# A CONTRIBUTION TO THE PATHOLOGY OF MYASTHENIA GRAVIS. REPORT OF A CASE WITH UNUSUAL FORM OF THYMIC TUMOR.[1]

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PLATES XXI–XXIII.

Since the publication by Wilks in Guy's Hospital Reports for 1877 of a case presenting the clinical features of bulbar paralysis, yet without any demonstrable lesions at autopsy, our clinical knowledge of this condition has been enriched by the publication of a fairly numerous series of similar cases. Various mental, sensory, secretory and vasomotor symptoms have been added from time to time by different observers to the motor phenomena that usually dominate the clinical picture. Most characteristic among the latter are extreme muscular weakness and the myasthenic reaction first described by Jolly in 1895. Jolly found that by subjecting the affected muscles to a tetanizing faradic current at intervals of one or more seconds the muscular contractions became progressively weaker, until a paresis or even paralysis resulted. The same effect follows repeated voluntary contractions of any group of affected muscles. In either case a short period of rest is followed by a return of the muscles to their former condition of excitability. Not less characteristic are intercurrent attacks of dyspnea and tachycardia with or without fever, symptoms pointing to an apparent bulbar affection. Of the many names proposed for this symptom-

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complex, that advanced by Jolly, "Myasthenia gravis pseudoparalytica," is most generally accepted.

Pathologically our knowledge of this condition is far less complete. A review of the literature prior to 1901 is contained in Oppenheim's exhaustive monograph on the subject. We have been able to collect from the literature forty-five cases with more or less complete autopsy records. To this number we desire to add the following case that seems to present some features of especial interest.

P. C., aged 52 years, a tailor, Russian by birth, was admitted to Mt. Sinai Hospital on December 15th, 1906, to the service of Dr. B. Sachs, to whom we are indebted for the clinical history and use of the case for publication.

*Family History.*—Negative.

*Past History.*—Had measles in childhood. Uses alcohol very sparingly, but is an excessive cigarette smoker.

*Present History.*—Six months prior to admission, after exposure, patient experienced a dull heavy sensation in chest together with difficulty in inspiration. At the same time he noticed diplopia and diminution in acuity of vision that glasses failed to relieve. During the past month vision has improved, but diplopia persists. There has been lachrymation for the past week. Very shortly after the onset, impairment of motion of shoulder girdle on both sides as well as atrophy of the affected muscles developed. Two months later, with impairment of the movements of the tongue, there ensued difficulty in phonation, and regurgitation of food through the nose. For the past three months there has been gradual atrophy of the facial muscles with difficulty in swallowing. The head has a tendency to fall forward on the chest. Patient complains of severe frontal headache, tinnitus aurium, and disturbance in senses of taste and smell. There has been marked emaciation and general weakness.

*Physical Examination on Admission.*—General condition fair. Moderate emaciation. Sensorium clear. Hearing, taste and smell normal.

Eyes—Pupils contracted, but reaction to light and in accommodation normal. Slight lateral nystagmus. Corneal reflex absent. Slight weakness of external recti. Very marked weakness of levatores palpebræ and of orbiculares palpebrarum. Diplopia at a distance of five feet. Color vision slightly disturbed.

Mouth—Tongue deviates slightly to left. Slight coarse tremor; no atrophy. Pharyngeal reflex diminished. Articulation indistinct.

Face—Flattening and falling in of cheeks. Jaw movements normal. Cannot purse lips, but can retract them to show teeth. Wrinkling of forehead normal. Jaw jerk and Chvostek's phenomenon present.

Lower Extremities—Patellar, Achilles, cremasteric and superior epigastric reflexes normal. Muscular power fair. Gait shows weakness but is otherwise normal. Romberg's symptom absent.

Upper Extremities—Movements of flexion and extension at wrist joint normal; at elbow weak. Range of motion at shoulder joint unimpaired, but all voluntary movements are weak, and even the slightest counter pressure can not

be resisted. Slight atrophy of both deltoids and of infra- and supraspinati. Repeated voluntary abduction of the arm is followed by complete transitory paralysis of the muscles. Ataxia, fibrillary twitching and hypertonicity are absent in the muscles of all the extremities. There is no reaction of degeneration, but a typical myasthenic reaction can be elicited by repeated stimulation with a tetanizing faradic current in the deltoid, spinati, and thigh muscles.

