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PATHOLOGICAL FINDINGS IN THE SYMPATHETIC NERVOUS SYSTEM IN THE PSYCHOSES.¹

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In contrast with the immense importance ascribed to the sympathetic nervous system and the unremitting study it has received on the part of physiologists, neurologists and clinicians, is the attention that it has received on the part of pathologists. Except for the work done in Addison's disease, the literature contains but a very few scattered pathological studies of the subject. Compared with what has been done by the neuropathologists on the central nervous system, that done on the sympathetic sinks into complete and astonishing insignificance.

I. SOME OF THE MORE IMPORTANT LITERATURE.

One of the most quoted as well as one of the earliest pathological studies was that by Hale White (16). Working entirely on material from non-insane patients, White found that the semilunar and the superior cervical ganglia quite regularly presented changes of marked character. Pigmentation that went on to the destruction or disintegration of the cell, disappearance of the nucleus, absence of the nerve processes, appearance of leucocytes without regard to pathological processes, increased connective tissue—these he records as occurring in most cases after early adult life. They were not present in ganglia of children. As a result of his pathological studies and of a study of the sympathetic ganglia in

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animals, White came to the following conclusions: First, the changes above described, occurring in the semilunar and the superior cervical sympathetic ganglia, are *not pathological*, but represent a *normal change* occurring in the life history of the ganglia. When such changes occur in the thoracic ganglia they are of some pathological importance. When they occur in the Gasserian ganglion (used as a control), in the cardiac and lenticular ganglia, they are of great pathological importance, representing then a disease process. Second, studies in animals convinced him that the semilunar ganglion, as well as the superior cervical, is a *recessive organ, one which tends to disappear as one goes higher in the animal scale, and without function in the adult human*. It has function in the child and, therefore, may be compared, on the ground of life history, with the thymus. On the other hand, the lenticular, cardiac and Gasserian ganglia are of decided importance because they functionate in the adult, and changes occurring in them are of pathological importance. Somewhere between these two series of ganglia are the thoracic ganglia of the sympathetic, which in part are recessive and in part functional.

It is important to note that this view is absolutely opposed to the belief that the semilunar ganglion is a *very active nervous organ* having the closest relationship with the condition of the abdominal and pelvic viscera, entertained by the later physiologists, neurologists and clinicians. (Langley, Eppinger and Hess (4); Higier (5).) Moreover, the biological studies of White are distinctly contradicted by the researches of His, Junior, and especially by the work of Kuntz (6). According to the latter, the semilunar ganglion is a *late organ*, one that is phylogenetically younger than the central nervous system, younger than the peripheral ganglia of which it is an outgrowth. The higher up in the animal scale, the more this prevertebral system comes into play. Consequently, it is by no means a recessive organ, but, on the other hand, is an *arriving organ*.

It is pertinent to state here that some facts which are the result of personal research contradicts White's views. For example, in the semilunar sympathetic in old people one finds cells with very good cell processes (Fig. 1, Plate V). Moreover, acute cell changes of a type occurring only in functioning cells occur in the

sympathetic ganglia of old people (Fig. 2, Plate III, cells A and B).

Vas (15), somewhat later, believed that the excessive pigmentation found in the sympathetic was not entirely pathological and in a large part represents the normal evolution of the nerve cell.

With both of the above opinions, that is, those of White and of Vas, Lugaro (11) is in disagreement. Conceding that pigmentation is a process of old age, its *excess* as found in cachexia and in other conditions indicates *excessive senility, true disordered function*. For Lugaro, the frequent finding of excessive pigmentation, cell destruction, nuclear changes and connective tissue increase in old age can be correlated with the physical disturbances of that time of life. He concludes that the superior cervical ganglion and the semilunar are *earliest* of all the sympathetic ganglia *to become aged*. It will thus be seen that of the two conclusions possible concerning these changes, which are, first, that it is a normal evolution, and, second, that it is an early senility, White has taken the one view and Lugaro the other.

Orth (14) finds increased pigment, atrophy of cells and a disappearance of the nucleus in cachexia and extreme old age.

