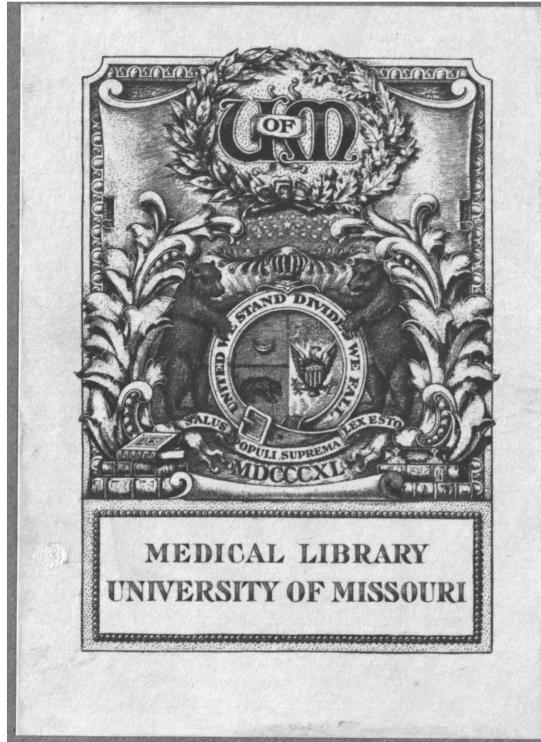


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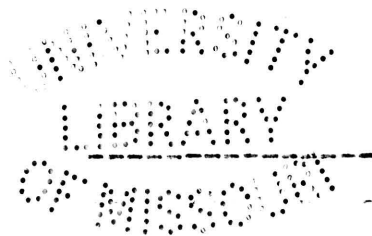
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Form 26

THE MORPHOLOGICAL CHANGES OF THE PURKINJE CELLS OF THE
CEREBELLUM IN HEAT EXHAUSTION IN CORRELATION WITH
THE CHANGES OF NORMAL FUNCTIONAL ACTIVITY.

by

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The Morphological Changes of the Purkinje Cells of the
Cerebellum in Heat Exhaustion in Correlation with
the Changes of Normal Functional Activity.

The condition of heat exhaustion, insolation or heat stroke has, in the past ten years, been thoroughly studied from a clinical point of view by observations of the signs and symptoms of the recovery cases, together with autopsies of the fatal cases. The condition is one of extreme exhaustion or depression, in which the temperature of the patient is considerably above normal, and apparently beyond the control of the heat regulating apparatus; and in which, as is made evident by the changes in the parenchyma of the organs, the metabolic processes are carried on at an extremely rapid rate.

In cases of recovery the patient may show no permanent effect, but in those cases in which there is a permanent disturbance, it is in most cases a lesion of the nervous system.

An autopsy of a fatal case will generally show a marked congestion of the thoracic and abdominal organs and of the meninges. The blood is dark and fails to clot readily. The kidney and liver show marked albuminous and alveolar degeneration. The heart muscle often shows albuminous degeneration and the spleen and lungs a marked congestion. The post mortem changes, especially those of the brain, occur shortly after death.

These conditions, the exhaustion, the inability of the heat regulating center to control the temperature and the permanent lesions of the nervous system, point to the brain as the center of activity of the changes taking place in heat exhaustion. And the object of this work is to determine the physiological pro-

cesses by the morphological changes in the nerve cells. With this in view, the Purkinje cell of the cerebellum of the cerebellum was taken as the type, because of its size and the ease with which the changes may be recognized; and because of the fact that in any condition in which the general nervous system is concerned, the cerebellum will probably take a part, owing to its function as one of the higher sensory and coordinating centers.

The Purkinje cells have been studied here in this laboratory under several different kinds of stimulation, and the results were in each case those of normal functional activity, though the activity may be carried to the point of exhaustion. Dr. Dolley, in a series of experiments of mechanical stimulation by manipulation of the intestines, found normal activity changes. Again a chemical stimulation produced by the injection of the toxins of certain bacteria gave evidence of the same type of reaction.