Neck and Trunk—Head held erect with difficulty, and for a short time only. Patient can not assume the erect from the recumbent posture unaided.

Thoracic and abdominal organs negative, except for a mild grade of pulmonary emphysema.

Urine shows a few granular casts; no albumin. Blood count normal.

From January 20 to January 23 there was a gradual but slight improvement in the patient's condition. The head could be raised from full flexion and maintained erect. Voluntary movements of the arms were performed with less fatigue, and the power of resistance to counter pressure was increased.

On January 24 it was noted that without premonitory symptoms, the pulse rate suddenly increased to 104 and the respirations to 70. Breathing was stertorous, but the pulse remained of good quality. Two hours later coma supervened. This condition lasted two hours, after which the symptoms partially abated in severity, the pulse, however, becoming irregular, and the dyspnea continuing. The following morning a similar attack occurred, death ensuing within five minutes of its onset. The course of the disease was afebrile throughout. A report of the autopsy performed twenty-four hours after death by Dr. E. Libman follows:

*Autopsy.*—Marked rigor mortis; well nourished. Lipomatosis of mesentery. Large lipomatous mass in falciform ligament.

Muscles—All skeletal muscles look pale.

Thyroid—Not enlarged; no macroscopic changes.

Thymus—Weighs 20 grammes; very firm; measures 5 cm. in length, 3.5 cm. in width and 2 cm. in thickness. On section is pinkish-white in color, very firm, lobulated, and cells can be very easily scraped from surface.

Trachea—Negative.

Lungs—Old adhesions over both lungs. They are intensely congested. Small old cheesy area at right apex. Bronchial lymph nodes and mediastinal nodes are anthracotic, some fibrous, others containing small cheesy areas.

Heart—Right auricle dilated. Tricuspid segments slightly thickened. Slight fatty overgrowth over right ventricle. Left auricle dilated. Mitral segments somewhat thickened. Chordæ tendineæ thickened and somewhat shortened. Aortic flaps thickened at insertion, slightly retracted. Corpora arantii thickened. Anterior coronary artery shows fairly marked thickening and atheroma at its origin. No congenital lesions.

Diaphragm—Negative.

Spleen—Old perisplenitis present. Pulp congested and rather soft. Weight 270 grammes.

Liver—Negative, except for slight congestion. Gall-bladder and ducts negative. Weight 1750 grammes.

Kidneys—Capsules not adherent; pelves rather large. On section both kidneys are congested and somewhat hard. Weight 330 grammes together.

Adrenals—Rather large, congested, medulla thick.

Esophagus—Somewhat dilated, fairly marked keratosis.

Stomach and Intestines—Congestion of stomach. Intestines practically negative, except for cecum, beginning of ascending colon, and lower part of descending colon, all of which show congestion.

Pancreas—Very large and congested. Weight 112 grammes.

Bladder—Negative.

Prostate—Contains few very small calcareous masses.

Spine—A few supra-cartilaginous exostoses.

Brain and Spinal Cord—No gross lesion.

## MICROSCOPIC FINDINGS.

The material was fixed in Zenker's fluid, formalin, Marchi's fluid and alcohol, and the sections were stained with hematoxylin and eosin, Van Gieson's stain, Unna's polychrome methylene blue, Mallory's connective-tissue stain, Gram's stain, Sudan III, Nissl's stain and Weigert's myelin stain.

