the other stains used.

Data of Observation.

Results of measurements.— The technic applied in measuring the liver cells - frogs and rats - consisted of the following scheme. Tracings were taken from the liver cells by means of the camera lucida from the Leitz microscope, ocular ten, oil immersion objective. The magnification was about 1050. These tracings were measured by the polar planimeter which gave the areas in square millimeters. The latter were then reduced to square micra. By these means the area of the cell as a whole was obtained first, then the area of the nucleus. Subtracting the nuclear area from the cell area gave the cytoplasmic area. By dividing the plasma area by the nuclear area, the nucleus-plasma coefficient was obtained, the figure of index by which the states of excitation and depression can be identified mathematically as it has been done for the nerve-cell. The preliminary data from the frog are set forth in Table I, the rat data in Table II.

The outstanding features of the data of Table I are the figures representing the measurements of the frogs stimulated by pilocarpine and heat exhaustion. Pilocarpine is a well known excitant agent to glands, while heat exhaustion is largely a depressant. The results obtained are in accordance, and are very striking when compared with each other on one hand, and with the results of measurements of the first normal on the other hand. For example, the cell area of the normal frog reads 347.57 square micra, the nuclear area is 42.95~~50~~ square micra, and the nucleus-plasma coefficient is 7.09. Now, these respective readings for the pilocarpine animal are 605.85~~50~~ square micra for the cell, 59.91~~50~~ square micra for the nucleus, and 9.11 for the nucleus plasma coefficient. The almost double increase of the cell area, the

relative increase of the nuclear area, and the difference in the two nucleus-plasma coefficients of 2.02 are points which indicate very clearly the state of excitation, since in this state the balance of the nucleus-plasma relation is in favor of the cytoplasm. The readings for the frog under heat exhaustion are as follows: 143.16~~88~~ square micra for the cell area, 40.45~~58~~ square micra for the nuclear area, and 2.53 for the nucleus-plasma coefficient. The decrease in these figures is so evident that no further comments are needed in order to see that these are figures representing a state of depression - a state characterized by a great shrinkage of the cytoplasm, a relative diminution of the nucleus, and a decrease in the nucleus-plasma coefficient as compared with the animal of control. The other experimental frogs in this table, and also the second normal give results complicated by conditions of starvation, since, as it was already stated, these animals were kept in the dog house from forty to sixty days. The influence of these effects is illustrated by the measurements of frog eleven. This animal was subjected to no other stimuli than fifty-three days of starvation and room temperature. The respective areas and the nucleus-plasma coefficient are figures of depression. For instance, the cell area is 202.09~~58~~ square micra - almost half the size of the first normal. The effect of excitation by secretin is indicated by the measurements of frogs thirteen and twelve. In spite of the fact of their long captivity, their measurements show an increase due to the stimulus on one hand as compared with the animals of depression. On the other hand, they show the effect of starvation in comparison with the pilocarpine animal.

Turning now to the second table the most interesting results are observed. As it has been already indicated the bile salts were undertaken as agencies to produce excitation alone. In glancing

over the measurements we can see that the areas of cell and nucleus and the nucleus-plasma coefficient gradually increase up to a certain point in accordance with the increase of the strength of the stimulus, which is equivalent to increase of dose and duration of time. As an example can serve the figures expressing the measurements of rats fifteen and sixteen. Rat fifteen has a cell area of 416.11~~55~~ square micra, whereas the cell area of rat sixteen reads 578.05~~59~~ square micra with a nucleus-plasma coefficient of 6.15, an outstanding figure in the whole table. These figures are strikingly different from the figures expressing the measurements of the controls. The largest cell area of the normals is only 344.34 micra, and its nucleus-plasma coefficient is 4.08. So it is quite obvious that the increase in size is due to the excitant stimulus, in this case the bile salts. The greater the stimulation, namely, with the increase of dosage and duration of time, the size of the respective areas and the nucleus-plasma coefficient increase accordingly. This, however, holds true to a certain degree only, since the measurements of rat eighteen show evidences of depression as indicated by the cell area which is the smallest of the series, namely 325.59~~60~~ square micra. The other figures for the same rat are proportionately decreased. This is evidently due to the fact that the dosage and duration of time were greatly increased, double as compared with that of rat sixteen. A remark ought to be made, however, that this state of depression is not the only one in the series, since rats thirteen, fourteen, and nineteen show also signs of depression in their size proportions as compared with the normals on one hand, and with the most excited on the other hand. The structural changes of the same animals show initial excitation followed by depression - the latter varying with the dosage.

