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THE SIGNIFICANCE OF THE REMOTE
NERVE CELL CHANGES
RESULTING FROM SHOCK

by

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Introduction

It is the purpose of this article to discuss the results of a number of experiments performed upon dogs to determine, if possible, the remote nerve cell changes resulting from shock.

The Sources of the Experimental Data
and the Operative Technique

(Table I.)

The data made use of in this article were obtained from experiments upon ~~thirteen~~ dogs. No attempt was made to discriminate between male and female animals. But an attempt was made to choose dogs of nearly the same age and size as possible, and all of those chosen were in good physical condition.

The dogs, except in Experiments I and M.E. 8, which

were worked in a treadmill, were placed upon the operating table, anaesthetized, the abdomen opened up and the intestines manipulated gently by hand for definite periods of time, as will be seen from Table I. The intestinal manipulation was for the purpose of producing peritoneal irritation, which, as is well known, is the most convenient way of producing shock. The operation itself was, of course, conducive to the same effect. The animals were then allowed to recover for varying periods. In the recovery experiments, the operations were performed under strictly aseptic technique.

Profound shock was indicated in each case by a complete relaxation of the entire body and a very low blood pressure. Operations for recovery from this profound shock were very difficult owing to the extremely exhausted condition to which the animal ~~were~~ necessarily brought. To tide the animals over this difficult period, transfusion was resorted to, since the only hopes of saving the animals in this condition lay in raising and maintaining the blood pressure.

The data as relating to the experiments are set forth in Table I. (page 9)

These experiments fall into two groups. The first group, which includes Experiments I, II, and III, was to establish controls. The second group (Experiments IV-XII) includes the recovery animals. Of these, Experiments IV, V, VI, and VII are recovery after moderate, and Experiments VIII., IX., X., XI., XII. after profound shock. The animals after moderate shock were allowed to recover from one to three weeks,

and those after profound shock, two, three, four and six months.

This group was then supplemented by Experiment Muscular Exertion 8, from the recovery series of normal activity after exercise in a treadmill, as studied by Dr. D.H.Dolley. This experiment affords a picture of profound exhaustion with a recovery period of only one month.

It will be noticed that Experiment I, in addition to Experiment M.E.8, was upon an animal which was exercised as well as shocked. Both are permissible as giving a picture of exhaustion for, as will appear later, the nerve cell changes are the same, whatever the exciting stimulus, whether normal or abnormal. In this Experiment I, the animal had been worked to a high state of exhaustion and then for another purpose than my own, in association with Dr.Dolley, was subjected to the shock of an operation lasting 35 minutes, in which the dog was completely bled out. Being then moribund, it was anaesthetized to death and the brain tissue taken by me as an example of profound exhaustion.

Microscopic Technique

As soon as each animal was killed, tissues from the cerebellum, including (a) the worm, (b) biventral lobes, (c) uvula, and (d) posterior inferior lobes, were immediately taken and hastily placed in a fixing solution composed of 90 c.c. saturated corrosive sublimate solution and 10 c.c. of 40% formaldehyde solution. In this they were allowed to remain for 3 to 5 hours, according to their thickness.

From the fixing solution the tissues were passed through the graded alcohols, and allowed to remain for 24

hours in each, except in the 80%, which was for 2 to 3 days, or until all the sublimate was taken out. Iodine was added in sufficient amount from the 50% on to remove all traces of mercury. The tissues were then passed through absolute alcohol and xylol, and then imbedded in paraffin. After the paraffin had been removed in the usual way by xylol, the sections were passed back through the graded alcohols to water, were stained in a 1% solution of erythrosin, followed by a saturated solution of toluidin blue. After differentiation in anilin oil and 95% alcohol, they were dehydrated in absolute alcohol, passed through xylol and mounted in xylol balsam.

Summary of the Nerve Cell Changes which
have already been Determined for Func-
tional Activity

The essential findings of the leading investigations are as follows:-

a) Hyperchromatism is regarded as an indication of initial activity by Vas ('92), Valenza ('96) and Odier ('98).

b) Initial Augmentation of size occurs in association with hyperchromatism, Vas ('92) and Lugaro ('95).

c) Shrinkage of cell body and nucleus with irregularity of form is an early manifestation of fatigue. Hodge ('92 and '94), Valenza ('96), Pergen ('96 and '97) and Pick ('98).

d) That enlargement of the cell is associated with chromatolysis. Van Durme ('01), Odier (nucleus) ('98) and Guerrini (nucleus) ('99 and '02).

e) Dolley ('10) has confirmed and extended these observations and has classified the stages as follows:-

1) The resting cell. It is lacking in intranuclear chromatin except within the karysome (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 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 shaped. Both stages 4 and 5 are to be further divided into an early, the pure Hodge's type, and a late division, characterized by sharp beginning of nuclear edema.