Reasoning, a priori, from these results we reached the conclusion that heat, as another form of physical stimulation, should produce the same changes.

If the morphological changes of the nerve cells are the expressions of the physiological activity, this indefinite, complex physiology must indeed produce a series of changes, themselves complex in their nature. The early investigators of this subject began their work on nerve cells of a low order, such as the cells of the sympathetic and spinal ganglia and the sensory and motor centers of the spinal cord and in their results there was a disagreement. This disagreement was due

to the fact that one investigator would find the changes of one phase while another worker would find the changes of a later or an earlier stage.

Among the early authors, Nissl and Vas attributed the augmentation of the chromatic substance to activity, Hodge and Mann to the state of repose. As to the changes in the size of the cell, one has admitted as a consequence of activity an increase (Vas), another, a decrease (Hodge). In the same way Vas has described an increase in the size of the nucleus in activity, while Hodge and Mann have found a decrease in volume.

Vas, experimenting on rabbits, stimulated the sympathetic a short distance above the superior cervical ganglion with a weak faradic current and found the nucleus notably larger. The cell body was increased about one third. The chromatic substance was a little more abundant but modified in its distribution, being sparse about the nucleus and lying in a coarsely granular ring about the periphery of the cell body.

Mann found that during rest the chromatic substance is accumulated in the cell body and consumed during activity. Activity is accompanied by an increase in the size of the cell body, nucleus and nucleolus in the sympathetic, sensory and motor nerve cells. Fatigue is accompanied by the shrinkage of the nucleus also of the cell and the formation of a diffuse coloring substance in the nucleus.

Lugaro attributed the various findings of the different authors, in part, to the remarkable difference in susceptibility of different individuals of the same species. The same amount of stimulation that would produce a certain degree of activity

in one animal, might in another animal of the same species show an entirely different stage. Lugaro repeated the work of Vas and expressed his results as follows:

1. The activity of the nerve cell is accompanied by a state of turgescence in the protoplasm of the cell body.
2. Fatigue produces a progressive diminution in the size of the cell body.
3. In the moderate degrees of activity, although the protoplasm of the cell body becomes turgescient, the nucleus is not subject to modification of volume.
4. When the activity is continued and prolonged for a long time, the nucleus submits to modification analogous to those of the cell body but less intense and slower.
5. The quantity of the chromatic substance in the cell body varies especially as to the individual characteristics by ratio of the size. While it is probable that the first phases of activity determine a slow augmentation of the chromatic substance, the latter phases accompanied by fatigue, show a diminution and more diffuse distribution.
6. The activity of the cell determines in the nucleus an augmentation of volume which gives way slowly to the action of reduction of fatigue.

Chiarini, Geurrini, Holmgren and others have described a part or all of these changes. These investigators have determined that in some stage of activity, fatigue or exhaustion, there is a stage of hyperchromatism and that there are changes in the size of the cell body and nucleus. Their main trouble is to agree on the sequence of events. The general idea

gathered from these reports is that there is, with activity, a decrease in amount of chromatic substance and a slow increase in the size of the cell. Beginning with fatigue, there is a slow shrinkage ~~shrinkage~~ of the nucleus and perhaps of the cell body.

Passing from the cells of the sympathetic and spinal ganglia to a cell somewhat higher in function and more highly differentiated in morphology, the Purkinje cell of the cerebellum, we find a cell more complicated in its changes yet more distinct than those of the lower ganglia.

The stages through which this cell passes from the state of rest to that of complete exhaustion have been thoroughly described and placed in their logical order by Dr. D. H. Dolley. For his material he did not resort to the stimulation of an individual group of cells, but to the fatigue of an animal as a whole by muscular exertion. An animal was placed in a tread mill and kept running, with brief intermittent periods of rest, until thoroughly fatigued. It was then killed with ether and the tissue fixed in the mercury-formalin fixative. Various modifications of this experiment, regarding the degree of fatigue and the period of recovery, were made so that a complete picture of the changes of activity, fatigue and recovery were obtained. These experiments, though necessary for the determination of the logical sequence of the different changes, are not at all necessary for the picture of the individual stages. In the cerebellum of the normal animal are to be found all the stages of activity and fatigue as described by Dr. Dolley.