*Muscles.*—A large number of sections from the psoas, longus colli, deltoid, supinator longus, rectus abdominis and diaphragm were studied and the results were fairly uniform in every muscle. The constant lesion in the voluntary muscles is the presence of smaller or larger areas of cellular infiltration. In all of the muscles examined we were able to find this lesion. In most instances these areas are seen without difficulty; at other times a long search is required and it may be necessary to section many pieces of muscle before a single area can be discovered. The cells in these infiltrations are of small size and uniformly round in shape. Their nuclei are relatively large, usually round or slightly oval in form, and stain intensely with hematoxylin and the nuclear aniline dyes. Morphologically these cells resemble small lymphocytes. No polynuclear leucocytes, plasma cells or eosinophile cells are present in the infiltrated areas, nor can any mitotic cells be seen. In sections where the muscle fibers are cut longitudinally these areas of lymphocytic infiltration are found to be situated between adjacent fibers which are separated slightly as a result. Occasionally the cells may be seen between two or three adjacent fibers. The infiltrations have a tendency, in longitudinal sections, to form long, narrow bands which are easily seen upon examination on account of their intense staining qualities. In the rectus abdominis an area of this kind was found which measures 0.95 mm. in length and 0.078 mm. in

width (see Fig. 1). In transverse sections the appearance is somewhat different. Here the cellular infiltrations are cut in the opposite axis and appear as oval or roundish areas which vary considerably in size. Some may show only 15 or 20 cells while others may present ten or twenty times that number. One of the smaller areas in the psoas muscle measured 0.1 mm. by 0.03 mm., while a larger area measured 0.3 by 0.15 mm. (see Fig. 2). Buzzard has suggested the term "lymphorrhages" for these cellular infiltrations, coining the word to designate that they are composed of lymphocytic cells infiltrating the muscle fibers as do red blood cells in interstitial hemorrhages. This terminology we shall adopt in our paper for the sake of convenience. Most of the transverse sections show from one to three small capillaries in the central part of each lymphorrhage. These capillaries appear quite normal and are often filled with blood (see Fig. 3). In the longitudinal sections it is more difficult to find these small vessels unless serial sections are examined. In the study of the deltoid several longitudinally cut capillaries are seen. It is possible, in some of these vessels, to see the perivascular lymph spaces with ease, on account of the presence of lymphoid cells which completely fill the dilated lymph spaces. In one of the capillaries the endothelium limiting the outer wall of the perivascular lymph space is clearly seen. This condition is identical with that to be described in the thymic tumor. In the other vessels the large number and compact arrangement of the cells obscure these details. The muscle fibers in the immediate vicinity of the lymphorrhages show no degenerative or atrophic changes.

Some of the muscle bundles have a tendency to stain more intensely than others, but this is frequently seen in normal muscles and can not be considered as a pathological process. In transverse sections Cohnheim's fields are well marked in most specimens. The striations are distinctly seen in all sections. In some of the muscles rather prominent bands of connective tissue which stain reddish by Van Gieson's method, may be seen. Some of these bands merge directly into the muscle fibers. At these situations the sarcolemma cells are increased in number and the transverse striations are somewhat indistinct. Some of these connective tissue bands have a more

or less wavy outline and show a few indistinct oval nuclei. They bear a striking resemblance to muscle fibers in shape and size and must be looked upon as a replacement fibrosis secondary to degenerative muscle changes. This lesion is most marked in the deltoid muscle. Otherwise only a normal amount of connective tissue is present. No evidence of fatty degeneration is seen in osmic acid preparations and no pigmentation can be found in any of the muscles. A few fibers are the seat of marked degenerative changes. This is particularly noted in transverse sections of the longus colli muscle. Here the fibers stain distinctly pinkish with Van Gieson's stain, and the muscle nuclei are increased in numbers. A few vacuolated cells with peripherally situated nuclei are also seen. The protoplasm is somewhat granular, quite different from the homogeneous appearance noted in ordinary hyaline degeneration (see Fig. 4). This lesion, as well as that described above as occurring in the deltoid, may be considered as an early degenerative atrophic change.

In the study of the psoas muscle a few small areas are seen which show a different picture. Here the sarcolemma cells are very numerous but the muscle fibers apparently are unchanged. A few cells are also present showing pyknotic nuclear changes. It is difficult to classify properly these cells, but we look upon them as polynuclear leucocytes with degenerating nuclei (see Fig. 5). Throughout the sections the walls of the blood vessels do not show any changes whatever. The medullated nerve fibers are likewise normal, and the sensory nerve-endings ("muscle-spindles") which are present in some of the muscles in large numbers are apparently free from any pathological changes.

