HISTOLOGICAL VARIATIONS IN AUTONOMIC GANGLIA AND GANGLION CELLS ASSOCIATED WITH AGE AND DISEASE *

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Histological variations in autonomic ganglia and ganglion cells have been described by a number of investigators. Some have regarded the more marked changes as representing pathological lesions; others have regarded all the observed variations as representing structural changes falling within the normal range of variability. Most of the studies of which the results have been published have been carried out on preparations of ganglia of the sympathetic trunks and prevertebral plexuses obtained at autopsies following death due to widely differing causes and within wide age limits; some have been on preparations of sympathetic ganglia removed in the surgical treatment of certain diseases. The studies carried out on material of the latter type have revealed no specific histopathological changes in the ganglia which could be correlated with the disease in question. The histological variations observed in such material fall into the same general categories as those observed in preparations of ganglia obtained from apparently normal individuals and individuals with other diseases. Certain investigators, notably Craig and Kernohan,[1] consequently have advanced the opinion that most of the histological changes observed in preparations of autonomic ganglia can be explained most satisfactorily on the basis of advancing age.

Some of the histological variations observable in preparations of autonomic ganglia undoubtedly are correlated with the ages of the subjects. Others probably are associated with disease either as causative factors or accompaniments. Regardless of the specific relationships of lesions of the autonomic ganglia or ganglion cells to a disease process with which they are associated, the functional modifications associated with them may play a significant rôle in the progress of the disease and its sequelae. The establishment of norms for human autonomic ganglia and ganglion cells in the

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several age groups, consequently, would be desirable, but, on the basis of our present knowledge, such an undertaking must be regarded as hazardous.

Materials and Methods

The present study is based mainly on preparations of ganglia of the sympathetic trunks and the celiac plexus obtained in an extensive series of autopsies following death at ages ranging from 5 weeks to 78 years. The cases have not been selected with reference to disease, but the causes of death vary within a wide range. Preparations of sympathetic ganglia removed in the surgical treatment of disease in approximately 50 patients, ranging in age from 6 to 71 years, also have been available for study.

Most of the material has been fixed in 10 per cent formalin and stained with toluidine blue and erythrosin, hematoxylin and erythrosin, or cresyl violet. The rest has been prepared by various modifications of the Cajal silver technic.

Histological Data

Relative Frequency of Ganglion Cell Types: As observed in silver preparations, nearly all the ganglion cells in the autonomic ganglia of children and young adults possess only long dendrites. According to de Castro,[2] all the autonomic ganglion cells conform to this type during fetal and early postfetal life. In our preparations of ganglia of young adults, ganglion cells characterized by short intracapsular and glomerular dendrites occur only rarely except in the cephalic parasympathetic ganglia, in which short dendrites are common. Those with both short and long dendrites are more abundant. Since ganglion cells of the latter type are more abundant in the ganglia of adults than in children, it must be assumed that short intracapsular dendrites may arise late in the process of differentiation. This opinion has been expressed by de Castro [2] who designated the short intracapsular processes "secondary dendrites." Preparations of ganglia in the more advanced age groups show both ganglion cells with short and glomerular dendrites and those with both long and short dendrites in greater abundance than in preparations of ganglia of young adults.

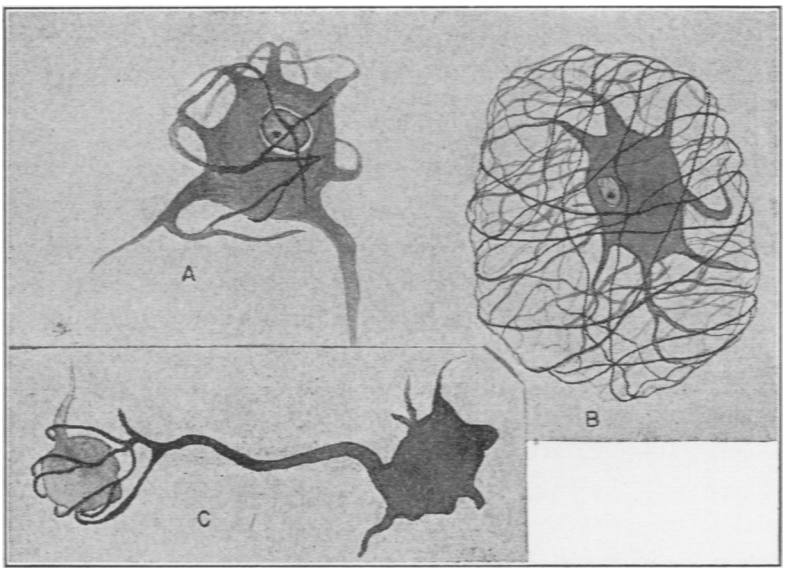
The progressive changes in the dendrites of the ganglion cells are less marked in the cephalic autonomic ganglia than in other