The measurements of the rats subjected to hydrogen gas inhalation are figures of depression. This is indicated by the cell area that reads 227.41 square micra, the nuclear area being 66.93 square micra, and the nucleus plasma coefficient 2.39. These figures are in agreement with the characteristics of depression, namely, a shrinkage of the cytoplasm, a relative decrease of the nucleus, and a smaller nucleus-plasma coefficient as compared with the normal. But even this state of depression is not pure as indicated by the other animal subjected to the same agent. These figures are relatively increased. It may also be added that although the measurements were taken only for two rats, material was obtained from four and microscopically examined. It was found that all showed signs of initial excitation - a fact which may probably be due to some sort of compensation going on in the liver on account of lack of oxygen, just as well as the heart and lungs show compensatory overactivity.

The resultant figures obtained for the series of rats subjected to diphtheria toxin are of the same character, namely, the increase in size is in accordance with the increase of dosage and duration of time up to a certain point. When this point is reached the depressant effect takes the overhand. These results are all mainly results of a combination of initial excitation and later depression, ranging from a marked excitant state to a marked depressant state according to the stimulus.

The same holds true for the animals subjected to heat/exhaustion. The animal subjected to a higher temperature for a short time shows initial excitation and marked depression whereas the one that was subjected to a milder temperature for a longer time is characterized by a marked excitation followed by depression.

In summing up these results, it is quite evident from the above survey of the ~~resultant~~ measurements that there is no such factor as a pure excitant or a pure depressant. Even in the case of the bile salts - which are probably mostly a pure functional excitant - it is noticeable that the increase in size of the respective areas of the cell ~~are~~^{is} in accordance with the increase of dosage and duration of time up to a certain point. With a still further increase of these two factors the results of depression come up. The same holds true for the diphtheria toxin, heat exhaustion, and to a slight degree for hydrogen gas inhalation. Consequently it is the combination of the two - initial excitation followed by depression - that is the ~~trend and~~ predominating state in the type of stimuli used. Their action is primarily dependent on the intensity and duration of administration and not on the nature of the factor itself. This is proved by the fact that a small dosage of a certain experimental agent used for a short time produced excitation mainly, whereas a larger dose of the same stimulant brought forth various stages of depression. The same results were also obtained by varying the time, namely, the same dosage of the same agent which when used over a short time resulted in a state of excitation, turned out to be a depressant when used for a longer time. By varying the combinations of intensity and duration varying results of states of excitation and depression were obtained. This indicates the fact that intensity and duration are the outstanding factors in stimulation, and that all physiological processes with their morphological changes going on in the organism under the influence of changed conditions depend entirely on the intensity and duration of the stimulus used. This is only a confirmation of the statement made by Verworn in his General Physiology: "The same

stimuli which in less intensity or shorter duration produce excitation, in greater intensity and longer time can lead to just the opposite effect, namely depression."

Microscopic Description. - Plates I and II represent the results of microscopic observation obtained from the frog's and rat's liver cells. The figures on these plates illustrate the cells of the liver in a normal condition on one hand, and those in conditions of stimulation on the other hand. Since the main factors of stimulation are excitation, depression, and a combination of the two, the drawings were subdivided accordingly, and they will also be discussed in the same order.

A remark ought to be made that the drawings of the frog's liver were made from a Carnoy's fixative, while those of the rat's from a bichloride-formalin fixation. This fixative was neutral in the case of figure four, ^{plate II,} and acid in the other cases. The stain used throughout was the erythrosin-toluidin blue stain.

Figures 1 in plates I from the frog and II from the rat are cells in a normal condition and there is no need to go into a description. It simply can be pointed out that the cell and nuclear walls are intact, the contents of the cell and nucleus are compact, and that the cytoplasm is granular in character in both frog and rat's liver. Passing on to figures 2 in plates I and II respectively it is quite noticeable that the cytoplasm and nucleus are very edematous as compared with the normal. Vacuolation is more characteristic of the frog's liver cell, while the rat's liver cell shows more granularity. Hyperchromatism of the nucleus is marked in both cases, while the increase of chromidial apparatus is very conspicuous in the rat's liver, and only slightly indicated in the frog's liver cell. Figure 2 in plate II shows beautifully the

