President's address / by Henry H. Donaldson.

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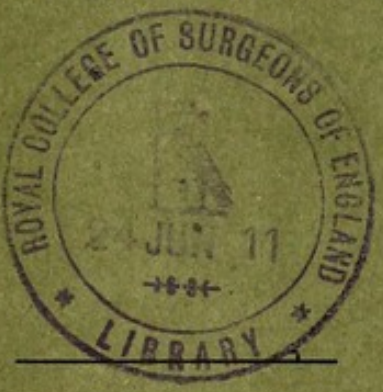

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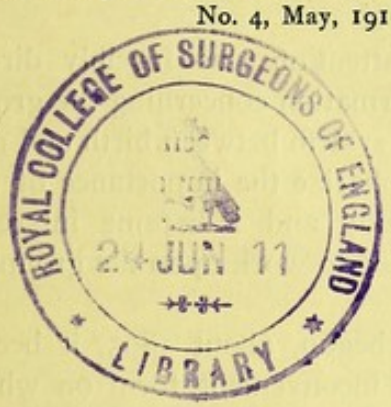

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PRESIDENT'S ADDRESS[1]

BY HENRY H. DONALDSON

THE WISTAR INSTITUTE

Your honorable council, in its wisdom, has decreed that the retiring president should deliver an address. I leave it to the council to explain. The decree however gives me the opportunity to thank you for the honor which has been intrusted to me during the past year. This honor now passes to more worthy hands and my sincere good wishes go with it.

During these past months I have often wondered how such neurological work as is not clinical, not even pathological, might be made to support the endeavor for which this society stands; the endeavor to bring forward our knowledge in clinical neurology and thus to contribute to the control and prevention of the diseases of the nervous system.

To assist in making plain the bearing of such work, I can follow no other than the simple well-worn way which leads to an explanation—an apologia the theologians called it—of some of those things which a group of us are laboring to do.

With then the hope of bringing the laboratory work on the normal nervous system nearer to the special work of this society, I venture to present a running account of several studies on the growth of the nervous system as carried on by my associates and myself during the past few years.

What I have to say bears the title "Studies on the Growth of the Mammalian Nervous System."

[1] Read before the Philadelphia Neurological Society, January, 1911.

Some years ago my attention was forcibly directed to the fact that we had little information concerning the growth changes in the mammalian nervous system between birth and maturity. It is hardly necessary to emphasize the importance of this interval. It seemed well worth study and I became interested in this phase of growth and planned to work upon the group of problems thus suggested.

When this work was begun, about 1895, it became evident at once that man was an inconvenient form on which to study growth, and that it was desirable to replace him by an animal of small size, with a short span of life and with powers of rapid reproduction.

These conditions were satisfied by the albino rat, but it remained to be determined whether the growth processes in the rat were sufficiently like those in man to be really worth a detailed study.

Experience has shown that they are remarkably similar, and so good is the essential correspondence that there is every reason to continue the work on this form which was first selected.

Before trying to study the growth of a single system, like the nervous system, it was important to learn how the entire animal grew from birth to maturity. This study yielded the growth curve which is familiar and the phases of which, in the case of the rat, repeat those found in man. Further, there is in the growth of the rat an early period when the females are heavier than the males—as we know them to be in the case of man—while at maturity, the males, like man again, are some 15 or 20 per cent. heavier than the females (Donaldson, '06). It was satisfactory thus to find at the start that the main features of human growth were represented in our chosen animal. There is however one striking difference between the two.

The rat grows some thirty times as rapidly as man, its span of life covering three years and thus being equivalent to a span of ninety years in man.

These determinations for the body growth justified the further study on the growth of the brain and spinal cord.

I will speak only of the brain. The brain from a mature rat weighs about two grams; the brain from a mature man about 1,400 grams. The brain of the man has then some 700 times the weight of that of the rat.

When the growth results are compared, we find between birth and maturity, that both brains have increased in about the same proportion, namely 3.5 times, and both have used the same fraction of the span of life, about one-twelfth, for the period of rapid growth; for as you know the human brain has nearly its full size at about the age of eight (Donaldson, '08).

Before attempting to analyze further the results just given, there is one more general change to be described.