Unfortunately the eye-muscles could not be obtained for examination.

*Tongue.*—After a long search through many sections it was possible to find a few small areas of infiltration in this organ. Apart from their small size these areas do not differ from those found in the skeletal muscles. Otherwise no changes are present, either in the muscular portion, vessels or nerves.

*Heart.*—It was impossible to discover any lymphorrhages in this organ. A moderate grade of interstitial myocarditis is present,

and a few small masses of hyaline matter may be seen in the connective tissue surrounding some of the larger blood-vessels. The arteries themselves are not affected. The muscle nuclei vary considerably in size and shape and many large irregular forms are seen which represent regenerative changes. The striations are distinct throughout.

*Thymus Tumor.*—Sections were cut from various parts of the tumor in order to determine its origin and relationship to the thymus gland proper. In only a few places could any normal thymus tissue be found. This, in some instances, was separated from the tumor by layers of connective-tissue, but in other places it was seen to be in direct relationship with the tumor. The thymus tissue has a normal appearance and contains a small number of Hassel's corpuscles, some of which show calcareous changes, while others contain keratohyaline cells and polynuclear leucocytes. In some of the sections the thymus tissue is divided by connective-tissue septa into small lobules. The tumor itself is separated from the surrounding structures by a well-marked connective-tissue capsule and with the low power this is seen to extend into the tumor mass which is thus divided into numerous lobes. The connective-tissue septa widen out in many places, inclosing islands of adipose tissue. Blood vessels of considerable size are present in these bands of connective-tissue, also scattered areas of blood pigment. Occasionally a few small fibers are seen running for a short distance from the septa into the tumor lobules.

Upon examination of the sections with the low power the tumor appears to be dotted with numerous slits, fissures and oval-shaped openings. With a higher power it is seen that these openings are widely dilated lymph channels or lymph spaces lined with endothelium. Some of the larger channels are of considerable length and have parallel walls; others are more or less oval in shape, due to the angle at which the section is cut. The tumor proper is of a very dense cellular structure. The cells are quite large, of an oval, polygonal or irregular shape, and contain large vesicular nuclei with numerous chromatin granules. The cytoplasm is granular and stains lightly with eosin or picric acid. Throughout the sections the cells have a tendency to form concentric bodies of fairly large

size, somewhat resembling those found in psammoma and certain types of endothelioma, but having no direct connection with any blood vessels. As many as twelve, fifteen, or more of these bodies may be counted in a single field. The cells in these concentric bodies are of spindle shape and their nuclei are long, narrow and curved as the result of compression (see Fig. 6). Some of the larger tumor cells contain two or more nuclei. A few cells show vacuolization of the cytoplasm, the nuclei remaining intact. A considerable number of nuclei throughout the sections show distinct nucleoli. None of the cells show any mitotic changes. A delicate stroma may be seen between the cells in those situations where the cells are less densely packed together. In some of the sections small islands of lymphoid cells are seen scattered between the tumor cells. No Hassel's corpuscles are found here, but these areas give the impression of being remnants of thymus tissue. Small masses of hyaline matter are seen here and there in the tumor, some of which are in close proximity to the blood vessels.

The lymph spaces are well filled with large spherical cells which show faint outlines and a coarsely granular cytoplasm. Most of the cells contain a small nucleus of irregular shape which is usually situated at the periphery. Besides these, smaller lymphocytic cells and granular matter are seen filling the spaces. Some of the larger cells show nuclear fragmentation. A few degenerated areas containing cholesterin crystals are seen.

The most interesting feature is the relationship of the tumor cells to the lymph spaces and blood vessels. All of the lymph spaces are lined by endothelial cells, as has been mentioned above. In some fields it appears as though several parallel layers of proliferated endothelium surrounded a considerable portion of the lymph space. These cells always stain more deeply than the tumor cells proper and in some situations form distinct bundles of spindle-shaped cells, merging gradually into the tumor cells. In other places the tumor cells appear to be directly springing from the endothelium of the lymph spaces (see Fig. 7). This is most distinctly seen where the lymph spaces have been cut more or less transversely, and in such instances the cells have a slight tendency to grow radially from their walls.