progressive decline of function in the liver cell of the rat by the progressive diminution of the chromidial apparatus in those cells that are in a state of great activity. It can be seen clearly how the cells pass from a condition of great activity to a condition of exhaustion. The latter is indicated by those cells which have lost their chromatin entirely. In some of these cells the nucleus still contains the karyosome, while in others the nucleus is exhausted, and in still others the nucleus has disappeared altogether. This state of exhaustion is also indicated in the frog's liver in figure 4, Plate I, where it has advanced far indeed. This hypochromatism is common to both these figures, and so is also the disappearance of the chromatin and plastin of the nuclei. But while chromotolysis pertains to both figures, karyorrhexis is only found in the frog's liver. It sums it up to say that all features of excitation are present in the cells in agreement with the experimental conditions. The frog was stimulated by pilocarpine - an excitant agent for glands, the rat with bile salts. As already brought out, this state of excitation is also indicated by the large size of the cell and relative increase of the nucleus as shown by the drawing.

Turning now to figure 3, of plate II, and figures 5 and 6 of plate I the conspicuous features of these drawings are: shrinkage in size of both cell and nucleus, with a relative advantage, however to the nucleus, hyperchromatism of the nucleus, and a great increase of its nuclear substance. The affinity of the nucleus for the basic stain as contrasted with the affinity of the cytoplasm for an acid stain is especially marked in figure 3, plate II. It is so conspicuous here that the nuclei look like dark spots on a bright field. Chromotolysis of the cytoplasm is complete since in this figure there is no trace of the chromidial apparatus. Karyorrhexis of the karyosome

is marked in both cases as well as the early stages of the loss of the nuclear membrane in some cells. Disintegration of nucleus and cytoplasm is common to both, and so is the density, turbidity, and granularity characteristic in both cases, frog and rat. These drawings are an illustration of a state of depression which was brought about in the case of one frog by thermal stimuli - heat exhaustion (fig. 5, Plate II), and in the case of the other by starvation and increased temperatures (fig. 6), and by trophic stimuli, hydrogen gas inhalation, in the case of the rat (fig. 3., Plate 2).

A combination of the factors of stimulation, initial excitation followed by varying degrees of depression, is illustrated by the drawings, figure 3, plate I, and figure 4, plate II. In these figures, especially that of the rat's liver, the effects of initial stimulation combined with depression are proved by the varying degrees of size of cells ranging between the extremes of pure excitation to almost pure depression. The general effect however is that of a prior excitation with a superimposed state of depression, the latter varying in degree. These characteristics are indicated by the uneven stain of the cytoplasm due to an edema of prior excitation which becomes obscured by the granularity of depression. Another factor pointing towards this combination of stimulation is the enlarged nuclei which in some cells are in proportion with the cell, while in others the enlargement is to the disadvantage of the cytoplasm. Some of these nuclei show traces of edema, while most of them are packed with the chromatin and plastin substances which are so characteristic of depression. The karyosome is absolutely and entirely missing in all of these nuclei, being disintegrated into a mass of basic granules scattered throughout the dense nuclear matrix, while chromatolysis, or the disappearance of

the chromidial apparatus is quite evident. Granularity and turbidity characterize the cytoplasm of both. In both cases the results are the same although the factor in one case - the rat - was heat exhaustion, while in the case of the frog there was a combination of secretin and starvation, the first usually an excitant, the second an agent of depression.

Interpretation of Results.

From this description of the liver cells in conditions of stimulation as compared with that of the normal state an homology can be made between the liver cells of the frog and rat on one side, and the nerve cell on the other. It is quite evident that the physiological processes going on in the organism under the influence of stimulation result in the same morphological changes in the structural make up of the liver cell as in that of the nerve cell. The states of hyperchromatism and hypochromatism as a result of the stimulus to work or activity, as well as the same states as a result of a stimulus inhibitory to functional activity take place in the liver cell just as well as in the nerve cell. In both cases the interpretation is that chromatin in the form of the chromidial apparatus is the energy giving material for the cell necessary for its functional activity and the potential energy of the chromidial apparatus is transformed into the kinetic energy. These states in functional activity with the attempt of the nucleus to furnish and supply the cytoplasm with the energy yielding material are most beautifully illustrated by the drawings of states of excitation (figure 2, plates I and II), just as well as the disintegration of the cell on account of the accumulation of waste products produced by a lack of oxidation and poor metabolism are illustrated by the cells of depression (figures 5 and 6, plate I and figure 3, plate II).