The brain, like other organs, has much water in it. I have followed in the rat the change in the percentage of this water from birth to maturity. It diminishes by approximately ten points and this diminution is very closely correlated with age. At birth the water forms about 88 per cent. of the brain, and at maturity, about 78 per cent. (Donaldson, '10).

The curve along which it falls corresponds to the reflection in a horizontal mirror of the curve for the growth of the brain in weight, and so, is like the brain weight curve turned upside down. It attains nearly its final value in about the first one-twelfth of the span of life.

For the percentage of water in the human brain, the data are meager, but so far as we can gather them, they correspond to those for the rat, and when adjusted for the rapidity of growth, the curve for man fits that for the rat. A very striking coincidence.

From what has just been said it is plain to see that the change in total weight and the change in the relation of the water to the solids are similar in the two species, while the rat in both cases, but especially in the case of the percentage of water, has given us results which are much more complete than those to be had from man.

Thus far we have been speaking of changes in the total mass of the brain, but we now turn to the structural units, the neurones. First, their number.

Our estimate for the number of neurones in the entire encephalon of man is about 12,000 million (based on Thompson 1899). Counted continuously at the rate of one each second, it would require 380 years to enumerate them all.

If the relations in the rat brain were similar to those in man, there would be in the 2 grams of rat brain 17 millions of neurones, a number which—large as it sounds—is probably an under esti-

mate. Taking this number as it stands, however, it appears that on the average there are 8,500 neurones in each cubic millimeter of brain substance.

The numbers are large, but if any of you should be inclined to protest that they were too large, I beg to call your attention to a set of facts with which you are more familiar.

One cubic millimeter of blood contains on the average five million of red corpuscles, and only half the cubic millimeter is occupied by these corpuscles; the rest is plasma. If the plasma were removed this same millimeter would accommodate 10 million. In contrast to this enormous number, I ask you to think of a cubic millimeter of brain substance which contains only 8,500 neurones—less than one thousandth of ten million. It is then the growth of these millions of neurones enmeshed in a light framework of supporting tissues (neuroglia and connective tissue) which we have been following in the observations earlier described.

The analysis of these units may be carried one step further. The neurones or nerve elements consist of the cell body and branches, and of these branches the axone is the best developed. This may or may not have a medullary sheath. It will be of interest for us to know how much of the encephalon is formed by the cell bodies and how much by the axones and supporting tissues. In man, the proportion by volume of the cell bodies is two per cent. of the entire mass of the brain, thus the cell bodies of the human brain weigh altogether about 28 gms. or one ounce (Thompson, '99). At first class postage rates they could be transmitted for two cents.

In the case of the rat, which has somewhat smaller cell bodies and also a smaller proportional development of the nerve fibers, I estimate the proportional volume of the cell bodies in the brain as 3 to 5 per cent. Concerning the supporting tissues, we have little exact data with which to work, but two to four per cent. in volume seems a liberal assignment for this purpose, while from 6 to 8 per cent. must be credited to the blood vessels and the blood. It is plain then that in both cases—man and the rat—some 88 per cent. of the volume of the brain is composed of the axones and their sheaths.

The axones therefore, medullated or unmedullated, are mainly responsible for the size of the brain and for the changes which it undergoes during growth.

This last fact becomes more plain when it is remembered that the medullary sheath of a medullated fiber has approximately the same volume as the axis which it surrounds (Donaldson and Hoke, '05).

Thus, for example, the human brain beginning at birth with very little medullation of its fibers, acquires at maturity very complete medullation. To do this it must enlarge, and the enlargement is in great part accounted for by the formation of the medullary sheaths.

Bringing together the foregoing observations, we may look upon the human brain as composed of about ten per cent. of supporting tissues, blood vessels and blood combined, and 90 per cent. of neurones. Two per cent. of the entire volume of the brain is in turn represented by the cell bodies of these neurones, the remaining mass, or 88 per cent., is nerve fibers, and so far as they are medullated, one half the volume of the fibers is to be assigned to the sheath and the other half to the axone. Thus a little less than one half the weight of the entire brain is composed of its functional neurones. In these respects the rat is very similar to man.

Such then are some of the broad features of the structure of the brain, and such the argument for the suitability of the rat as an animal in which to study its growth.

