The Effect of Advancing Age upon the Human Spinal Cord

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L. Raymond Morrison 1897–1950

Preface

In 1929 a special unit for the care and study of patients with rheumatoid diseases was set up in the Medical Clinic of the Massachusetts General Hospital in Boston. On the clinical side, the program was concerned with improved therapy, and on the research side, with more comprehensive descriptions of individuals affected with rheumatic diseases, more detailed accounts of anatomical and physiological changes produced in the joints, and (somewhat later) with the chemical and physiological alterations in the connective tissue—the tissue in which the pathological changes of the rheumatic diseases are found.

A recently published volume, *Rheumatoid Arthritis: A Definition of the Disease and a Clinical Description Based on a Numerical Study of 293 Patients and Controls,** relates one aspect of our comprehensive study of rheumatoid arthritis. The patients included in this series were systematically questioned and examined in regard to clinical features in which the nervous system might have been involved. Confirmation was thus obtained of our impression that neurological manifestations form an integral part of the syndrome of rheumatoid arthritis. Histological examinations of the spinal cords of some of the patients were also undertaken in an attempt to establish the anatomical basis for the various muscular and neurological symptoms and signs that are frequently encountered in this disease. For the purpose of comparison, similar examinations were made in cases of rheumatic fever, lupus erythematosus, periarteritis nodosa, dermatomyositis, and scleroderma without pathological evidence of arthritis. It soon became apparent, however, that control material must be collected in order to show the changes which occur normally with increasing age, decade by decade. Without benefit of the latter, it was impossible to determine the specificity of the spinal cord lesions observed in rheumatoid arthritis and seemingly related diseases. Control material was therefore collected along with the pathological. The present monograph represents the results of our effort to establish a base line, or normal control, for any studies of the human spinal cord in which the factors associated with increasing age must be taken into account.

Although certain members of the arthritis study team participated in the review of the clinical records, the interpretation of the clinical findings, and the collection of spinal cords from the rheumatic disease patients and the so-called controls, Dr. L. Raymond Morrison was re-

* See footnote, page vi.

sponsible for the description and interpretation of the observed histological alterations. Though Dr. Morrison was the neuropathologist to the Psychiatric Service at this time, he soon became a most active part-time member of the arthritis study team. He had spent twelve years studying the collected material and three years working on the monograph at the time of his death in August 1950.* When an ardent and gifted investigator is suddenly cut off by death in the midst of his active career, the loss to science is immeasurable. To his family and friends, the tragedy is poignant.

We have taken up the task where Dr. Morrison left off. Fortunately, there was little to add. The illustrations were well-labeled, and the text was complete except for a few omissions, which were covered in most cases by adequate notes on file in the laboratory, and only few paragraphs had to be omitted because we were not certain of the author's meaning. On the whole, the work of completing the manuscript for publication was largely a matter of assembling the manuscript and illustrations, putting them together, and inserting the references in the right places. Editorial changes were minimal. Needless to say, it was a privilege to participate in this last collaborative work with a colleague whom we so much admired.

Although the sources of funds for the support of this care-of-the-patient and research program have been recognized in the three previous Commonwealth Fund publications,† we wish to acknowledge this generous support once again. We particularly wish to express our gratitude to the Commonwealth Fund for a large annual grant for each of the past twenty years. This continued support has enabled us to complete several long-term research projects.

It was due to the interest, encouragement, and cooperation of Dr. Frank R. Ober, Dr. James H. Means, and the late Drs. Cecil K. Drinker and S. Burt Wolbach that this research venture in the field of rheumatic diseases was finally launched. Little did we suspect, when we embarked on it in 1928, that it would lead to a study which would attempt to ascertain the effect of advancing age on the human spinal cord.

This histological study of the effect of advancing age upon the human spinal cord, initiated by one of us (W. B.) and Dr. Morrison, was aided by various past and present members of the Lovett Fund group and the

* An obituary, summarizing Dr. Morrison's professional life and scientific accomplishments, appeared in *Archives of Neurology and Psychiatry,* 65:788 (1951).

† Bennett, G. A., Waine, H., and Bauer, W., *Changes in the Knee Joint at Various Ages with Particular Reference to the Nature and Development of Degenerative Joint Disease.* The Commonwealth Fund, New York, 1942.

Ropes, M. W., and Bauer, W., *Synovial Fluid Changes in Joint Disease.* Published for the Commonwealth Fund by Harvard University Press, Cambridge, 1953.

Short, C. L., Bauer, W., and Reynolds, W. E., *Rheumatoid Arthritis: A Definition of the Disease and a Clinical Description Based on a Numerical Study of 293 Patients and Controls.* Published for the Commonwealth Fund by Harvard University Press, Cambridge, 1957.