Blood vessels are very numerous throughout the tumor. These consist principally of newly-formed capillaries, though small arteries with thin walls are also present. Some of the latter show well-marked hyaline degeneration. A zone of lymphocytes surrounds each capillary. This may be seen in transverse as well as in longitudinal sections. In transverse sections these cells appear as a mantle in close relationship to the capillary wall. The anatomical position of these cells can be seen very clearly in longitudinal sections. Here we have a narrow band of cells on either side of the capillary and parallel to it. The cells are seen to be bounded on one side by the endothelium of the capillary and on the other side by a second row of endothelium which must be looked upon as the outer wall of the perivascular lymph space. In other words, these cells are confined to the perivascular lymph spaces. Just beyond these cells are clear spaces due to retraction or shrinkage and bounded by the tumor cells proper (see Fig. 8). The first layer of cells grows at right angles to the vessel walls and this radial arrangement may readily be seen with the low power. They also stain more intensely than those situated at a greater distance from the vessels. There seems to be no doubt that the tumor cells originally sprung from the endothelium of the perivascular lymph spaces, from which they have become detached (see Fig. 9). In a few fields, however, the tumor cells may still be seen in close relationship to the lymph spaces, but as a rule retraction is quite constant. The endothelium of the capillaries is normal throughout and has no bearing on the formation of the tumor.

In this connection it might not be out of place to say a few words regarding the discussion which has arisen concerning the perithelium of bood vessels and its relationship to perivascular tumors. The perithelium of the blood vessels is supposed to represent the endothelium of the perivascular lymph spaces, but in most cases it is difficult or impossible to discover the presence of a second layer of endothelium to form an outer wall of these lymph spaces. In the usual type of perithelial growth with a radial arrangement of the tumor cells these are always closely united to the vessel wall. This is not the case in our tumor, in which a well defined zone containing lymphocytic cells separates tumor cells from vessel wall.

As far as the presence of any outer endothelial boundary is concerned, a study of our case demonstrates such a layer in those sections where the capillaries are cut longitudinally. The fact that a dilatation of all the lymph vessels with marked lymph stasis is present in our case may account for the comparatively easy recognition of the perivascular lymph spaces. It is possible that many of the recorded cases of perithelioma in which the cells appear to arise directly from the adventitia of the blood vessels and where the perivascular lymph spaces are not dilated, belong in this group. Our case demonstrates the fact that tumor cells may encircle and grow radially from a blood vessel and still have no direct attachment to the vessel wall proper, but arise from an outer layer of endothelium bounding the perivascular lymph spaces.

The proper classification of this tumor is somewhat difficult. Inasmuch as the growth is perilymphatic in character, it bears the same relationship to lymphangio-endothelioma as a perithelioma does to haemangio-endothelioma. It is therefore a perilymphatic lymphangio-endothelioma.

*Thyroid Gland.*—The alveoli are lined by the usual layer of epithelial cells and are well filled with colloid material. The blood vessels are all distended and filled with blood and the picture is that of an acute congestion. Otherwise the sections appear quite normal.

*Lungs.*—Sections show an intense acute congestion. The alveoli are filled with a finely granular exudate. In some of the alveoli desquamated epithelial cells are seen, many of which are filled with coarse granules of a black or brownish color. A moderate amount of anthracosis is present, most marked in the connective tissue stroma surrounding the larger blood vessels.

*Liver.*—In this organ a few areas of lymphocytic infiltration are seen. The cells here are in every way identical with those described in the muscles. The areas are rather small and are situated apparently in the capillaries between the liver cells. None of these areas are found in the vicinity of any of the larger blood vessels or ducts. The liver shows a moderate degree of fatty degeneration and chronic congestion, with secondary atrophy and pigmentation of the liver cells.

*Spleen.*—The capsule shows a moderate grade of perisplenitis.

An intense degree of acute congestion is present. Some of the blood vessels are surrounded by coarse granules of brownish pigment. Hyaline degeneration is noted in the walls of many of the arteries.