The changes he describes as follows:

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 stages of progressive hyperchromatism, in which, in the pure type, the initial enlargement 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 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, and a late division, characterized by the sharp beginning of the nuclear edema.
- 7 and 8. Two stages leading to the primary disappearance of cytoplasmic chromatin.
- 9 and 10. The stages of secondary restoration of cytoplasmic chromatin. The chromatin is first piled up about the nucleus and then passes out.
11. The stage of the 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 main ideas in appreciating these stages are that this

extranuclear functioning nuclear material, the so-called Nissl substance, is derived through the nucleus, that it is used up in the course of the work and continually replaced by the mediation of the nucleus; that at first the supply is in excess of the demand, the hyperchromatism, but with long continued drain, the supply falls short of the demand and there results a progressive diminution in chromatin, the hypochromatism, and finally no chromatin at all".

Associated with these changes of the chromatin content are changes in size of both cell body and nucleus. From the state of rest of stage 1 the volumes of the cell body and nucleus are increased in stage 2 to approximately twice their original size. But this increase is of short duration for in stage 3 the volumes are considerably less than in the preceding stage. In stages 4 and 5 the cell body is still more shrunken but the nucleus at this point begins to increase in size. In stage 6 the cell body has begun to enlarge, and from this point until the cell is completely exhausted there is a gradual increase in the volumes of the nucleus and the cell body.

Following Hertwig's idea that for every cell the volume of the cell body bears a certain relation to the volume of the nucleus, ^{having expressed this} the relation being called the nucleus-plasma coefficient, Dr. Dolley has determined this coefficient for each of the thirteen ^e different stages. These values when plotted, complete a curve which appears constant for homologous cells of different individuals of a species. And although the value of the coefficient for any stage is not the same as that of the corresponding stage of another species, the trend of the



curve is the same for man, dog and rabbit. The curves for the dog as determined by Dolley is represented in figure 1.

This nucleus-plasma curve was determined for the cells of the rabbit as follows: For each of the first ten stages, ten cells were measured and the average for each taken. The volumes of the cells were measured in terms of millimeters from projections with the camera lucida, the relative volumes giving the same value for the coefficient as would the absolute volumes. This curve is represented in figure 2.

Source of material.—As an experimental animal for this work the field of material was limited to the cat, dog and rabbit; and as the same breed and size of dog could not be obtained in sufficient numbers, the cat and rabbit were chosen for the experiments. A few experiments on the cat, however, served to eliminate this animal as unfit material because of its excitability. The cats used, seemed, in their natural environments quiet and not easily excited, but when placed in the hot air oven they became very restless. Their excitement increased with the increase in temperature and reached a stage such as to make the results (to) the heat worthless because of a complication with the results of excitement. So for the remaining experiments, the rabbit alone was used and the results are assumed to be those of heat alone since no other factor seemed to enter the experiments. The rabbits were not excited when placed in the oven and remained so regardless of the temperature.

The normal or control brains were obtained by killing a rabbit quickly with ether. The brain was removed at once and placed in the fixative.

The exhausted brains were obtained by heating the rabbits in a hot air oven. The oven used was one fitted with a door in which there was a small window for observations throughout the experiments. A thermometer and a thermostat were placed in apertures in the top. The latter kept the temperature constant within the range of two degrees centigrade. A false floor of wood was placed in the oven about four inches above the original floor, beneath which were two small gas burners. A steady current of air passed in at bottom and through the top of the oven.