Department of Pathology, Massachusetts General Hospital. Miss Margaret E. Carroll, who participated in this study from its inception, prepared the excellent histological sections and helped in many other ways. Dr. Pedro M. Catoggio of Buenos Aires, Argentina, gave valuable assistance during the three years (1946–1949) that he was a member of the group. We wish to express our gratitude to each of them. Without their help, the study would not have been possible. We wish, finally, to thank the Division of Publications of the Commonwealth Fund for their excellent editorial assistance in the preparation of this and previous manuscripts for the printer.

We hope that the present publication will not only prove useful to students of diseases of the spinal cord but will also assist others to interpret the neurological manifestations of rheumatoid arthritis and related diseases.

W. B.
S. C.

June, 1958

Contents

Part I

Histology

Introduction

The histology of the normal spinal cord is often complicated by pathological alterations of various kinds and degrees. While one or more of these changes might be present in a given case without causing symptoms, they must still be considered signs of disease, for a greater intensity of the same sign or a different combination of others might produce clinical effects and under those circumstances the cord would be called abnormal.

Our knowledge of the histology of the normal spinal cord must be derived from the study of the cords of healthy young adults, who die suddenly and whose life histories contain no accounts of serious illness. But such cords must be considered "ideal," for relatively few cases fulfilling this combination of requirements come to autopsy. The usual cord met with in practice is from a person of advanced years, who has suffered from more or less serious diseases and whose death followed a rather lingering illness. Even though the patient has had no recognized neurological disease, the chances are that his spinal cord will not be the same as an entirely normal spinal cord. The effects of fever or toxemia from a terminal illness may make themselves felt, certain systemic diseases like diabetes or arteriosclerosis may leave signs in the spinal cord, and (last but not least) age itself may produce alterations that would not be found in the cord of a healthy young adult. For these reasons it seemed important to study a series of run-of-mill spinal cords, as they came to autopsy in a general hospital, from persons with no neurological symptoms. Such an undertaking is useful and indeed necessary in building up control material for the study of pathological cords, especially if the lesions are not severe. The usual tendency has been to contrast supposedly pathological cords with a theoretically normal, or ideal cord. But this may lead to unjustifiable emphasis upon insignificant variations, particularly if the series of cases is small. In order to establish something like a picture of the usual, non-neuropathological, supposedly normal spinal cord, it is necessary to find how far such a cord can deviate from the ideal normal. The purpose of this investigation is to detect the alterations that occur in cords that one would naturally assume to be normal and to attempt to find some order or relationship in the intensity or frequency of the most common or most constant alterations.

The criteria by which a cord is called normal have been many years accumulating, and while some of the standards have been arrived at by specific and purposeful investigations, most of the judgments are based

merely on a knowledge of general principles. Bruce's splendid *Atlas*[1] gives in clear and precise detail the number and the grouping of the nerve cells of the gray matter of the thirty-one different levels of the spinal cord. In addition to the more or less mathematical presentation of the arrangement of the nerve cells, the author also illustrates and carefully describes the configuration of the cord at its various levels, as seen in Weigert preparations. With the aid of this *Atlas* one can come pretty close to identifying sections from any level of the cord and detecting alterations in the number and distribution of the cells, as well as to recognizing the intensity and distribution of myelin. Earlier contributions were so sketchy in their presentations or so limited in their scope that no complete picture of the cord could be obtained. Of course Bruce's *Atlas* was merely topographical and none of the more refined details of structure were described or illustrated. But the normal standards for nerve cells had already been established by the work of Nissl,[2] and many other details of nerve cell classification and cytology have been added since.[3] The theory of the distribution and reaction of neuroglia in the brain that was so thoroughly developed by Cajal and his co-workers has served as the basis of many of the assumptions about glia. Some authors have questioned the accuracy of these assumptions and Jakob[4] and his pupils[5] have tried to show that the glial reactions in the cord are rather different from those in the brain. Hassin[6] goes so far as to imply that the normal spinal cord does not contain microglia. The blood supply of the cord, while fairly well understood since the investigations of Adamkiewicz[7] and Ross,[8] is still being worked out even in its grosser anatomical pathology. The meninges like all other structures of the cord have been studied in great detail in all sorts of pathological conditions, but the attention devoted to their histology under non-pathological circumstances has been mostly academic or else rather perfunctory. Either the "ideal" textbook picture with its various well-defined layers was assumed to be normal or the theory that normal meninges vary in the thickness was accepted with very little concern for its implications.

With this situation in mind an attempt was made to learn something more about the average, non-neuropathological spinal cord so that the information could be used, as stated above, as a control for other spinal cord investigations. While some of the changes that occur are certainly due, as has been said, to the effect of general systemic disease on the nervous system, the more constant alterations due to advancing age are what chiefly command attention. Just when do these lesions first begin to appear? And is there any tendency toward a regular progression in their severity as age increases?