parts of the autonomic system, since short dendrites are relatively abundant in these ganglia in the younger age groups as well as in the more advanced. Intracapsular dendrites are not uncommon in the cephalic autonomic ganglia in all age groups. Many of them are very short and terminate in knob-like enlargements; others are much longer but do not penetrate the ganglion cell capsule. The extracapsular dendrites also are relatively short. Slavich [3] has emphasized the preponderance of ganglion cells with short dendrites in the cephalic autonomic ganglia.

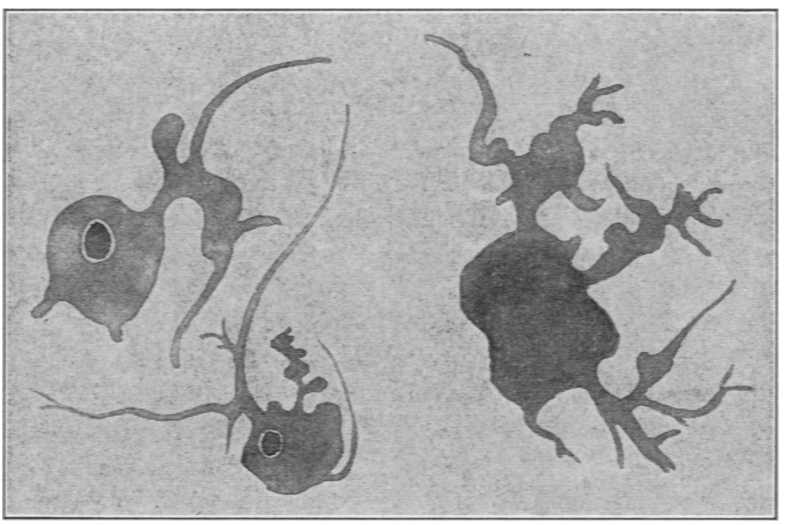
Dendritic Modifications: Silver preparations of ganglia in the more advanced age groups show various modifications of the dendrites of some of the ganglion cells. Intracapsular dendrites and arborizations of extracapsular dendrites are more abundant in many of the ganglia in the advanced age groups than in any of the younger ganglia. New dendrites obviously arise relatively late in life. Some investigators, particularly de Castro [4, 5] and Levi,[6] have supported the assumption that autonomic ganglion cells may undergo continuous growth and differentiation throughout life.

In some of the ganglia in the more advanced age groups (40 years or over) elaborate pericellular dendritic nests are not uncommon. These are formed by dendrites which are wrapped around the ganglion cell bodies from which they arise or the cell bodies of other ganglion cells in the vicinity (Text-Fig. 1). These structures, which de Castro has designated "false articulation nests," probably owe their origin to the enormous elongation of the dendrites involved. In the most elaborate ones the dendritic branches superficially resemble the terminal branches of axons (Text-Fig. 1B and Fig. 4). In the simpler pericellular nests formed on the cell bodies of ganglion cells by the terminal branches of dendrites of adjacent ganglion cells the processes involved retain their typical dendritic appearance (Text-Fig. 1C).

Budding and hypertrophy of the dendrites occur frequently in some of the ganglia in the advanced age groups. Short dendrites not infrequently present a tuberose or beaded appearance and terminate in club shaped enlargements. Longer dendrites sometimes present irregular local thickenings by virtue of which they appear highly distorted (Text-Fig. 2). In some instances dendrites give rise to new processes of variable length and caliber which form more or less complex brushes and tracts (Figs. 1, 2, 3).



TEXT-FIG. 1. Simple (A) and complex (B) pericellular nests formed by dendrites of same cells, and simple pericellular nest (C) formed by dendrite of adjacent ganglion cell, in celiac ganglion, age 44 years.



TEXT-FIG. 2. Celiac ganglion cells with thickened and distorted dendrites, age 78 years.