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

7) and 8). Two 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 the secondary disappearance of cytoplasmic chromatin. With the complete using up of the previous supply, the karysome 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 chromatin content contained within the karyosome.

13) The exhausted cell.

Dolley has also demonstrated that the changes in shock are identical with those of normal functional activity. The physiological basis for this is that shock is caused by mechanical stimulation.

As the foundation for the present work, the changes of progressive activity were first studied. These findings have been confirmed. In addition to observation a series of measurements of ten cells to a stage was made and the cell and nuclear volumes calculated. From this data a curve of the nucleus-plasma relation has been constructed (Figure 1). For comparison, the average curve constructed by Dolley ('10, '11) for the dog is also presented. The course of these curves is obviously identical with the exception of the last stage. As the volumes themselves correspond with those given by Dolley, this discrepancy undoubtedly depends upon the smaller number of cells used in making the average.

The recovery from states of normal activity has been studied by Dr. Dolley. As would be expected from what has been said regarding shock, the exactly same changes in that condition in shock have been demonstrated by the writer.

The essential causes of recovery as given by Dr. Dolley for normal activity, and confirmed by myself for shock, are as follows:

There are three courses the cell may take. The first, which may be termed the regular course, is followed by cells fully capable of going back to the normal resting type. In

young and virile animals, the bulk of the cells fall into this group. On the part of the cell body, the essential changes are the uniform decrease to normal size and the gradual restoration of the chromatin content (Nissl substance). The nucleus, however, recovers more slowly, both as to size and as to the chromatin content of its karyosome. This harmonizes with the previous findings that in activity the nucleus comes to exhaustion first. The other two courses embrace cells which have become qualitatively damaged as the result of immediate and previous activities. Both temporary and permanent disorganization of structure result. The temporary disorganization is regarded as capable of great subsequent improvement. It follows in general the regular course as outlined, but not so perfectly nor completely, and exhibits an additional feature of irregularity of contour. The irregularity is due to loss of substance. As proved by comparison with old dogs, at some time in an animal's life history this irregularity becomes permanent and characteristic in a considerable number of fully recovered normal cells and is the first indication of senile change. The essentially permanent changes of disorganization embrace more marked distortion of shape, deficiency in extra-nuclear chromatin, loss of the karyosome, and, finally, partial and then complete loss of the nucleus. Such changes as these last form a striking feature of the picture of senility, and the subsiding, qualitatively damaged cells of activity give the full clue to their origin.

The method followed out in studying these changes was to differentiate all the cells possible into the thirteen stages of activity. 600 cells were thus diagnosed in each experiment. All cells, the stages of which could not be determined because not properly in section, were classified as undiagnosed cells and divided into two classes, hyperchromatic and hypochromatic, according to the amount of chromatin appearing, as compared with that in the normal cell. In the series of recovery experiments the recovering and permanently damaged cells were counted along with other diagnosed cells. The recoveries were further divided into three classes according to the degree of recovery each cell had reached.

Comparison of Differential Counts
of Cells (Table II)

It is obvious from the differential counts of the first three experiments that the dog of forty minutes shock was very little affected as compared with those of the dogs in profound shock of $2\frac{1}{4}$ and $2\frac{1}{2}$ hours, respectively, without recovery. In the former a large proportion of the cells are in the hyperchromatic stages and many cells are found in the recovery and resting stages: Whereas, in the two dogs of profound shock the reverse is found. Here the cells appear in large numbers in the exhaustive stages, few are found in recovery and practically none in the resting stages.

The vast difference that is seen to exist between the two dogs in profound shock in Experiments II. and VIII, is accounted for by the fact that the dog in Experiment II. was quite resistant, whereas the other dog was quite susceptible to the operation (Remarks Table I.). It might also be suggested since the latter dog lived for a short time after the operation, that during this time many of the cells that were yet active went on into exhaustion, and hence a greater number of his cells are found in exhaustion and the stages just preceding that condition. If this be the case, then there is no doubt but that cell activity continues to increase for a time even after the exciting cause has discontinued.

The counts in the series of moderate shock experiments (Experiments IV. to VII.) are seen to be very similar to those in the forty minute shock (Exp. III.). All the cells in each of these experiments are fairly well distributed among the different stages of both progressive and regressive activity. There are, however