The pathology of the cord in old age is fairly well known, although most of the information was arrived at piecemeal. Disease of the blood vessels of the cord was reported by Webber[9] in 1882 and later by Campbell.[10] Thickening of the dura was first pointed out in 1855 by Rokitansky,[11] who observed even then that calcification occurs less often in the dura than in the pia-arachnoid. Charcot[12] first called at-

tention to the lipoid disease of the nerve cells that Nissl later called "pigmentary atrophy," and it is to Virchow that we are indebted for the knowledge that old nerve tissue is overrun with neuroglia.

Studies on the spinal cord that are confined to the effects of old age are not numerous but they are quite good. Campbell[10] in 1894 and Hamilton[13] again in 1910 (both using cords of mental patients, although ruling out as far as possible neurological disease) made thorough studies of senile changes. They both found arteriosclerosis, loss of myelin in lateral and posterior columns, hypertrophy of ependyma, and the presence of corpora amylacea. In addition Hamilton found the same fatty degeneration of nerve cells previously reported by Charcot and an overgrowth of glia in the degenerated tracts. In reviewing the whole subject in 1931 Critchley[14] was able to find very little additional in the literature.

This present study was attempted not so much in the hope of adding supplementary findings, as to ascertain when these degenerations first occur and to trace them through their ultimate development. No attempt, or at least very little, was made to correlate the histological findings with the systemic diseases of the patients, for there were too few cases of any one diagnosis in this series to make such a correlation valuable. Nevertheless any histological changes that were encountered, even though they had no connection with the process of aging, were mentioned and described, for the purpose of the study was to call attention to all alterations as they occur in the normal cord, regardless of their cause.

Thirty-one spinal cords were used in this series, ranging from the second through the ninth decade. The diseases were those commonly found in a general hospital—malignant hypertension, rheumatic heart disease, cancer of the stomach, miliary tuberculosis, etc.

The cords were studied in the following way. After a gross inspection blocks were cut from the cervical, thoracic, and lumbar levels and fixed in the appropriate solutions for frozen sections, celloidin, or paraffin embedding. Paraffin embedding was used only for Bodian preparations. Studies were made by using the following stains: hematoxylin and eosin, cresyl violet, van Gieson, Weigert (myelin), Weigert (elastic tissue), Bodian (axons), Oil red O (fat), and Holzer. In many cases to elucidate special points of interest, phosphotungstic acid hematoxylin, Hortega's silver carbonate, Dockrill's silver carbonate, and Cajal's gold sublimate were also used.

Second and Third Decades

This group comprises five cords from patients ranging in age from eleven through twenty-nine years. In each case the dura consists of even and regular collagenous bands with no patches of fibrous thickening and no evidence of calcification. The pia-arachnoid is more than filamentous, and in the van Gieson stain it appears as a substantial collagenous membrane measuring about 65 micra thick. It is somewhat thicker and denser over the anterior spinal artery. In one case there is a slight thickening over the dorsal aspect and a mild infiltration of lymphocytes and plasma cells on the ventral surface (Fig. 1). This cellular reaction is slight and consists of only twenty or thirty cells within the entire circumference of the section. Many of the cells are scattered in the region of the anterior spinal artery, but there is no perivascular cuffing. In another case the soft meninges are definitely thickened and measure about 85 micra. Over the dorsal surface of the cord they fit snugly up around the entering posterior roots (Fig. 2), and beyond the pial line an overgrowth of collagenous fibers extends centrally up into the substance of the cord toward the posterior horn. These fibers also extend peripherally into the posterior root, making a heavy endoneurium.

In the four youngest cases the white matter is solid and compact but in the twenty-nine-year-old case it is loose and slightly edematous, especially around the edge. In all cases the perivascular spaces are moderately dilated in the gray as well as in the white matter. In two cases there is a mild perivascular (adventitial) infiltration of lymphocytes, with occasional polymorphonuclear leucocytes or plasma cells scattered thinly throughout the gray and white matter at all levels of the cord. In four cases the central canal is patent and is bounded by a compact layer of ependymal cells. In the twenty-nine-year-old case, however, the cells of the central canal have begun to proliferate and are not only several rows deep but are also grouped in clusters near the canal in the gray commissure.