Structures of this kind have been reported by de Castro, particularly in cases of tabes, alcoholism and multiple sclerosis. Dendritic glomeruli involving two or more ganglion cells also are not uncommon in most of the autonomic ganglia.

Chromidial Substance: The chromidial substance in the ganglion cells may be studied satisfactorily either in the toluidine blue-erythrosin or the hematoxylin-erythrosin preparations. In most of the ganglia of children and young adults in our series the chromidial substance is distributed more or less uniformly throughout the cytoplasm in the majority of the ganglion cells (Fig. 5A and B). Some cells contain a more abundant supply of chromidial substance than others; consequently they react more strongly to the basic stain. In those with only a meager supply of chromidial substance this material usually is distributed in the peripheral zone of the cytoplasm (Fig. 5C), leaving the perinuclear zone relatively devoid of chromidial bodies. Less frequently the chromidial substance is aggregated in the perinuclear zone (Fig. 5D). These observed variations in the quantity and distribution of the chromidial substance in the ganglion cells probably are associated with different phases in the functional activity of these cells.

In some of the ganglia obtained at autopsy, particularly in the advanced age groups and nearly all of those in the surgical series, the supply of the chromidial substance is relatively meager in the great majority of the ganglion cells. The chromidial substance present in these cells in most instances exists in minute granules or as chromidial dust (Fig. 5E). Most of the ganglion cells which contain but little chromidial substance also exhibit some diminution in the size of the nucleus and in the quantity of intranuclear chromatin. Some of these ganglia also include hyperchromatic ganglion cells. The latter usually exhibit shrinkage both of the nucleus and of the cytoplasm (Fig. 5F).

Pigmentation: Melanotic pigment in the cytoplasm of some of the ganglion cells is a common phenomenon in all the ganglia of individuals 30 years of age or over in our series. Ganglion cells containing some melanotic pigment also occur in some of the ganglia in the younger age groups. The youngest in our series which show ganglion cells with appreciable amounts of melanotic pigment are sympathetic trunk ganglia of a patient 11 years of age with progressive muscular dystrophy. Traces of melanotic

pigment in ganglion cells have been reported in younger material. Some of the ganglia in our series which fall within the age limits of 18 to 25 years show moderate pigmentation of some cells, but none below the age of 35 years show marked pigmentation. Some of the ganglia in the most advanced age groups also show only moderate pigmentation.

The quantity of melanotic pigment in pigmented ganglion cells varies within wide limits. In moderately pigmented cells the pigment granules may be distributed in a narrow peripheral zone or aggregated in a restricted portion of the cell body, usually adjacent to the base of one of the larger dendrites. In occasional cells the pigment appears aggregated in a cap shaped mass at one side of the nucleus. As the pigment increases in amount it replaces more and more of the cytoplasm until the entire cell body outside the nucleus appears filled with this material. In some ganglion cells masses of pigment granules occur also in the dendritic processes. In cases of excessive pigmentation masses of pigment outside the ganglion cells are not uncommon, although some of the ganglion cells remain devoid of pigment (Fig. 6).

Many moderately pigmented ganglion cells exhibit no other histological changes except some reduction in the quantity of chromidial substance. Excessive pigmentation probably always is accompanied by other degenerative changes in the ganglion cells and results in the death of many of these cells. As the normal cytoplasmic constituents are replaced by pigment granules the ganglion cells undoubtedly become functionless. In silver preparations of heavily pigmented ganglia the dendrites and axons of many of the ganglion cells that are most heavily laden with pigment are not impregnated, although the processes of adjacent ganglion cells which are devoid of pigment or only moderately pigmented are impregnated perfectly (Fig. 6). Excessive pigmentation undoubtedly results in necrosis of a large percentage of the ganglion cells. In the most heavily pigmented ganglia in our series the majority of the ganglion cells obviously are necrotic. Even in these ganglia many of the ganglion cells are devoid of pigment. In moderately pigmented ganglia only the most heavily pigmented cells appear to be necrotic.

The most heavily pigmented ganglia in our series are those that have been obtained following death from carcinoma. They fall

within an age range of 46 to 77 years. In general the younger ones are less heavily pigmented than the older but the difference is not very marked except in the most extreme cases. The youngest ganglia in this group are much more heavily pigmented than most of the other ganglia in the same age group and some of those in the most advanced age group. The excessive pigmentation of the autonomic ganglion cells in this group of patients undoubtedly is associated with the malignant disease. Excessive pigmentation of the autonomic ganglion cells probably is a constant accompaniment of carcinoma, particularly in its advanced stages.