In both cases the homology is complete between nerve and liver cell. Further, it is quite evident that the reaction of irritability of the living cell is the chief factor in both cases, nerve and liver cell, which is shown by the fact that no matter what kind of a stimulant is used, the morphological changes are the same in brain and liver. It is also evident that the dynamic conception of the dependence of structure on function holds true in the liver cell as well as in the nerve cell, since the structural changes are homologous in both cases provided the same group of stimuli are used. This homology between nerve and liver cell is still more complete when a closer observation of figure 1, plate II is made. It is seen here that along with the type of the resting cell of the liver which is characterized by little chromatin within the nucleus, by a large karyosome and by a small amount of extranuclear nuclear material in the cytoplasm distributed through the cell in varying form according to the individual cell, there are also seen cells with hyperchromatism of nucleus and cytoplasm on one hand, and hypochromatism of the same in other cells on the other hand. These cells are either in a state of greater activity than the resting cell or in a state of ^{under}~~over~~activity. Since this is found in the normal liver cell it is quite obvious that the morphological changes taking place in the liver cells as a result of abnormal function are identical with those of normal function. In other words, the same changes that occur in the nerve cell also take place in the liver cell. The homology can be carried still further, namely that in both liver and nerve it can be seen that the stimulants can not be subdivided into agents of pure excitation or pure depression. On the contrary, it is quite obvious that the predominant part is a combination of the two and that the ruling factors in stimulation are the intensity and

duration of time of the stimulus on one hand, and the reaction of irritability of the functional cell on the other. In other words, the reaction of stimulation to the "altered external vital conditions" comprises all normal and abnormal functioning processes taking place in any of the functioning cells - liver or nerve.

Review of the Literature.

Virchow ('32) classifies cloudy swelling as a parenchymatous inflammation possessing a very degenerative character and leading to a loss of function of the organ affected by it.

In an other article "Reizung and Reizbarkeit" ('05, Irritation and Irritability) he states that the common cause of cloudy swelling of the liver and kidney is an increase of metabolism and the taking in of more food stuff as a result of irritation, and he thus connects up cloudy swelling with hypertrophy.

In his "Cellularpathologie" ('71) Virchow states that the tissue under the influence of irritability takes up more food stuff, thereby undergoing a temporary enlargement of the cells, which causes a disturbance of structure and function of the cell.

In still another place ('97), he says that cloudy swelling is due to an increased activity of the cell, stating thereby: "The swelling and cloudiness consist of a permanent intake of freed or loosened material which is transformed into granules in the cell, so that the main cause of the swelling is due not to the usual food intake, but to a transformation of it".

Benario ('91) in his investigation on cloudy swelling does not agree with Virchow's ideas. He says that the nucleus undergoes the same changes as the cell protoplasm. He sees in the enlargement of the cell not an increase of the vital cell substances since he is

of the opinion that an increase in volume can take place without any active work, and it was never observed that cloudy swelling leads to a lasting increase of cell substances. Neither does he consider cloudy swelling as a preceding stage of hypertrophy. He thinks that cloudy swelling from its very beginning is very degenerative in character. The enlargement of the cell is due to a swelling, and the cloudiness to a passive chemical transformation of the albuminous molecules of cell protoplasm. The main feature of degeneration Benario sees in the disintegration of the karyosome, or in karyorrhexis, and also in the fatty degeneration that constantly follows cloudy swelling.

Zeigler ('98) sees in the cloudy swelling a disorganization of the protoplasm as a result of the absorption of fluid, the latter causing a separation of the protoplasm into solid and liquid particles. The cell body atrophies while being transformed into a mass of granules. It is accompanied by fatty degeneration, by a swelling and then a disintegration of the nucleus.

Thoma ('94) considers cloudy swelling not a result of increased metabolism as Virchow does, but on the contrary, a result of the lack of food. The albuminous degeneration is a regressive metamorphosis which is characterized by the appearance of granular disintegrating products, due to the separating out of fine molecules of albumin.

Cohnheim ('82) thinks that cloudy swelling is nothing else than a curdling of liquid albuminous bodies.