*Kidneys.*—A moderate degree of chronic interstitial nephritis is seen. The epithelium of the tubules shows parenchymatous degeneration. The whole organ is acutely congested and the capillaries of the Malpighian bodies are very prominent.

*Adrenals.*—In the cortical substance of one adrenal a large lymphorrhage is found. This is situated in close proximity to a small artery. The cells in this area are the same as those described before (see Fig. 10). Otherwise these organs show an acute congestion involving the cortex as well as the medulla.

*Pancreas.*—This organ is the seat of post-mortem degenerative changes.

The other viscera do not show any pathological changes.

*Nervous System.*—Sections from the face, arm and leg centers of the motor cortex, and from various levels in the pons, medulla and cord were examined. Special attention was paid to the study of the nuclei of the third, fourth, sixth, ninth, tenth, eleventh and twelfth nerves. No pathological changes were noted in the nerve cells in any of these regions. No degeneration of any tract was found either by the Weigert or Marchi methods. Sections from the hypophysis were also normal.

In the perivascular lymph spaces of several small capillaries lymphocytic infiltrations were found. One of these vessels was situated in the grey matter near the tenth nucleus, the others in the outer part of the pyramidal tract ventral to the olivary body (see Figs. 11 and 12). No lesions were found in any of the larger blood vessels at the base.

## REMARKS.

Under this heading only those cases in which an autopsy has been performed or excised muscles examined will be discussed. The first recorded lesion that may be regarded as typical of myasthenia gravis was published by Weigert in 1901 in the pathological study of a case observed clinically by Laquer. In the perimysium, as well as between the fibers of the diaphragm and deltoid, the only muscles

examined, Weigert found small areas of cellular infiltration. These cells resembled for the greater part the small round cells normally present in the thymus. A few epithelioid cells identical with those found in the thymus were also demonstrable. No Hassal's corpuscles were found. There was a similar lesion in the cardiac muscle. Occupying the site of the thymus, but not adherent to the subjacent structures, there was found a soft tumor, 5 cm. by 3 cm. in diameter. Microscopically this tumor showed large hemorrhagic areas in which lay scattered islands of tissue consisting almost exclusively of lymphoid cells but interspersed with a few epithelioid cells. A few Hassal's corpuscles were also present. As the small round cells had apparently invaded the walls of some of the smaller veins and filled their lumina, Weigert concluded that the tumor was a lymphosarcoma, and the cellular infiltrations in the muscles metastases.

Weigert's observations regarding the presence of cellular infiltrations in the skeletal muscles have been confirmed by a number of subsequent observers—Goldflam, Link, Hun, Burr, Buzzard, Steinert, Boldt, Osann, Marburg, Frugoni. Not all of these authors, however, are in accord either as to the nature or the significance of these infiltrations, points that will be discussed subsequently.

It is noteworthy that in eleven cases (including our own) or about 20 per cent. of the cases that have come to autopsy, some abnormality of the thymus has been demonstrable. The earliest case of this group is that of Oppenheim who in 1899 reported a lymphosarcoma of the mediastinum about the size of a small apple occupying the site of the thymus. Weigert's case has already been mentioned. Hun, in 1904, also reported a lymphosarcoma of the thymus, consisting microscopically of islands of epithelioid cells without any tendency to the formation of Hassal's corpuscles. Surrounding these islands were small, round cells resembling lymphocytes. In Case VII of Goldflam's series, a diagnosis of mediastinal tumor, the ultimate cause of death, was made, but no autopsy was obtained. Thymic hypertrophy or persistent thymus has been recorded by Link, Hoedlmoser, Burr and Buzzard (Cases II, IV). Finally, Buzzard's Case V presented a thymus weighing 59.4 gms. and containing in its lower portion a multilocular cyst. Hoffmann

questions the origin of many of the reported cases of primary neoplasms of the thymus, particularly the lymphosarcomata. He believes that the great majority of tumors found in this organ have their origin either in the lymph nodes or other structures in the anterior mediastinum and involve the thymus secondarily, and cites a case where a large lymphosarcoma was found in the anterior mediastinum of a child of 7½ years of age, the thymus remaining intact. Weigert himself drew attention to the absence of infiltration of the tissues surrounding the tumor in his case. This has been noted in both Oppenheim's and Hun's cases as well as in our own. Despite the absence of metastases and of infiltration of the surrounding tissues in our case, we feel justified, in view of the microscopic findings, in concluding that we are here dealing with an actual neoplasm arising primarily from the thymus. Regarding the question of metastases, it is a well established fact that tumors of endothelial origin often remain localized for many years.