So far we have dealt with growth changes under the usual or normal conditions. We turn now to our attempts to modify growth by altering some of the surrounding circumstances. The influence of exercise comes first.

Ordinarily the albino rat does not get all the exercise it can take or that it should have. To meet this difficulty, some rats have been reared in revolving cages in which they take exercise, running often many miles a night as the automatic records show (Slonaker, '07).

Such rats have brains which are thereby slightly improved by 2–3 per cent. as regards their weight, while the percentage of water in them is unmodified (Donaldson, '11). When it is appreciated that this represents the first attempt we have made to test the effects of exercise, and that it was necessarily applied to animals in which the brain was already two-thirds grown, it will be seen that we have something to expect from further experiments along this line. Nevertheless, this is the only condition

which thus far has yielded us an improvement in the growth of the nervous system.

On the other hand, retardation and deficiencies of growth are easier to effect. For example:

At least one disease, the pneumonia of rats, produces not only a loss of body weight, but also a slight loss in the weight of the brain, from one to three per cent. (King, '11). Here again the rat reacts in the same way as does man: for the hospital records for man show that in cases of chronic disease the brain weight is less than in corresponding cases dying after acute illness (Gladstone, '05).

Our most satisfactory experience in this direction however has been with underfeeding. When rats 50 days of age, and thus with a nervous system two thirds grown, are systematically underfed for three weeks, they may at the end of this period have lost 25 per cent. of their initial body weight, and four per cent. of their initial brain weight (Hatai, '04). So far as the brain is concerned, this is a serious change, for in all periods of nutritive stress, the central nervous system is a preferred creditor with the blood. Indeed death by starvation produces a loss in brain weight of only about three per cent. (Voit, 1889), which is distinctly less than can be accomplished by prolonged underfeeding. At the end of such a period the underfed animals are much depressed in all of their activities, and it is of interest to determine what can be done for them.

If such a rat be returned to a normal diet—then like a young child recovering from a prolonged illness—it begins to grow with more than normal vigor, and at the end of the growing period may be as heavy and have as heavy a brain as its normal companions (Hatai, '07).

Further, so far as our tests show, such an experience does not modify the rat's ability to learn, for, by a series of experiments, it has been possible to determine that such a rat can learn to get its food under complicated conditions just as well and as rapidly as a normal animal (Hayes). This interesting result tempts one to make comparison with man.

In doing this it is necessary to proceed with the utmost caution. To put the question which at once arises, as simply as possible—Are these underfed rats in the laboratory like your underfed children in the clinic? The answer is "no." It might be pos-

sible to produce underfed children quite comparable with our rats, as when a sound population, through some catastrophe like an earthquake, was suddenly subjected to starvation, and indeed this condition does occur in sporadic cases, as we know from the memoirs of not a few distinguished scholars of the last two centuries. But these are not the individuals that come into your hands or that largely appear among the less fortunate population of our greater cities.

In the clinical group, in one way or another, the very fabric of the nervous system is usually defective, and the underfeeding is forced upon the children through the deficiencies of the parents, who in many cases have transmitted something of their own weakness to their offspring.

What underfeeding may accomplish in the way of alterations in such cases is not yet known, but it can safely be assumed that its effects will be more serious and lasting than those we obtain from our animals.

This instance has been purposely elaborated because it serves to illustrate one reason why the laboratory work so often fails to meet clinical needs. Every effort is made in such laboratory studies to carry on the experiments under simple conditions which are so controlled that the variations due to each single factor may be isolated and determined. Too often those experimental limitations are forgotten and the results, without the qualifying conditions under which alone they are true, are taken over and applied to the human invalid.

The resulting situation is unsatisfactory to at least three parties and should put both clinicians and laboratory workers on their guard. In this present instance the laboratory results show that normal individuals with sound nervous systems may be underfed for relatively long periods without permanent damage, but these same results show nothing concerning the effects of underfeeding on individuals with subnormal nervous systems. That is another story and the laboratory can contribute to the telling of that story only when rats with subnormal nervous systems can be obtained for experiment.

Returning from this digression, I wish to describe still other effects of underfeeding, asking you always to remember that the experiments have been on animals otherwise normal.

The attempt was made to see how far it would be possible to modify the percentage of water in the central nervous system.