At all levels of the cords of the four youngest cases myelin sheath preparations show a slight paling around or close to the edges of the lateral and posterior columns. When seen in longitudinal section, the sheaths in these pale areas appear swollen. The bizarre myelin figures include granular and fragmented balls. In addition to this peripheral paling, the lupus erythematosus case shows a patch of demyelination close to the lateral pyramidal tract on one side. Compared with the anterior column, the posterior column is slightly and unevenly pale and the

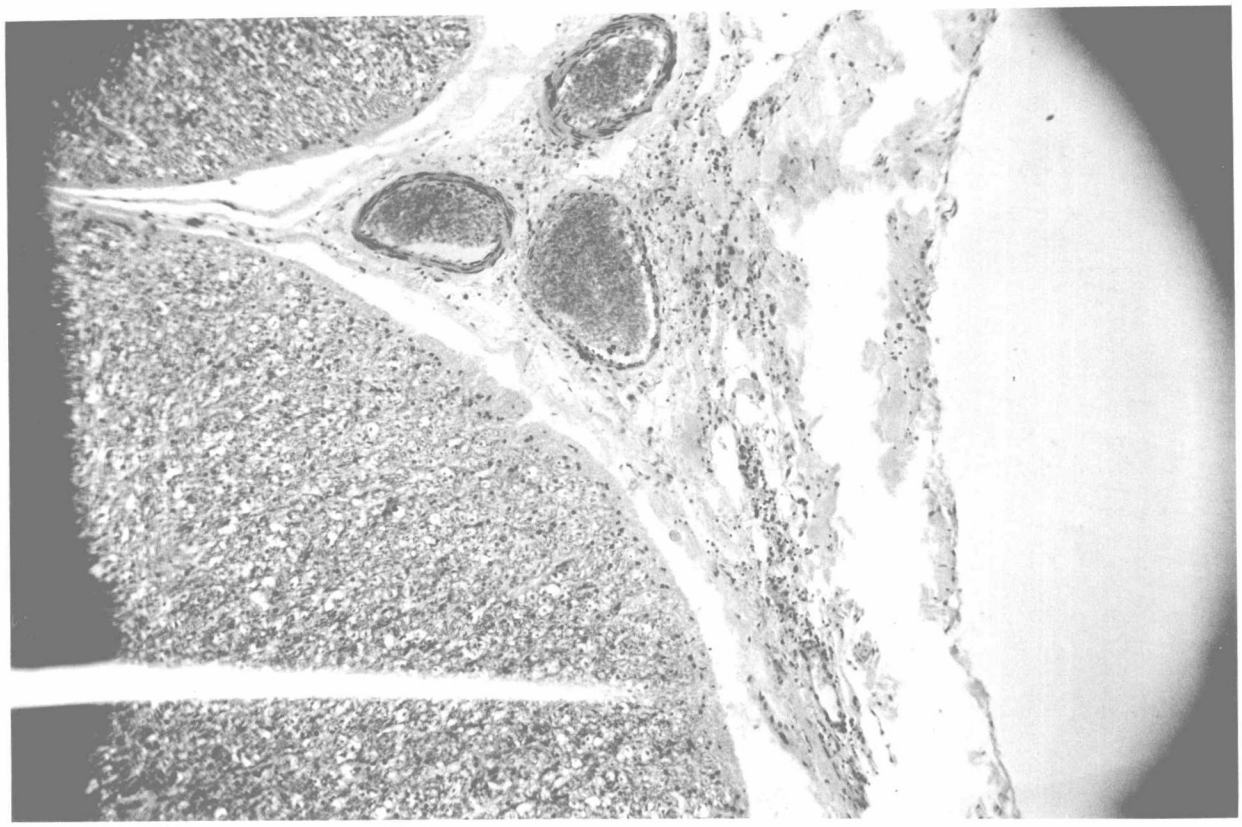

Figure 1
Mild infiltration of meninges. H & E stain

sheaths are more widely separated, giving the impression of slight degeneration, but on high power the individual sheaths show practically no swellings or fragments—they are merely farther apart. In one case, with collagenous overgrowth in the posterior roots, the paling and thinning are much more conspicuous, especially at the base of Goll's column near the posterior commissure; and some swelling of the sheaths and occasional myelin balls are visible on high power in longitudinal section. In all cases the posterior roots are practically normal, showing the conventional honeycombing or herringbone structure.

The silver stain for axons and neurofibrils shows that most of the axons are of uniform caliber and are distributed evenly at all levels of four cords. In the fifth cord no empty sheath spaces are seen on cross section, but the axons are packed a little more closely together in the posterior column, and on longitudinal section a few examples of fragmentation, beading, excessive tortuosity, and thickening of the axons are seen at all levels. The nerve roots show no changes. A few tan bodies, hyaline in character and having slightly crenated edges, are scattered in the anterior valley of the gray matter between the anteromedial and anterolateral cell groups at the cervical and lumbar levels of the fifth cord and at the cervical level of one other cord. These tan bodies occasionally have little wisps of neurofibril still attached to them like tails, and in some of the cords to be described later they are plainly seen in