a larger number of cells in the recovery stages, a condition naturally to be expected since these dogs were allowed to go for variable periods after the operation. The larger number of recovering cells also accounts for the smaller number yet in the final stages toward exhaustion, since cells in these latter stages have had an opportunity to enter into the process of recovery. ^{Incidentally,} The recovering cells found in the forty minute shock are undoubtedly such cells as were either in recovery from previous activity or ready to enter into recovery when the operation was begun. In these ^{moderate shock} experiments, some equally striking differences in the stages of activity and recovery are seen when compared with the two profound shock dogs (Experiments II and VIII). All of which might be said to point to the fact that the greater the amount of shock the greater will be the degree of cell activity, or, in other words, that cell activity will vary in proportion to the amount of shock. This fact is further emphasized by the following points: First, the second experiment in the moderate shock series, which received one hour of shock, does not show a condition as near the normal as does the first experiment which received only half as much shock; Second, the third experiment, which had twice as much shock as the first and twice the time of recovery, has only returned to practically the same stage in recovery. The fourth experiment, with three weeks recovery ^{and} showing a decidedly more normal condition than does the 30 minute dog with one week's recovery, indicates ^{rather} a greater recovery after this ^{length of} time. In this connection, it should be further noticed that there are a few ^{permanently} damaged cells present in all the moderately shocked dogs.

Discussion of Moderate Shock Series

The experiments in even such a moderate degree of shock as these bring out one thing quite clearly, that, even after a moderate shock, recovery will require months, rather than weeks, to be completed. None of these dogs have yet returned to a normal condition. This fact is forcibly brought out by the large number of cells yet appearing as exhausted and also approaching exhaustion. It further appears that there are a very few normal cells present even at the end of a three weeks' recovery, and that in none of the experiments are there very many nearly recovered cells. The facts all clearly indicate that in the dogs a process of recovery is still actively going on. The experiments also suggest the minimum amount of shock that might result in permanent damage to the nervous system, for in each of them, including even an half-hour of shock, a few permanently damaged cells were found. In the first three experiments of the table, if any damaged cells were present, ^{they} were classified as undiagnosed cells. None, however, were expected and none observed.

Discussion of the Profound Shock Series (~~IX~~ to ~~XII~~)

The series of profound shock suggest at the outset that a proportionately larger time will be required to recover after a prolonged shock than after a moderate one, and that from such a shock considerable permanent injury will result. The cells in this series, as in the moderate shock series, are found to be distributed among all the stages. A larger number, however, are found to be yet completely exhausted and

many are seen to be damaged. There are many more cells in each of these conditions than are found in the same conditions in the former series. This would seem to indicate that the profound shock had forced a large number of cells into exhaustion, and in a very short time, and that now they are ~~endeavoring~~ ^{returning} in equally large numbers to get back to their former normal state. This would indicate that these dogs are yet a long ways off from the completely recovered condition. With the permanently damaged cells ranging in number from 11% to 16% of the total count, with the number of completely exhausted cells nearly as great, and with many of the remaining cells yet among the final stages of activity toward exhaustion, all of these conditions after one, two, three and even four, and six ^{months} _{of} recovery, all doubt of a permanent injury having resulted to the dogs would be dismissed. But further to strengthen the idea of permanent damage having resulted here, it might be noticed that as the time of recovery goes on the number of damaged cells appearing is increased. This, of course, is because of the fact that many of the cells appearing as recovery cells in the short periods of recovery have begun to show evidence of their permanent injury.

In these experiments, none of the dogs had completely recovered either after a profound or moderate shock. On the basis of Dr. Dolley's experiments, it was thought that the time would be ample. But it is seen that it was not, for even after a moderate shock the dogs have not perfectly recovered after a period of weeks. This throws still further light on the severity of shock as compared with any other abnormal con-

dition yet investigated. Practically, this is of great importance in the light it throws on the after effects of surgical operation. While it would be of interest to determine the maximum time that might be needed for recovery after so much strain, it would vary within ^{such} wide limits on account of the great individual differences between animals ^{that it did} *that it did* not come within the scope of these experiments. The essential fact which is apparent here is that recovery is a matter of months rather than weeks.

Summary and General Conclusions

From these experiments, the following general conclusions can be summarized:

- First: That the mechanical process of nerve cell activity, as stated by Dolley, is indicated by thirteen stages varying from the normal resting cell to that of exhaustion, and that from exhaustion the cell then goes into a state of recovery.
- Second: That shock has the same stimulating effect upon nerve cells as does normal functional activity, hence in excessive degree it produces premature senility.
- Third: That cell activity will vary in proportion to the amount of shock.
- Fourth: That after a profound shock several months is required for the nerve cells to recover.
- Fifth: That a moderate shock may be followed by complete recovery, but that a profound shock will result in a permanent damage. If the shock be carried to excessive degree, there result the same changes of permanent damage, in greater or less degree, that are found in old age.

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Anatomically, therefore, the remote effects of shock are of the same nature as those of senility.

TABLE NO. 1.
EXPERIMENTAL DATA.