The animals were placed in the oven at a temperature only a few degrees above the normal body temperature and allowed to remain at this temperature for a short time. This was followed by a very slow increase until they were taken from the oven. The degree to which they were heated varied with the individual susceptibility. In those animals which were to be heated several times for the cumulative effect, complete exhaustion was not always obtained because of the fact that, if recovery was expected, the animal had to be removed before complete exhaustion was manifested. And in some cases they were removed before they had been sufficiently heated to produce marked exhaustion.

In every case the animal died from the effects of the heat. The brain and cord were removed as soon as was possible. Sections were taken from the worm, uvula, biventral and post, inf, lobes of the cerebellum, from the cortex and basal ganglia of the cerebrum, from the medulla and cord.

The duration and temperature of the individual experiments are expressed in Table 1.

Note on clinical observations.—Rabbit no. 1 when taken from the oven had a very high respiration and heart rate and was sweating profusely around the muzzle and feet. When first taken from the oven, the animal was still able to walk, but within a very few minutes it was unable to stand. Reflexes were greatly exaggerated. Thirty minutes later the animal could again stand and walk about though the movements were not properly coordinated. Following this was another period of depression during which the rabbit died. This fact was noted, when rabbits were allowed to recover in a warm room, that if they survived the second depression, recovery was assured; if they died it was during this period. In several instances cold applications were used to hasten recovery. On three of the animals were placed cold, wet towels and the animals died in a very short time. Two other animals were placed in snow packs. The snow when brought in contact with the warm skin produced at once clonic convulsions and the animals died within a very few minutes. The brains of the animals dying with convulsions were not used for heat exhaustion brains.

Technic, microscopic. The technic used in these experiments for fixing, imbedding and staining has been the same throughout the work. For fixation, a solution consisting of 90 parts of a saturated aq. solution of bichloride of mercury and ten parts of 40% formalin was used. The tissue was kept in this solution 5 to 6 hours, the time depending upon the thickness of the sections, then run through the graded alcohols, 24 hours in each, to 80% alcohol. The alcohols from 50% to 95% were iodized. In 80% the sections were left for 48 hours, then

placed in 95% for 24 hours, absolute alcohol for several hours and imbedded in paraffin.

The sections were cut 5 micra in thickness and stained by the following method.

Xylol	3 min.	30% alcohol	3 min
"	" "	water	" "
Abs. alcohol	2 "	Erythrosin(40 deg.Cent.)	1 min.
"	" "		
95%	3 "	washed in water	
80%	" "		
70%	" "	Toluidin blue	5 - 7 min.
50%	" "		
-----		washed in water,	

sections then decolorized in 95% alcohol, differentiated in a solution of 10% aniline oil in 95% alcohol, dehydrated in absolute alcohol and cleared in xylol.

Dolley, in his work on the nerve cells, has used this method for many different experiments and found it to be one of the best as well as the most convenient methods for staining brain tissue. And as the results have been consistently satisfactory, no other method has been used for the work on heat. The erythrosin gives a good picture of the cytoplasmic and linin structure and the toluidin blue stains both the chromatin of the karyosome and the extranuclear chromatin or Nissl substance.

The results of heat exhaustion. The results of these experiments are in general the same, differing only in degree of severity.

In taking up the changes of the Purkinje cells the first thing which strikes the eye of the observer is the high percentage of the large, edematous, hypochromatic cells. In some of the brains it would seem at first glance that all of the

cells have reached the higher stages of activity, nevertheless in every case are to be found cells, though few, corresponding to the hyperchromatic stages. The actual percent of the early stages differ in the different individuals, owing to their difference in susceptibility. Counts on several of the brains are shown in the following table.

		hyperchromatic	medium	hypochromatic
Normal	1	539	98	369
"	2	500	70	430
"	3	623	54	323
Rabbit	1	375	42	583
"	4	90	8	902
"	8	69	12	919

Rabbits 1,4 and 8 were exhausted animals.