Lukjanow ('91) ascribes cloudy swelling to a new formation of granules, since according to Altmann's theory the normal substance of the cell is of granular structure. This increase in granular bodies is due, probably, to a change in function of the nucleus.

Birch-Hirschfield ('95) considers cloudy swelling as the preceding step to fatty degeneration. He sees in it the accumulation of albuminous bodies in the cell protoplasm, since this degenerative change starts with an inflammation, so it may be based upon a progressive importation of albumin. In other cases it may be the expression of a disintegration of the proteid.

Schilling ('94) was the first one who investigated cloudy swelling experimentally. He experimented on rabbits. The experiment consisted in ligating one of the veins of the kidney and after forty eight hours he found the other kidney to be in a state of cloudy swelling on ^a examination ^{gross}. Therefore he thought that cloudy swelling precedes compensatory hypertrophy of the kidney due to the overloading of the blood with urinary substances. Microscopically he found a ~~diminution~~ in the Altmann's granules, and also a change in their staining reaction. Besides he also noticed breaks (edema?) in the cytoplasm which he correlated with the characteristic granules of cloudy swelling - all these changes being noticed in the primary convoluted tubules only. He finally came to the conclusion that the degenerative character of cloudy swelling makes its appearance very early in the process.

Galeotti ('93) experimented on lower animals with various poisons. He was of the opinion that the granular bodies found in a pathological condition differ from those in the normal cell by their shape and staining reaction. As soon as the process of parenchymatous degeneration begins the normal granules diminish in number, so that he came to the conclusion that the granules in cloudy swelling are rather a product of change in shape and aggregation of the albuminous molecules of the cytoplasm than a new formation of the same, since their staining reaction is the same throughout.

Landsteiner ('03) in his investigations about cloudy swelling states that the normal epithelial structure of kidney, liver, and rectum is of a filaceous and thready nature which is transformed into granular substances under the influence of abnormal conditions. The increase in size of the cells is in all probabilities due to a chemical disintegration of the protoplasm.

Adami ('08) makes the following statements about cloudy swelling: "There appear to be three stages in cloudy swelling: the first, of increase in the chromatin of the nuclei; the second, of accumulation of the chromatin in clumps at the periphery of the nucleus, the achromatic substance being accumulated in the center (chromatolysis); the final stage is such extensive loss of chromatin that the nucleus is almost unrecognizable, if it does not undergo karyorrhexis. The indications are those of stimulation, giving place to exhaustion of the nuclear material, with loss of chromatin" The preliminary increase in size and staining power of the nucleus and cytoplasm, would suggest (1) "That in cloudy swelling we deal with increased absorption on the part of the cell, and that the albuminous globules are the indication of matter assimilated and not utilized". (2) "Cloudy swelling is an indication of increased absorption of food stuffs with imperfect conversion and utilization of the same". (3) "It is possible that both opinions are correct up to a certain point".

In making a survey of the above discussions about cloudy swelling it is evident that the most valuable contributions to cloudy swelling were made by Virchow, Adami, Schilling and Galeotti. Every one of these investigators has approached the general problems of stimulation, but approached it from one ~~or the other~~ side only, namely, ~~either~~ as excitation alone, ~~or depression alone~~. It was in

fact for the most part a vague and unconscious approach, for the concept of stimulation in its modern interpretation has waited the generalization of Verworn. Great credit is due to Virchow, that so many years ago when the science of cytology was only in the beginning of its development, and when the experimental method was of the rarest application, he was the first man to correlate cloudy swelling with inflammation, and to look upon it as a product of stimulation, and unutilization of assimilated foodstuffs.

Schilling approached the problem from the point of view of hypertrophy due to compensation, a view that is correct, since the process of hypertrophy is a process of stimulation, but also he sees in cloudy swelling excitation only. The other investigators of cloudy swelling discuss chiefly the structure of the cytoplasm. Some of these scientists are of the opinion that the granularity of the cells in cloudy swelling is a result of that process, others, on the contrary, think that the normal structure of the cell is granular in character but that in a state of cloudy swelling the form and shape of the granules change from a finer character to a more coarse one, and they also are aggregated in clumps and masses instead of being individually scattered through the matrix of the cell.

It may be added that this last view agrees with the results obtained in this investigation. As a fact the cytoplasm in the normal liver cell has a granular structure. But in this state the granules are very fine and evenly distributed through the cell, whereas in a state of stimulation the granules are gathered in masses and clumps, and the form of the individual granules is coarser and larger in appearance than those in the normal cell.