This percentage of water, as I have stated, is a function of age and under ordinary conditions, whether a rat be over size or under size, well nourished or ill nourished, with a large brain or a small brain, the percentage of water remains practically unmodified by these conditions. Moreover, when rats are severely underfed for three weeks and killed while stunted, the brain having actually lost in weight, the percentage of water in it is reduced by only 0.2 of one per cent., but even in these rats when they are returned to normal conditions, this deviation disappears and no trace of it can be detected later (Hatai, '04; Donaldson, '11).

This percentage of water in the central nervous system is apparently the best index yet available of the normal process of senescence, and so far as these experiments go, it fits with human experience to find that hardship, which includes underfeeding, need not necessarily shorten the span of life. There is then at least this one process in the central nervous system which is highly resistant to modification by the reduction of the food supply.

Though the evidence is not so conclusive, there seems to be a second process which behaves in the same way, namely medullation; that is the formation of the sheaths of myeline about the axones of the nerve elements (Donaldson, '11). The study of the rat shows that medullation in the brain does not begin until that organ has attained a certain percentage of water, that is, has undergone developmental changes of which the percentage of water is an index. It is further most probable that it does not begin in any axone until that axone has made functional connection with other elements, be they neurones or cells of other classes.

Medullation then is the final phase of the growth process in the neurone. Exclusive attention to the fact that in some instances functional control is coincident with the appearance of the medullary sheath has led to the inverted notion that the neurones cannot function until they are medullated. The fact is that they do not become medullated until they are in a position to function, although they may function without becoming medullated; as in the case of a new born rat which has not a medullated fiber in its central nervous system. But there is one more point in connection with this process: Just as the percent-

age of water is not modified by underfeeding, so medullation, which is essentially dependent on the establishment of connections by the growing axones, is not modified by underfeeding, for medullation progresses even in brains in which the increase in weight has been arrested. This is a most striking and paradoxical result, but it is supported both by chemical and histological evidence (Hatai, '04; Donaldson, '11). Let me point out one bearing of this result as I see it.

If in a pathological brain uninterrupted neurones are found with deficient or defective medullation, this condition must imply a deep seated modification in the metabolism of the elements, a modification much more fundamental than any I have been able to cause by the severest underfeeding.

The foregoing observations permit us to draw some general conclusions concerning the metabolism of the central nervous system. In the first place this metabolism is astonishingly well regulated in the presence of nutritional disturbances. Of all the systems, the central nervous system makes the strongest and most persistent claim under adverse conditions on the food substances in the blood. It not only for a long time resists a loss in the weight, but even when thus altered it still continues to mature as is shown by the change in the percentage of water, which falls with age, and by the continuance of medullation which indicates that the increase in structural complexity is not arrested. Moreover, the metabolic changes, whatever the conditions of nutrition, are carried on mainly in the ounce of nerve cell bodies which form but two per cent. of the weight of the entire human brain—and slightly more in the case of the rat.

The waste products then of metabolism, produced by this small quantity of nerve cell substance, are the contribution of this master system to the total waste thrown into the body fluids. Under these circumstances it is hardly strange that variations in this waste from the nervous system should escape detection.

Benedict and Carpenter ('09) found that when students were made to pass college examinations in the calorimeter chamber, nothing in the measured output clearly indicated their mental exertion; while the examination papers showed that such exertion had taken place. In view of what has just been said, this result should not be interpreted to mean that the mental exertion involved in passing an examination did not modify the metabolism

of the nerve cells, but merely that the variations in the amount of waste products were less than could clearly be detected by the methods then employed.

This completes my review. The investigations which have been put before you are mainly studies of the nervous system during normal growth, or when such growth has been modified by underfeeding.

The results can be used I hope to make more complete and clear our notions of the construction and activities of this system, the diseased conditions of which are your chief interest, and thus add to the data by which your reasoning must be controlled.

Once or twice I have turned aside to point out what seemed to be the immediate bearings of the laboratory results on the problems of the clinic. When thus turning, I trust that I have had your company. Be that as it may, my purpose has been accomplished if I have made plain what is going on in one laboratory in the endeavor to contribute to neurology, comprising as neurology does the structure and functions of the nervous system in health as well as in disease.