The changes which are found in these cells appear to be those of normal activity, since they show the usual changes in size and chromatin, yet on closer inspection they are somewhat atypical in their appearance. The different stages as they are found in the heat exhausted animals may be described as follows:

1. The cells of this stage show marked changes though they are considered the normal resting cell, or at least just beginning activity. The amount of the extranuclear chromatin is about that of the normal cell. It is about evenly distributed throughout the cell body and though it appears dimly reticulated, it has a more homogeneous appearance than the chromatin of the normal cell. The nuclear substance is dense and has scattered through it small darkly stained granules of chromatin. These granules are also scattered around the nuclear membrane, most of them retaining their globular form, but a few are to be found flattened against the membrane. The karyosome appears as

a denser area of nucleolar substance in which are imbedded several of the chromatic granules.

2. Only a very few cells of this stage were to be found. They are cells considerably larger than the cells of the resting stage and having a large rounded nucleus. The Nissl substance appears as a homogeneous base with a faint reticulum, with small irregular nodes of heavier massed chromatin scattered through it. The greatest concentration of the Nissl substance is at the axon end of the cell and around the nucleus, and gradually decreases toward the opposite end. At this end and near the beginning of the dendrite, the cytoplasm is almost clear of chromatin and is stained a deep red. The nucleus is large and rounded. The nuclear substance is dense and has the chromatic granules in it as described for stage 1. But the nuclear substance as a whole has a decided tinge of blue, as evidence of a soluble intranuclear chromatin. The karyosome is an irregular body staining with the acid stain and being set with several granules of chromatin, remnants of the original karyosomal chromatin.

3. The cell of this stage is smaller than that of the preceding stage, with a variable appearance, owing to the difference in chromatin contents and its affinity for erythrosin. The chromatin of the cell of this stage may be so dense that the nucleus is invisible. It appears as a dense homogeneous mass fading out at the dendritic end. In some of the cells where the nucleus is visible, the chromatin is arranged in areas varying in density and giving the cell a mottled appearance. The cytoplasm where it is visible is a fine feathery network staining in some cells

a light pink, in others a deep red. The nucleus of this stage is small and irregular and stains like the nucleus of stage 2, though a deeper blue. The karyosome and the karyosomal chromatin have the same appearance as described for stage 2, and in fact this condition holds true for all of the first nine stages.

4 and 5. In these two stages the cells are small and shrunken, but the nucleus begins to enlarge in the latter part of stage 5. The contour of the cell body as well as that of the nucleus is very irregular. The amount of Nissl substance is considerably lessened in amount and again shows the reticulated network.

At this point it might be well to describe certain cells, very abnormal in their appearance, but which, judging from their size and shape, belong to stage 5. The nucleus is small and so darkly stained that its structure cannot be determined. The cell body stains a deep red and shows no evidence of Nissl substance. This cell represents one extreme and the cell as described above represents the other, and between the two range all gradations from one to the other. All of these cells have about the same size and shape, and though some of the cells of stage 3 resemble them to a certain extent, they occur only in stages 4 and 5.

6, 7 and 8. Following the decrease in volume of the cell body and nucleus of the stages four and five there is a gradual increase in size and decrease in Nissl substance through the stages 6, 7 and 8. The cell body is regular in outline and edematous and contains very little chromatin. The nucleus is large and the nuclear substance is more abundant than in the

cells of these stages in undisturbed functional activity. The appearance of the intranuclear chromatin is the same as in stage 1.

9. Here again is to be noted considerable difference in cells belonging to the same stage. The majority of the cells of stage 9 differ from the cells of the preceding stage only in size and amount of edema. But further differentiation is marked in some of the cells of this stage by the fresh output of chromatin. This new chromatin, which is characteristic of stage 9 in normal activity, appears in the cytoplasm as a crescentic body lying close to the nuclear membrane on that side which is nearest the dendrite.

10 and 11. During these two stages of activity the cell uses up what little chromatin it has received in stage 9 and continues to increase in size. The cytoplasm seems split from the outer wall of the cell by a large edematous area which entirely surrounds the cell. The intranuclear chromatin is somewhat reduced in amount, the granules appearing much smaller in most cases, than in the earlier stages. The nucleus still retains a goodly amount of the original nucleolar substance.