Among all these investigators the most advanced view is advocated by Adami. He like Virchow considers cloudy swelling as a product of stimulation. He points out the features of excitation,

as for instance the changes in the chromatin of the nucleus, the hyperchromatism, and also the loss of chromatin - which is hypochromatism. He discusses chromotolysis and karyorrhexis, and he also points out the possibility that there is either an inability in the cell to utilize the assimilated foodstuff, or the utilization of the food is not in proportion with the increased absorption of the cell, and finally he adds that it may be both cases together.

It is quite evident that there are all factors of stimulation--excitation, depression, and the combination of the two. Adami, however, points out the excitation state only, thereby looking upon it in the restricted sense, in which stimulation is generally regarded by physiologists and clinicians at the present time.

The one-sidedness of Adami just as well as that of the other investigators in this field can be ascribed to the fact that they did not consider the conception of a dynamic theory, a theory which postulates, as already mentioned, that structure is dependent on function, and not function on structure as is the belief of the disciples of an adynamic or passive theory. It is quite obvious that with the latter view in mind the problem of cloudy swelling could hardly be attacked. The possible solution of this problem can be approached when and only when the dynamic theory is accepted. This theory teaches that the structure of the cell is only relative, whereas the irritability of the cell is absolute. This theory further advocates that the reaction of irritability is the alpha and omega of all the primary processes going on in the cell, and that all the morphological changes occurring in the cell are the results of physiological reactions ^{due} to the "alteration of the external vital conditions", normal or abnormal. Therefore it will only be logical to finish up this paper with the same statement that was placed in its

beginning, namely: "Irritability, stimulus, stimulation; the property, the agent, the process; the action of the stimulus on cells possessing irritability results in stimulation". It is the irritability that is responsible for all the normal changes occurring in the cell, to which cloudy swelling is now added from the pathological.

Conclusions.

1. The reactions of stimulation or more properly the reactions of irritability, in its forms of excitation or depression, or a combination of the two, are the same in the liver cell as in any other functioning cell, for instance the nerve cell.
2. The state known as cloudy swelling is only the series of morphological changes in the liver cell due to the forms of stimulation, excitation, or depression, though mainly a combination of the two.
3. There is no specificity in the reaction of stimulus as excitation or depression since the reaction depends entirely upon the intensity of the stimulus and its duration in time.

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TABLE

Nucleo-Cytoplasmic Relations of the Rat's Liver in

Number of Experiment:	Days from capture	Dates	Days of adminis- tration	Experimental: agents	Relative area of cell.
1	over night	10/5 /20	none	none	347.57 sq. mic
10	40	11/6 /20 11/15/20	none	none	314.52 sq. mic
5	34	10/11/20 11/9 /20	29	Pilocarpine	605.85 sq. mic
13	57	12/3 /20 12/8 /20	5	Secretin	541.43 sq. mic
12	67	11/3 /20 12/14/20	42	Secretin	352.00 sq. mic
11	53	10/5 /20 11/27/20	42	Starvation and room temperature	202.09 sq. mic
15	101	10/5 /20 1 /16/21	35	Heat	143.16 sq. mic

States of Stimulation.

	: Relative : area of : Plasma	: Nucleus : plasma : coefficient:	: : Remarks :
mic.:304.62 sq. mic:		7.09	:First normal or control.
mic.:265.87 sq. mic:		5.46	:Effect of Starvation.
mic.:545.94 sq. mic:		9.11	:Excitation and exhaustion : uncomplicated.
mic.:461.60 sq. mic:		5.78	:Mild and long administration.
mic.:282.60 sq. mic:		5.07	:Forced administration. Some : starvation.
mic.:159.43 sq. mic:		3.73	:Abnormal conditions.
mic.:102.71 sq. mic:		2.53	:Heat exhaustion and starvation.