Other Cytological Variations: In the ganglia of children and young adults in our series, except those obtained from surgical cases, the ganglion cells appear highly uniform in their internal structure and present no variations that could be regarded as pathological. Preparations of some of the ganglia obtained at autopsy beyond the ages of young adults and those of nearly all the ganglia in the surgical series show changes other than pigmentation and variations in the chromidial substance, in some of the ganglion cells, which obviously represent degenerative processes. These changes include hyalinization of the cytoplasm in ganglion cells with a meager supply of chromidial substance, hydropic enlargement or edema of a small number of ganglion cells, vacuolization of the cytoplasm in some, neurofibrillar changes in some, and destruction of cytoplasm by phagocytic cells in variable numbers (Fig. 7).

Interstitial Tissue: In toluidine blue-erythrosin and hematoxylin-erythrosin preparations of ganglia of young children the connective tissue framework appears relatively meager. The ganglion cell capsules are inconspicuous and the ganglion cells are closely aggregated in groups which are separated from one another by bundles of axons and long dendrites. Cells probably homologous with neuroglia are present among the dendrites as well as in association with the axons. In preparations of the ganglia of young adults the interstitial connective tissue is somewhat more abundant. The ganglion cell capsules are less delicate than in the younger material, but the ganglion cells within groups remain closely aggregated. The groups are separated somewhat more widely by the increasing volume of the dendrites and axons.

Preparations of the ganglia in the more advanced age groups

which exhibit the narrowest ranges of variation in the ganglion cells show a moderate progressive increase in the amount of connective tissue in the framework of the ganglia and slight thickening of many of the ganglion cell capsules. The interstitial tissue, plus the ganglion cell processes, makes up an appreciably greater percentage of the volume of the older than of the younger ganglia.

Some of the ganglia in our series in all the age groups show relatively wide variations in the interstitial tissue. Some of these variations undoubtedly are associated with acute or chronic infections or other inflammatory processes.

Preparations of all the ganglia obtained following death from acute infectious disease show evidence of marked hyperemia of the interstitial tissue and infiltration with wandering cells, including mainly lymphocytes and mononuclear leukocytes. These cells appear in greatest abundance in the perivascular lymphatics, but also occur throughout the interstitial tissue and, in many instances, within the ganglion cell capsules. In some of the ganglia the interstitial connective tissue shows evidence of hyperplasia.

Preparations of ganglia of individuals with chronic infectious disease usually show less hyperemia of the interstitial tissue than those of ganglia obtained from cases of acute infectious disease. Infiltrating cells also are less abundant, but hyperplasia of the interstitial connective tissue is more marked and proliferation of the cells lining the ganglion cell capsules is not uncommon. Hyperplasia of cells other than those of connective tissue origin also takes place, which accounts for a large percentage of the cellular elements present throughout the interstitial tissue. These factors probably are associated with the inflammatory process.

The above account of the changes observed in the interstitial tissue in autonomic ganglia in acute and chronic infectious disease is in general agreement with those of Staemmler [7] and Mogilnizcky.[8, 9, 10] These investigators regarded the hyperemia, infiltration and hyperplasia of the interstitial tissue, with accompanying changes in ganglion cells, in the autonomic ganglia in infectious disease as related to the disease process, but not as direct factors in the etiology of the disease.

Preparations of most of the ganglia removed surgically in our series show changes in the interstitial tissue comparable with those observed in the ganglia in instances of chronic infectious

disease. Inasmuch as changes such as these afford evidence of chronic inflammation in the ganglion, they may be regarded as accompaniments of the diseases in question.

Comment

The histological data set forth above show that preparations of autonomic ganglia falling within any given age group exhibit certain variations common to all the ganglia in that group, but the ganglia of certain individuals in every age group exhibit a wider range of variation than those of others. This is due in part to the presence of certain variations in some cases which are not common to all in the same age group and in part to the existence in exaggerated form of certain of the common variations. The ganglia in every age group which exhibit only those variations that are common to all ganglia within that group undoubtedly may be regarded as most nearly normal. The variations they exhibit, consequently, are related to age. Variations that exist in some of the ganglia in a given age group and not in others obviously depend on factors other than age. Some of these variations undoubtedly are pathological in some degree. The existence in exaggerated form of certain variations common to all ganglia in the same age group probably is causally related to pathological lesions in the body which either affect the entire organism or at least result in modifications of metabolic functions.