Most of the other writers on the sympathetic, as studied from a pathologists's point of view, have paid their attention to the cells found in the intestine and heart. Thus Blaschko (1), working in enteritis, finds acute cell changes in Auerbach's plexus and suggests that diarrhoea accompanying enteritis is a nervous phenomenon. The researches of Leupold (9) substantiate a similar conclusion. Cotton and Southard (3) find axonal reaction changes in a case of mental disease in which this reaction was found widely spread throughout the central nervous system, thus making up the pathological entity called central neuritis by Adolf Meyer. Of great importance are the degenerative changes recorded by Lissauer (10) as occurring in the heart ganglionic cells after acute and chronic alcohol and chloroform poisoning, as well as through disease.

The views of Y. Manquelian (12) are of decided interest. On the ground that he has demonstrated sympathetic nervous cells in the aorta and in many of the organs, he believes that the interpretation of bodily symptoms without reckoning the peripheral nervous system is vitiated by the omission. Glandular activities and

disease processes are affected by and affect the nerve cells scattered throughout the body.

2. PERSONAL STUDIES.

The material examined was in part obtained from 50 consecutive autopsies performed at the Taunton State Hospital during the past year. In the main, only the semilunar ganglia were studied, usually from formalin, zenker, and alcohol fixed material. The stains mostly used were eosin-methylene blue, Van Gieson, toluidin blue and cresyl violette, Bielschowsky and scharlach R. In addition to the above material, 40 sets of slides from as many cases autopsied at Worcester State Hospital during 1903 and 1904 were restained in the eosin-methylene blue and examined. Furthermore, certain animal material was sectioned, and results will be here recorded.

It is not my intention to describe every variety of change found. Certain outstanding and peculiar variations will be considered, not in relation to mental syndromes, for no such relationship can at present be even considered, but in wider relationships.

1. *Brief Description of the Normal Semilunar Ganglion Cell.*—

It is a multipolar cells with a large, slightly eccentric nucleus of ordinary structure. The Nissl granules are not so distinct as, for example, in the Gasserion ganglion or in the motor cells of the cord, but they are readily demonstrable and are not peculiar. The cell is smaller than the Gasserian ganglion cell, but is like it and all peripheral cells in that it lies in a capsule lined by endothelial cells. These cells have the usual satellite functions and line each process of the cell as well as its body.

Cells having a double nucleus are comparatively common in the semilunar ganglion. The meaning of such cells is debatable in other parts of the nervous system, but in the semilunar ganglion it is undoubtedly normal, and in certain species of animals (the rabbit, the guinea-pig) it is extremely common. In man, such cells differ in no other fundamentals from their neighbors. Both in man and the animals the double nucleated cells are not found in the intestine or other peripheral organs.

A peculiar phenomenon which is here mentioned, perhaps irrelevantly, is the occurrence, though very uncommonly, of cells having double nucleoli. These double nucleoli have almost, though not

quite, the appearance of mitosis. Double nucleoli are fairly common in the sympathetic ganglion cells of certain animals; for example, rabbit, guinea-pig and, by personal observation, in the intestine of a bull (Fig. 1, Plate IV, cell B). Whether it is pathological in man, I cannot say. It was found only in a few cells of a young epileptic and in a senile dementia case, a man, aged 95.

2. *Axonal Reaction*.—So far as I know, this has not previously been described in the cells of the semilunar ganglion. Here, as elsewhere, there is a displacement of the nucleus to the periphery, a swelling of the body with central chromatolysis, and in some cases the nucleus is extruded. The meaning of this phenomenon is well established and relates to an acute disorder, which may or may not arise through injury or irritation of the axon. This

FIG. 1.—Showing emigration of nucleolus. A—Eccentric nucleolus. B—Further stage. C—Nucleolus, entirely out. D—Cell without nucleolus.

phenomenon occurring in isolated cells in very many cases was particularly prominent in five (Fig. 2, Plate III).

(a) An acute exhaustion psychosis in a woman of 50 without acute infection and terminating in death owing to failure of compensation of the heart, of which the mitral valve was chronically diseased.

(b) Three cases of enteritis ending in death. In these cases, occurring twice in senile dementia and once in general paresis, the axonal reaction was very prominent in cells scattered throughout the ganglia.

(c) One case of senile dementia, more properly a psychosis due to failure of compensation and cerebral arteriosclerosis in a male, aged 68, who died of pulmonary tuberculosis; tubercular glands of peritoneum—no tuberculosis of sympathetic. Very decided axonal reaction throughout the ganglia together with much more chronic changes later described.