Bunge in his text-book on physiology states that the thymus is an organ functioning only during fetal life in warm-blooded animals, a statement supported by the researches of R. Fischl, who extirpated this gland in young dogs and chickens without observing any resulting effect upon growth or development. Even Basch, who preceded Fischl in these experiments, while coming to diametrically opposite conclusions, has not recorded any condition even remotely simulating that of myasthenia gravis. It is not feasible to enter into a discussion of all the physiological experiments conducted with the view of solving the vexed problem of the etiology of this disease. In general it may be said that neither feeding with thymus extract nor its subcutaneous administration has led to any satisfactory conclusion. As Weigert, and subsequently Buzzard, have suggested, it is possible that a certain group of cases presenting the symptom-complex known as myasthenia gravis may ultimately be attributed to an abnormally functionating thymus. That other so-called ductless glands may also play a rôle in the causation of this disease is suggested by a typical case reported by Tilney in which a large adenoma of the glandular portion of the pituitary body was present. The occurrence of Basedow's disease as a complication of myasthenia gravis has been occasionally re-

ported, but there are no grounds to assume a causal connection between these two conditions.

In 1898 Goldflam found in pieces of muscle excised from the deltoid in a case of myasthenia gravis, cellular infiltrations similar to those described by Weigert, but containing no epithelioid cells. At the autopsy performed two years later a lymphosarcoma of the right lung (no microscopic examination) was found. The author concluded that the muscular infiltrations were metastases from the lung tumor. Hun also regards the cellular masses found in the muscles of the chest and upper arm in his case as metastases from the thymic tumor. This view of the metastatic nature of the cells in the muscles is difficult to uphold. Weigert, who first propounded this theory, has himself suggested the possibility that these cells represent a reaction to metabolic processes dependent on a perversion of the thymic function. In Hun's case the passive part played by the lymphoid cells of the thymic tumor as contrasted with the active proliferation of the larger epithelioid cells makes it difficult to understand why the latter should be almost wholly lacking in the muscle metastases. Finally, it may be pointed out that the same condition has obtained in the muscles even in the absence of thymic tumor, as well as in our own case, in which the tumor is an endothelioma incapable of producing lymphoid metastases.

Both lymphoid and endothelioid cells of the types found normally in the thymus have been described by Weigert, Hun, Burr and Steinert. The last author derives the endothelioid cells from the neighboring capillaries. In the remaining cases collections of lymphoid cells alone have been present. Their close connection with capillaries was first pointed out by Link, an observation subsequently confirmed by Hun, Buzzard, Marburg, Frugoni and the authors. A few polynuclear leucocytes were noted by Goldflam and Hun, the latter also describing a few eosinophile cells. A recent hemorrhage was found by Link in one preparation, while Hun records the presence of many red blood cells in the lymphorrhages. The nature of the cellular changes described by Marburg and Frugoni require separate consideration. In addition to lymphocytes among which a few polynuclear leucocytes are scattered, Marburg describes cells resembling the former, but differing in the shape of

their nuclei which are oval and frequently show mitotic division. These he regards as proliferating, young sarcolemma cells. Frugoni believes that many of the cells present in the muscular foci correspond to the "Tochterplasmazellen" of Unna, a few, however, being true plasma cells. In addition, both authors found degenerative changes in the muscle fibers in the neighborhood of the cellular foci. They conclude, therefore, that the latter represent a reaction to a degenerative myositis.