TABLE

Nucleo-Cytoplasmic Relations of the Rat's Liver in

Number of Experiment	Experimental Agent	Number of Doses per Day	Total Dosage	Days of Adminis- tration	Relative area of cell.
1	none				:344.34 sq.mic.:
2	"				:356.27 sq.mic.:
3	"				:283.12 sq.mic.:
4	"				:285.12 sq.mic.:
13	Bile salts 5%	2	4cc.	2	:308.02 sq.mic.:
14	" " "	2	8cc.	4	:309.36 sq.mic.:
15	" " "	2	8cc.	4	:416.11 sq.mic.:
16	" " 5%	2	8cc.	4	:
	" " 1%	1	8cc.	8	:578.05 sq.mic.:
17	" " 1%	3	18cc.	6	:519.91 sq.mic.:
18	" " 1%	8-- $\frac{1}{2}$ cc. every hour.	73cc.	15	:225.59 sq.mic.:
19	" " $\frac{1}{2}$ %	9-- $\frac{1}{2}$ cc. every hour.	80cc.	16	:345.32 sq.mic.:
23	Hydrogen gas inhalation	6 hrs. gas inhalation 3 hrs. rest.		2	:227.41 sq.mic.:
25	Hydrogen gas inhalation	4 $\frac{1}{2}$ hrs. gas inhalation 4 $\frac{1}{2}$ hrs. rest.		8	:260.82 sq.mic.:
2	Heat exhaustion	3 hours a day, 50°C.		6	:121.09 sq.mic.:
12	Heat exhaustion	2 $\frac{1}{2}$ hours a day, 40°C.		23	:410.23 sq.mic.:
5	Diphtheria toxin 1:1000	Every other day	5 cc.	5	:461.13 sq.mic.:
7	Diphtheria toxin 1:100	1	6 cc.	2	:
	1:10	1	12.5cc.	5-10	:323.44 sq.mic.:
	1:5	1	6 cc.	3	:
6	Diphtheria toxin 1:100	1	10 cc.	5	:273.24 sq.mic.:
9	Diphtheria toxin concentrated	1	2 cc.	4	:341.40 sq.mic.:
20	Diphtheria toxin 1:1000	1	22 cc.	15	:339.44 sq.mic.:
21	Diphtheria toxin concentrated	1	22 cc.	15	:252.44 sq.mic.:

t States of Stimulation

ve	: Relative	: Nucleus	:
	: area of	: plasma	: Remarks
	: plasma	: coefficient:	
mic.	:276.68 sq.mic.:	4.08	:
mic.	:295.29 sq.mic.:	4.85	:
mic.	:236.32 sq.mic.:	5.05	:
mic.	:229.47 sq.mic.:	4.12	:
mic.	:232.97 sq.mic.:	3.73	:Initial excitation with slight depression.
mic.	:247.43 sq.mic.:	4.00	:Excitation a little more advanced.
mic.	:356.83 sq.mic.:	5.01	:Excitation more advanced.
mic.	:497.22 sq.mic.:	6.15	:Most advanced excitation and exhaustion.
mic.	:446.12 sq.mic.:	6.04	:Advanced excitation, exhaustion--a very : slight trace of depression.
mic.	:169.83 sq.mic.:	3.04	:Initial excitation followed by <i>marked</i> : depression.
mic.	:274.15 sq.mic.:	3.85	:Excitation. Great exhaustion. Slight : effect of depression.
mic.	:160.48 sq.mic.:	2.39	:Almost complete depression with signs : of excitation.
mic.	:200.82 sq.mic.:	3.34	:Almost complete depression with signs : of excitation.
mic.	:100.55 sq.mic.:	4.89	:Excitation and marked depression.
mic.	:328.82 sq.mic.:	4.03	:Marked excitation and depression.
mic.	:382.19 sq.mic.:	4.84	: Pure Excitation, exhaustion, with a : trace of depression.
mic.	:261.37 sq.mic.:	4.21	: Excitation and depression equally : marked.
mic.	:223.61 sq.mic.:	4.50	: Mostly depression.
mic.	:270.85 sq.mic.:	4.47	: Mostly excitation, slight depression.
mic.	:276.97 sq.mic.:	4.43	: Mostly excitation, some depression.
mic.	:193.16 sq.mic.:	3.26	: Excitation and depression.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 1

Figure 2

Figure 4

Figure 3

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COLUMBIA

ZOOLOGICAL LABORATORY

February 11, 1922.

Dean Walter Miller,
211 Jesse Hall.

Dear Dean Miller:

I have examined the dissertation, entitled
"A Cytological Study of Stimulation of the Liver", which
has been presented by Miss Anna Davidman for the Master's
degree, and recommend its acceptance. In my opinion, it
fully meets our requirement for the Master's dissertation.

Sincerely yours,

George Rejzner

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