3. *Emigration of the Nucleolus*.—This rare change, probably acute in character, is here described, I believe, for the first time. As the name indicates, the nucleolus leaves the cell to disappear into the interstitial tissues. Eccentricity of the nucleolus is not uncommon. The meaning of this phenomena is unknown. It was prominent in a senile dementia case, man of 95 years of age (Fig. 1).

4. *Neurathrepsia*.—This term is here used to cover a very large number of changes of a chronic type which lead to the destruction of the cell. It was first used by Levaditti (7, 8), and is in contrast with the term *neuronphagia*, which, properly used, means the "eating up" of the nerve cells by phagocyte and satellite cells as seen in anterior poliomyelitis and rabies. In neurathrepsia, owing to defective metabolism, there is progressive change in the nerve cells with or without corresponding increase in the satellite cells. As Van Gehuchten pointed out years ago, if degenerative changes are slow, satellite cells do not multiply. If the changes are rapid they do multiply.

(a) Pigmentation (Type No. 1). The usual lipochrome is common in the sympathetic. It appears early, frequently starts around the nucleus and in the sympathetic is very often excessive to the point where no cell structure can be made out and where masses of pigment only can be seen. In such cells, by Bielschowsky's neurofibril method, the cell processes are difficult to make out and the fibrils cannot be distinguished. In cachexia, and especially (as it seems to me) where the intestinal atrophy is marked, the largest part of the cells present have no nuclei, and are represented by irregular groups of pigment without cellular structure (Fig. 2, Plate V).

(Type No. 2.) Oxyphilic granules, that is, granules which take the acid stains, such as the eosin-methylene blue, are prominent in the process here described. These granules, called oxyneutrophilic by Marinesco, are frequently found together with the lipochrome and independently of it. The granules are very often very fine and scattered, and on the other hand are seen as large granules which are quite compactly arranged. These granules are much more common in the prevertebral than in the central nervous system, and occur more frequently in the semilunar than in the Gasserian ganglion. They represent undoubtedly pathological

changes of a chronic kind. It is certain, however, that they also occur in more acute conditions. In a young bull suffering from tubercular enteritis certain cells of Meissner's plexus in the intestines show this change in decided manner (Fig. 1, Plate IV).

5. *Nuclear Changes*.—These are exceedingly common in this condition. Viewed from the technical standpoint they consist in a gradually increasing affinity for acid dyes, so that while the normal nucleus is unstained in eosin-methylene blue preparations, the abnormal in the final stage may be of a deep red. Morphologically, the nucleus presents first an irregular border and then

FIG. 2.—Showing shrinking of nerve cell and intra-capsular homogeneous red-staining mass (epileptic dementia). *A*—Intracapsular mass. *B*—Shrunk nerve cell. *C*—Nucleus, presenting hyperchromatia.

becomes more and more shrunken until in extreme cases it has a half-moon shape. Filamentous change of the nucleoplasm is part of the process. Finally, it must again be mentioned that in marked pigmented neurothrepsia the nucleus disappears from the cell structure. This, however, is not so common as most of the writers seem to think, and it is possible that they may have been misled by the fact that the irregular arrangement of the sympathetic ganglion cells lends itself to deceptive planes of section in which no nuclei can be found.

6. *Capsular changes*.—In the old, where the degenerative changes progress to a marked extent, one of the most apparent

phenomena is the irregular relation between the capsular nuclei and the nerve cells (Fig. 2, Plate V). In the young, this arrangement is very regular. In the old, the capsular nuclei are increased, swollen, and overlies the nerve cell. Where the cell is completely destroyed there is usually a definite increase of capsular cells. This multiplication of satellite cells is not so marked, in my opinion, as the corresponding neuroglial increase under similar circumstances in the central nervous system.

In certain old cases, especially marked in a case of epileptic dementia in a man 75 years of age, the nerve cells are decidedly irregular and shrunken in appearance. Under favorable circumstances this is found to be the result of a homogeneous red staining mass which appears in the capsule and, gradually encroaching on the cell, causes an atrophy by pressure (Fig. 2). I have not found this change in the Gasserian ganglion.