Changes in the autonomic ganglia indicated by the variations in the successive age groups which, according to the criteria suggested above, may be regarded as related to age include the following: growth and differentiation of the ganglion cells from birth to maturity; development of secondary dendrites and other dendritic modifications in some of the ganglion cells during adult life; deposition of melanotic pigment in moderate amounts in some of the ganglion cells, particularly after the age of 30 to 35 years; exhaustion of the chromidial substance in some ganglion cells; degenerative changes in occasional ganglion cells particularly in advanced age, including hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia in moderate degree, and necrosis; moderate progressive increase in the quantity of interstitial connective tissue from birth to advanced age; and thickening of the ganglion cell capsules in some

degree and the occasional existence of free cells within the ganglion cell capsules, particularly in advanced age. Changes which, according to the same criteria, may be regarded as pathological include the following: elaborate development of dendritic nests, dendritic brushes, and so on, and excessive budding and hypertrophy of dendrites; marked chromidial changes in large numbers of ganglion cells, including diminution of the supply of this substance in some cells and hyperchromatism in others; excessive deposition of melanotic pigment in the ganglion cells; marked degenerative changes in considerable numbers of ganglion cells, particularly in the less advanced age groups, including hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia and necrosis; hyperemia and infiltration of the interstitial tissues and hyperplasia of both connective tissue and non-connective tissue elements; and marked thickening of ganglion cell capsules with proliferation of the cells lining them.

Histological variations in autonomic ganglia which obviously are related to the age of the individual probably depend on progressive changes in the metabolic processes in the organism. Those that are related to disease undoubtedly depend on factors associated with the disease processes in question. The common occurrence of hyperemia and infiltration of the interstitial tissue in the ganglia in acute or chronic infectious disease, and other conditions in which lesions of ganglion cells are common, strongly suggests that acute or chronic inflammation in the ganglia bears a causal relation to the ganglion cell lesions in many cases. The ganglion cell lesions in such cases, consequently, must be regarded not as causes but as accompaniments of the disease in question. Certain ganglion cell lesions, *e.g.*, excessive pigmentation, probably result from functional depression of the ganglion cells (Dolley and Guthrie [11]). Since excessive pigmentation is a constant accompaniment of certain pathological states, *e.g.*, arsenic poisoning, cachexia and senile atrophy, it probably must be regarded as a direct result of the pathological state in these cases.

All the observed histological variations in autonomic ganglia that have been regarded as related to disease fall into relatively few general categories. Those associated with diverse diseases, furthermore, may be essentially similar; consequently they cannot be regarded as specifically related to the disease in ques-

tion in any given case. This point of view has been supported by nearly all investigators who have studied the histological variations in autonomic ganglia in relation to disease. As the author [12] has previously pointed out, however, most of the variations observed in autonomic ganglia which obviously are related to disease are indicative of hyperactivity of the ganglion cells. Therefore, it seems not improbable that the autonomic dysfunction associated with these changes may have played a rôle in the disease process in question, particularly in cases in which vasoconstriction was a factor in the disease. The autonomic dysfunction resulting from necrosis or physiological depression of a large percentage of the ganglion cells in certain cases probably also plays a rôle in the disease process in these cases.

Summary

Histological variations in autonomic ganglia and ganglion cells have been studied in preparations of ganglia obtained at autopsy in an extensive series of unselected cases and ganglia removed in the surgical treatment of disease in approximately 50 cases. These ganglia represent an age range from early childhood to senility. The ganglia in every age group that exhibit only variations common to all the ganglia within that group have been regarded as most nearly normal. The variations observed in them, consequently, have been regarded as related to age. Variations not common to all the ganglia within a given age group and certain variations common to all the ganglia in the same age group but existing in exaggerated form have been regarded as pathological in some degree and causally associated with pathological lesions in the body.