12. This stage marks the entire absence of chromatin either extra- or intranuclear

These changes, though having the general appearance of activity changes, may be contrasted with the changes of activity as follows;

The intranuclear chromatin, which in the normal cells is only found imbedded in the karyosome, making it appear as heavy chromatic body, is broken up into fine granules and

scattered through the nucleus. This condition is found in the cells of heat exhaustion in every stage, beginning with resting cell and disappearing only in complete exhaustion. In stage one and two and in some of the cells of stage three the extranuclear chromatin is present in an amount about that of the normal activity cells, but it appears much more homogeneous as if it were dissolved in the cytolymph. In some of the cells of stage three and five the amount is below normal. In the later stages it is below normal in the greater proportion of the cells. The nucleolar substance is much more abundant in the later stages of heat exhaustion than in the normal. The nuclei of the former increase in size but do not get very edematous.

Following the work of the cerebellum, sections were examined from the basal nuclei, medulla and cord and the type of cell found most abundant was a large, edematous cell having very little or no Nissl substance. In the cord, the cells of the posterior horn were farthest advance in the scheme of activity. In many of these cells were to be recognized the same changes in the intranuclear chromatin that have been described for the Purkinje cells.

Review of literature.- Goldschneider and Flatau, in 1897, experimentally exhausted rabbits by placing them in a thermostat at a temperature of 45 degrees centigrade. The animals were left in the oven for periods varying from thirty minutes to two and one half hours. In these animals they found the anterior horn cells were entirely changed. Only a trace of the normal arrangement and appearance of the Nissl substance remained.

The cells were increased in size and had a pale blue homogeneous appearance. The nuclei corresponded to the normal. The karyosome was irregular and stained darkly. The changes were found in the spinal cord, in the motor nuclei of the medulla and the pons. The latter showing the changes somewhat better than the cord.

G. Marinesco in 1905 and 1906 produced in new-born animals, dogs, cats, rabbits and guinea pigs, exhaustion by exposure to the afternoon sun of the months of August and July. He finds that the cells have lost their striated appearance due to the presence of Nissl substance. The cell is pale and edematous at the edges. The nucleus is swollen and slightly lighter colored, showing no reticulation. The nucleolus was more or less vacuolar. Marinesco describes certain cells in the guinea pigs, killed by insolation, which stain a peculiar yellow ochre, and contain neither reticulum nor fibrillae. Amato's experiments are similar to those of Marinesco. He obtained exhaustion by the same method, and his results he expresses as follows:

Cerebral cortex. The small pyramidal cells are greatly changed, the nucleus is swollen and sometimes distorted and more diffusely colored. The cytoplasm has an irregular, reticulated appearance. The cells have entirely lost their form. Other cells have a thickening of the protoplasm lying closely around the intensively colored nucleus. The large pyramidal cells are better preserved but the chromatic substance is lacking in the cytoplasm which stains a diffuse light color, thickened around the nucleus and split around the edges with vacuoles. Some of

these cells have entirely lost their form. The polymorphic cells are markedly changed. In some cases only a small diffusely colored nucleus is to be recognized. The intranuclear chromatin is broken up into small granules and scattered through the nucleus. These changes are the same as found by the writer.

For the Purkinje cells he describes the same change, an edematous cytoplasm free from chromatin, large light staining nucleus and the intranuclear chromatin broken up into granules.

Ewing, for insolation, heated rabbits in a dry air oven. The brains were hardened in Lang's fluid and stained by Nissl's method. He says of his results, " In the medulla all of the chromatic bodies of the nerve cells have disappeared, although some of the cells show a faintly visible network or a few dark granules in the cytoplasm. Large clear vacuoles were seen in the cells. The cell bodies look waxy, staining a light blue, their outlines were very irregular. The nuclei were almost without exception diffusely stained dark blue. About the nucleoli were often two to five dark granules, while the nuclear membrane was irregularly invisible. In the cord the chromatic bodies of the stichochromes had almost entirely disappeared, the cell bodies looking waxy, swollen and staining diffusely light blue, the periphery being very pale. In many cells traces of the chromatic bodies could be detected, (1) in the form of very pale, ragged masses of the same general shape as in the normal condition. (2) In the form of fine granules scattered through the cytoplasm; and (3) as a diffuse colorization of the entire cell. The dendrites showed an irregular network composed of granules, or occasionally a ragged spindle. The

nuclei were very darkly stained, their position was usually central, and they resembled the nuclei of the medullary cells.