7. *The interstitial connective tissue* (Fig. 1, Plate III) shows an increase, as might be expected. One very curious feature of the semilunar ganglion is the almost complete absence of true, inflammatory reaction processes. Plasma cells, even in general paresis, are practically never seen and the entire lymphocytic and leucocytic series are conspicuously absent. This in spite of the fact that the ganglia are *surrounded by* and *interspersed with* very small but very active lymph glands of a curious kind in which all manner of cells are found. The paucity of inflammatory reaction is in decided contrast with the condition of two related structures. First, the central nervous system and the Gasserian ganglion, in which such changes are very common, and, second, the adrenal gland, in which lymphocytes, plasma cells, etc., are more often found, perhaps, than in any other non-lymphatic structure of the body.

Scattered through the ganglion, however, are occasional eosinophilic cells of the type found in inflammations. These cells are of two kinds; one with coarse granules (Fig. 2, Plate IV), the other with a nucleus like a plasma cell and a finely granular body. This last type is similar to cells found in the aforementioned lymph glands.

A very suggestive finding is to be recorded in the eosinophilic cells found in an intestine of a young bull killed because of tubercular enteritis. In this case there were many eosinophilic cells, as is normal for this species of animal, and, besides, many plasmas,

etc., because of the tubercular inflammatory process. *The curious thing was that the eosinophilic cells seemed actively phagocytic for the injured nerve cells, and selectively so* (Fig. 1, Plate IV). Since the eosinophiles have never before been seen to be phagocytes, this observation is important.

To summarize the above findings. First, the semilunar ganglion is apparently often acutely injured in general infections and in enteritis, as is shown by the presence of the axonal reaction and other changes above described. Second, the semilunar ganglion is the seat of degenerative processes to an extent probably greater than cord, brain or Gasserian ganglion. These degenerative changes are here designated under the general term neurothrep-sia (Levaditti). It is probable that these changes represent an early and marked senility, and in this I am in accord with Lugaro. Third, there is a decided absence of marked reactive changes (lymphocytes, plasma cells, etc.), such as are prominent in the central nervous system, Gasserian ganglion, and the related organ or adrenal. Even in general paresis these are absent. Fourth, there is a curious, though not prominent, increase of eosinophilic connective tissue cells which, in the case of the bovine tubercular enteritis here cited, seemed to have a phagocytic attraction for injured nerve cells.

It is to be emphasized that the above findings apply, in my experience, only to the psychoses.

Conclusions.—Two prominent conclusions stand out as worthy of emphasis. First, the semilunar and other sympathetic ganglia and the autonomic ganglia merit the close attention of pathologists. The part the vascular and glandular system under their control plays in all the great vital processes as well as in the creation and modification of the emotions, indicates that a more comprehensive and systematic study may throw light on the problems of old age as well as on the psychoses. Regarding the latter, it may be stated that quantitatively greater changes in the cases of insane people may well have a value equivalent to qualitative changes, since in many of the psychoses the evolution of the disease is from temperament to insanity. Second, the interpretation of morbid phenomena needs to take into account the presence of nerve cells in the organs, such as the aorta, the heart, the intestines, stomach, genitalia, etc. Symptoms may well arise because

of injury to these peripheral cells either as an antecedent, or as a consequent, of the disease process. We have, as recent experiments show, drugs that have a peculiar and selective power on the nerve cells of the autonomic and sympathetic systems. These should be experimentally as well as therapeutically used in conditions where the symptoms are even in part vasomotor and glandular.

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FIG. 1.—Interstitial connective tissue proliferating. Cells *A* and *B*, mitosis. *C*, nerve cell. $\times 1000$. E. M. Blue.

FIG. 2.—Axonal reaction. Cell *A*—Nucleus almost extruded. Cell *B*—Nucleus peripheral. $\times 340$. Cresyl Violet.

FIG. 1.—Intestine of bull; tubercular enteritis. Cell *A*—Nerve cell, in Meissner's plexus showing large oxyphilic granules. Cell *B*—Swollen nucleus, nerve cell, with two nucleoli. Cell *C*—Eosinophile. $\times 1000$. E. M. Blue.

FIG. 2.—Interstitial connective tissue of ganglion. Cell *A*—Eosinophilic reaction cell, with large granules. Cell *B*—Eosinophilic reaction cell, small granules, plasma cell nucleus. $\times 1000$. E. M. Blue.

FIG. 1.—Showing multipolar cells. $\times 140$. Bielschowsky.

FIG. 2.—Cells *A*, *B* and *C* showing disintegration and replacement. Ep. dementia; 75 years. $\times 350$.