The variations that have been regarded as related to age include all changes resulting from normal growth and differentiation both in the ganglion cells and in the interstitial tissue, changes in the chromidial content of ganglion cells associated with normal functional activity, deposition of melanotic pigment in moderate amounts in some ganglion cells, and degenerative changes in occasional cells, particularly in advanced age. Those that have been regarded as related to disease or pathological lesions in the body include the following: marked chromidial changes in large numbers of ganglion cells; excessive deposition of melanotic pigment

in ganglion cells; marked degenerative changes in considerable numbers of ganglion cells, such as hydropic enlargement of the cell body, vacuolization or hyalinization of the cytoplasm, neuronophagia and necrosis; hyperemia and infiltration of the interstitial tissue and hyperplasia of both connective tissue and non-connective tissue elements; and marked thickening of ganglion cell capsules and proliferation of the cells lining them.

The observed variations in the ganglia that seem to be related to disease fall into a few general categories. Those associated with diverse diseases, furthermore, may be essentially similar; consequently, they cannot be regarded as specifically related to the disease in question in any given case.

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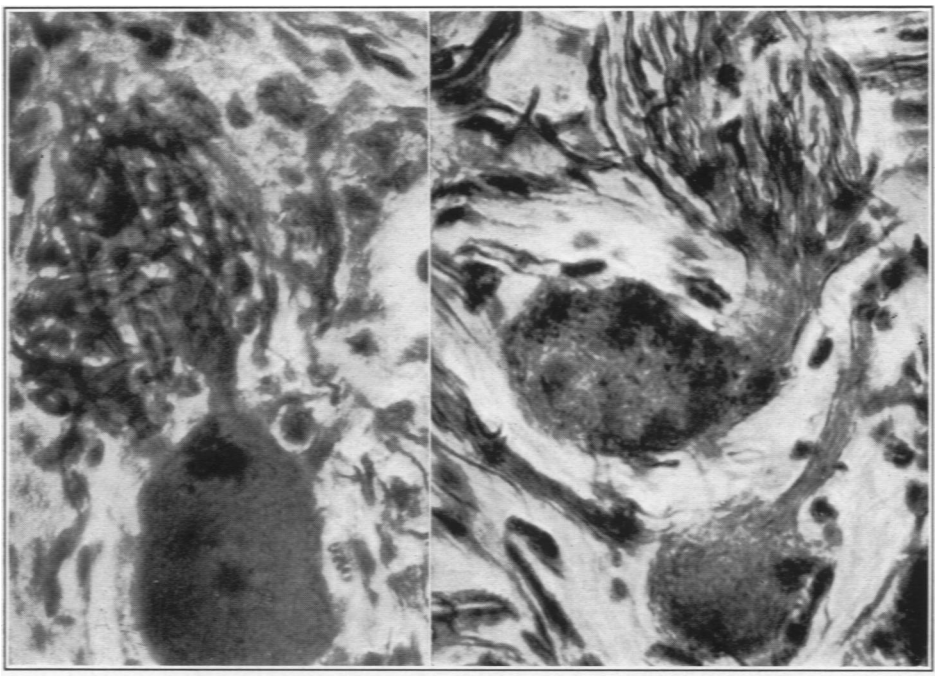
DESCRIPTION OF PLATES

PLATE 147

FIGS. 1, 2, 3 and 4. Ganglion cells showing pathological dendritic modifications from a patient aged 78 years.



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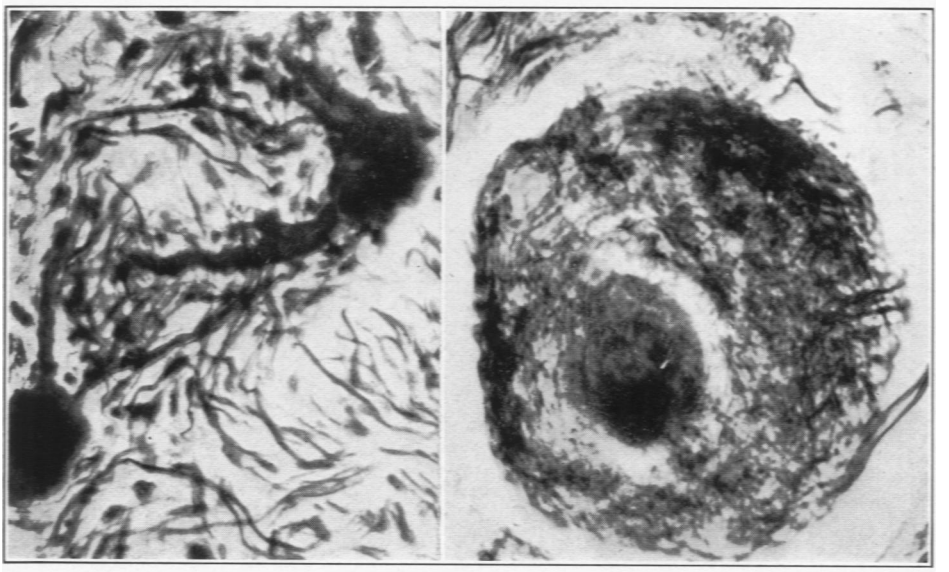