Summary. Following these changes through the different stages we have found that they correspond to the changes of normal activity, in regard to their changes in size and shape and in general in regard to their changes in extranuclear chromatin. Judging from these results, the primary effect of heat must indeed be that of stimulation. But the changes in intranuclear chromatin, the subnormal amount of extranuclear chromatin and the failure to use up the nucleolar substance point to another effect, either directly due to heat or indirectly to the products of heat. To explain this effect, one must consider the intrinsic function of the cell, the formation of chromatin. The formation of chromatin, while apparently taking place in all stages, is more pronounced in the earlier stages of activity and again the stages of 8 and 9. Following Hertwig's theory of the formation of chromatin in general, the Nissl substance is formed through the cooperation of the cytoplasm and nucleus, and during its formation the acid staining substance is consumed. There are the following points to be interpreted.- First, in the cells of heat exhaustion this substance is not consumed, as it undoubtedly is when there is an active formation of chromatin under perfectly normal conditions. Second, in all stages and particularly in the stages where chromatin formation is normally most active, the marked deficiency of available chromatin shows that the supply is not keeping up with the demand. Third, the chromatin of the karyosome is normally the last to disintegrate, and this only occurs

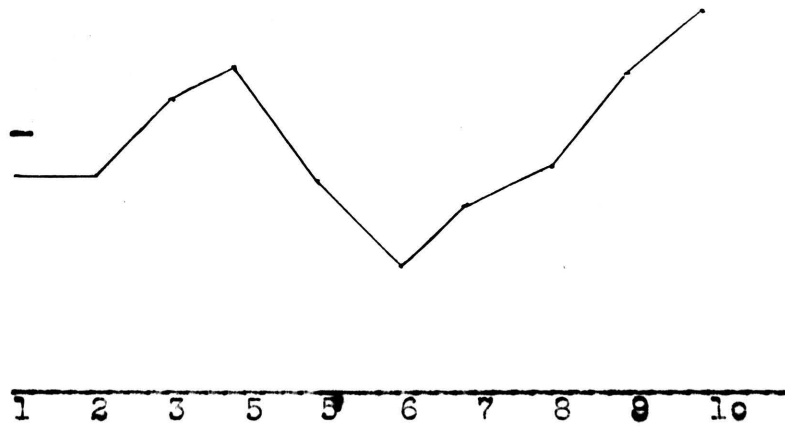
when the formation of chromatin through ordinary channels has ceased. The premature dissolution of the karyosome then affords strong indication that it is under a similar influence, when taken in connection with the other points. That is, the ordinary continuous formation of chromatin has ceased in such a degree that the karyosome is affected structurally, and its reserve supply is demanded. These facts point uniformly to an impairment of the chromatin formation and are considered to indicate, anatomically, a state of depression.

If the first effect of heat is a stimulation, the secondary effect is in all probability not the direct effect of the heat, but the effect of the products of heat, as the waste products of metabolism are very abundant since the metabolic processes are carried on at such a high rate. From physiological experiments, such waste products depress the functions of the cells. It seems reasonable that this is the anatomical explanation in part at least of ^h physiological depression. In terms of this explanation the primary effect of heat is one of stimulation, for the cells are not so altered as to fail to show their generally exhausted condition. On top of this, there comes the waste products, produced in excess by the overactivity, not only of the brain, but as the peculiar feature of this form of stimulation, of all the body cells. The mass effect of this is to throw the previously active cells into depression.