No. of Exp.	Purpose	Breed	Sex	Age	Condition	SHOCK		Duration of Recovery	OPERATIVE TECHNIQUE	Remarks
						Duration in Hours	Produced by			
I	Control Animals	Terrier	M.	3 Yrs.	Good		Fatigued in Treadmill.	0	Total work, 68 minutes. (worked 3-min., then rest 2 min.) Blood transfused to another dog for another experiment.	Dog was fatigued to exhaustion when taken from treadmill.
II		"	F.	2 Yrs.	"	2½	Opening Abdomen and then Manipulating Bowels.	0	Tracheotomy tube in this animal for convenience Manipulation of Intestines.	Dog quite resistant. Shocked vigorously one hour, rest 45 minutes; then shocked one and one-half hours, and killed.
III		"	F.	1 Yr.	"	2/3	same	0	same	Operation without accident.
IV	Experimental Animals	Mongrel	F.	6 mo.	"	½	same	1 wk.	Aseptic operation for recovery	No accident. Full stomach at beginning. Vomited three times immediately after operation.
V		Hound	M.	6 mo.	"	1	same	2 wks.	same	Operation without accident.
VI		Mongrel	M.	6 mo.	"	1	same	3 wks.	same	same
VII		"	F.	1 Yr.	"	1	same	1 wk.	same	Operation without accident. Vomited immediately afterwards.
VIII		"	F.	8 mo.	"	3*	same	Lived 1½ hrs.	same. transfused	Dog quite susceptible to shock, & showed signs of it in 1½ hrs. Never rallied further than to raise head a few times.
IX		Terrier	M.	1 Yr.	"	2¼*	same	3 mo.	same. Transfusion for 15 minutes	Operation without accident. Transfusion held gently in check. Rapid recovery. Ether required to close wound.
X		"	F.	1 Yr.	"	2	same	2 mo.	same. Transfusion until return of good blood pressure after a drop following a haemorrhage.	Slight loss of blood caused by cutting of small artery and also from femoral vein before ligating. Recovery rapid.
XI		Hound	M.	1 Yr.	Lank	3.3	Fatigued in Treadmill.	4 wks.	Worked in treadmill 108 minutes, including rest in one day, & 90 minutes on 4th day following.	Good recovery.
XII		"	M.	4 mo.	Good	2¾	Opening Abdomen & Manipulation of the Peritoneum.	4 mo.	Aseptic operation. Transfusion for 10 minutes.	~~A.L. Jones did the peritoneal manipulation —~~ If was not quite so regular, so severe, nor so ~~thoroughly~~ distributed as that of the other experiments.
XIII		Cur	F.	6 mo.	Thin	2¼	same	6 mo.	same	Developed mouth trouble — only liquid or semi liquid food taken last 3 mo. of recovery period. When killed, weak and emaciated.

* Profound shock.

** By Dr. D.H. Dolley.

TABLE NO. 2.
DIFFERENTIAL COUNTS OF CELLS

No. of Experiment.	Duration of		Cells in immediate exhaustion	Earliest ⁸⁴ middle degrees of recovery. ("Poorly recovered.")	Cell body near normal size, nucleus lagging. ("Medium recovery")	Changes of senile character. ("Damaged Cells.")	"Nearly recovered. (Marked temporary & moderate temporary disorganization.)	Changes of Progressive Activity					Undiagnosed Cells.	
	SHOCK	RECOVERY						Normal resting cells	Enlarged Hyperchromatic cells	Maximum Hyperchromatic cells	Shrunken Hyperchromatic cells ** ALL TYPES	Final stages up to Exhaustion.	Hyperchromatic	Hypo chromatic
III	40 _{min}	0	0	55	4	not taken	8	27	55	85	204	150	34	268
II	2½ _{hrs.}	0 (killed)	18	0	0	"	0	13	59	70	418	21	14	386
VIII	2¼ "	0 (died)	146	1	0	"	1	0	34	75	96	247	43	121
IV	½ "	1wk.	40	103	33	4	50	19	37	47	145	132	53	262
VII	1 "	1 "	12	64	38	4	65	13	50	171	71	122	61	126
V	1 "	2 "	40	100	27	5	50	10	18	43	103	219	110	272
VI	1 "	3 "	4	109	56	1	80	34	67	45	70	134	86	179
M.E. 8*	3.3 "	1mo.	39	120	59	68	209	13	7	19	57	7	not	taken
X	2 "	2 "	92	55	26	76	19	12	58	42	93	127	21	45
IX	2¼ "	3 "	83	70	44	88	51	30	54	87	54	38	60	73
XI	2¾ "	4 "	79	54	29	83	33	3	37	38	32	282	39	66
XII	2¼ "	6 "	61	56	29	119	49	19	76	52	22	184	65	68

* Fatigue, treadmill; total time, 3 hours, 18 minutes; total work, 1 hour, 3 minutes; total rest, 1 hour, 18 minutes.
** Includes many closely corresponding recovery cells.

Table II

Fig. 1.

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