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Plate 148

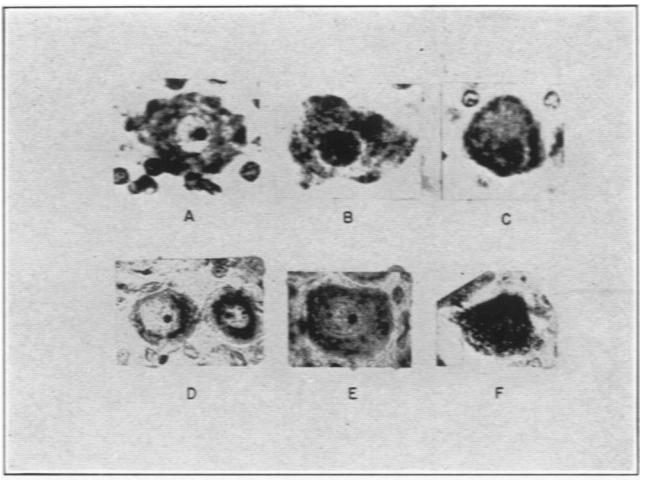
Fig. 5. Autonomic ganglion cells illustrating variations in distribution and quantity of chromidial substance.

A = uniform distribution, chromidial bodies large; B = uniform distribution, chromidial bodies small; C = peripheral distribution; D = perinuclear distribution; E = chromidial dust; F = hyperchromatic cell.

Fig. 6. Heavy pigmentation in sympathetic trunk, patient with carcinoma, age 77 years.

Fig. 7. Ganglion cells.

A = hyaline degeneration; B = hydropic enlargement; C = vacuolization; D = neuronophagia.



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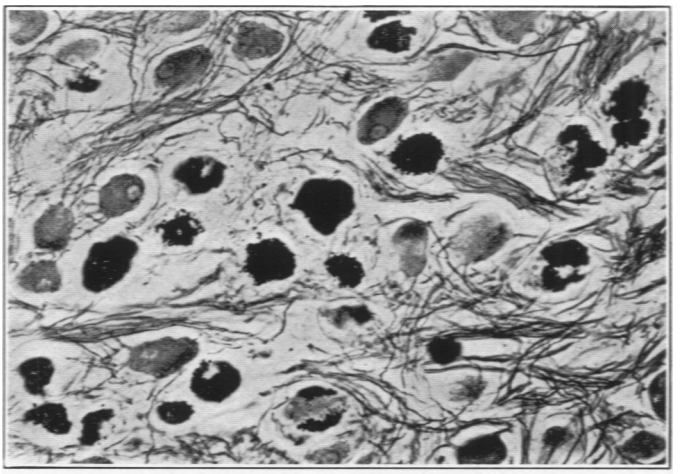

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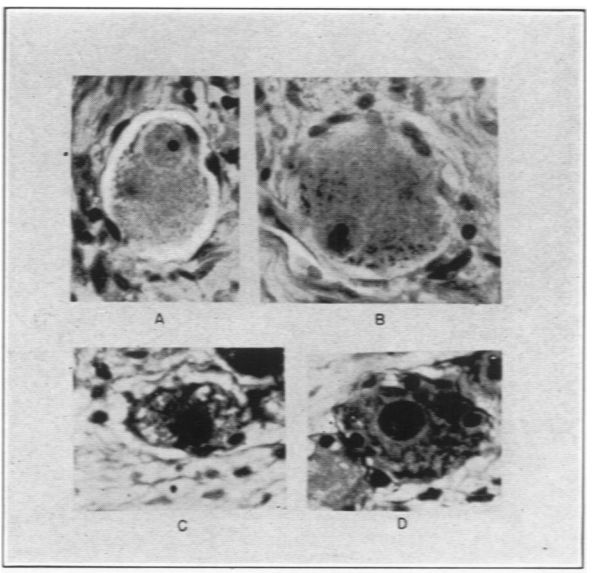

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