The intranuclear chromatin of the *Purkinje* cells, if it cannot be accepted as directly transformed into extranuclear chromatin, is concerned in the formation of the Nissl substance as the chromatin of the simple, unmodified cells is concerned

in any of the functions of that cell. When the products of metabolism have become sufficient to produce a depression of the formation of Nissl substance, this chromatin inside the nucleus, in an attempt at accommodation, is broken up and scattered through the nucleus, apparently passing to the nuclear membrane, near the seat of the formation of chromatin.

_Figure No. 1.



_Figure No 2.

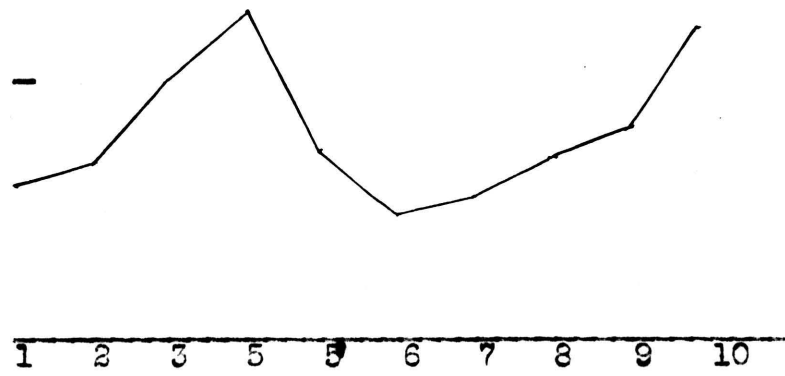


Table No.1.

Rabbit No.-sex-wt.	date	Placed in oven		Removed from oven		time of death.	Time in oven		Remarks
		time	temp.	time	temp.		hrs.	min.	
1. male 1295 gm.	1/30/12	2.00	35	3.33	48	4.55	1	33	Exhausted
2 female 2045	2/16/12	3.58	38	5.15	45		1	17	Not exhausted
	2/17/12	3.10	35	5.10	48		2		Exhausted
	2/19/12	2.34	38	4.15	47		1	41	"
	2/20/12	2.20	38	5.27	47		3	7	"
	2/21/12	3.20	38	5.20	45		2		Not exhausted
	2/22/12	9.35	43	11.40	48		2	5	Exhausted
	2/22/12	7.24	40	9.05	45		1	41	Not exhausted
	2/23/12	2.50	40	4.30	46	4.35	1	40	Exhausted
3. female 1785 gm.	2/22/12	2.10	40	3.30	48	3.30	1	20	Exhausted
4. female 2215	3/5/12	10.10	38	11.45	44		1	35	Not exhausted
	3/8/12	2.35	39	5.09	48	8.30	2	34	Exhausted
5. male 3550	3/11/12	2.15	38	4.50	45		2	35	Exhausted
	3/12/12	10.23	40	12.50	43		2	17	"
	3/12/12	8.04	38	10.00	45	10.40	1	56	"
6. male 2256	3/14/12	2.08	38	4.00	45	4.30	1	52	"
7. male 1520	3/20/12	3.13	38	4.40	47		1	27	Not exhausted
	3/21/12	2.10	40	3.45	45		1	35	"
	3/22/12	4.39	39	6.00	45		1	21	"
	3/23/12	2.13	40	4.00	45	5.00	1	47	Exhausted
8. female 1650	3/26/12	8.30	39	9.50	41		1	20	Not exhausted
	3/26/12	2.00	38	3.35	41		1	35	"
	3/27/12	9.50	40	11.20	42		1	30	"
	3/27/12	2.21	39	4.00	44		1	39	"
	3/28/12	8.55	40	10.55	43		2		"
	3/28/12	2.05	39	4.10	45		2	5	Exhausted
	3/29/12	3.00	39	5.00	45		2		"
	3/30/12	8.53	41	10.48	46		1	55	Not exhausted
	3/31/12	9.25	40	11.35	44	3.15	2	10	Exhausted

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