Lymphocytic infiltration in the internal organs were first recorded by Buzzard, who found them in the adrenal in all the cases in his series, in the liver in four cases, and in the kidney, thyroid and peripancreatic fat tissue in one case each. In the liver and adrenal the neighboring cells of the organs had undergone simple degeneration, as the author states, from the pressure exerted by the infiltration. Marburg regards these foci as analogous to the muscular infiltrations; that is, as a reaction to a destructive inflammation affecting the parenchyma cells. The presence of the lymphorrhages in the liver and adrenal we have been able to confirm in our case, but have seen no degenerative changes in the parenchyma cells such as Buzzard describes. Moreover, although extensive muscular changes are present in our case as evidenced by granular degeneration, areas of proliferating sarcolemma cells, and the formation of new connective tissue, these lesions bear no relation to the location of the lymphorrhages. We must therefore conclude with Buzzard that we are here dealing with true lymphocytic infiltrations that are not the result of an inflammatory reaction. In discussing the origin of these cells, Buzzard is inclined to believe that they are derived from the blood current in the capillaries, basing his conclusion upon his findings in the heart in Case III of his series in which the capillaries of this organ were engorged with lymphocytes. In the lymphorrhages in our case these cells very evidently lie in the perivascular lymph spaces, both in the central nervous system and in the muscles. We are inclined to the view that here as well as in the other situations in which they are found, the lymphocytes are derived from the dilated perivascular lymph spaces.

Slight and localized degenerative changes in the muscles have been described by a number of other writers on myasthenia gravis.

Both Link and Goldflam record a few atrophic fibers at the site of the lymphorrhages. Sossedorf and Liefman found an increase in the adipose and connective tissue of the tongue as well as atrophic fibers and evidences of inflammation. Dejerine and Thomas found granular degeneration of the muscle fibers of the tongue and larynx but lay no stress upon its presence. Raymond and Alquier report homogeneous degeneration of the sarcoplasm with fragmentation. Fatty degeneration has been recorded by Senator (a doubtful case), by Marburg as well as by Frugoni in preparations fixed in osmic acid, and by Steinert in fresh preparations. By the last three authors the fat droplets are described as occurring in longitudinal rows simulating the normal striations. As mentioned above we have been unable to confirm this lesion in our case, although numerous sections were studied with this point in view. Tilney found swelling of the muscular fibers, indistinct striations and proliferation of sarcolemma cells. In Buzzard's series of five cases, the fibers of the skeletal and ocular muscles were for the most part normal. Here and there, however, were fibers with rounded contour and diminished affinity for acid stains. Only in Case V, a rapidly fatal case, was the degeneration in the fibers adjacent to the lymphorrhages, more advanced. Here hyaline and granular degeneration were quite marked, a few fibers showing vacuolization and proliferation of the sarcolemma cells. A few lymphocytes infiltrated individual muscle fibers. Similar changes, also in a relatively small number of fibers, were present in the case reported by Frugoni. Muscular atrophy has been reported in only a few cases clinically, most often in the tongue. Histologically, we have been able to find no instance of extensive atrophy recorded although Buzzard considers that the changes found in the muscles in his series of cases may represent a beginning atrophy of the fibers. In our case the muscular lesions are mostly degenerative in nature, but atrophic fibers are present in most of the sections made from the deltoid and longus colli muscles. The situation of these atrophic changes would correspond to the atrophy of the deltoid noted in the clinical examination.

Although numerous minor changes in the nervous system, as well as a few anomalies, have been described by different investi-

gators, no constant pathological lesion to which the recognized symptom-complex can be attributed has as yet been demonstrated. The lesions of the central nervous system recorded in our collected series may be thus summarized:

I. Anomalies of brain and spinal cord.
   - (*a*) Reduplication of central canal in dorsal and lumbar segments of cord. In the latter situation three canals all lined by epithelium pursue a short course (Senator I).
   - (*b*) Analogous condition in the lower and middle thirds of the aqueduct of Sylvius (Oppenheim II).
   - (*c*) Median dorsal fissure in cord from third to fifth lumbar segments. Pons, medulla and cerebellum smaller than normal (Burr and McCarthy).
   - (*d*) Cellular proliferation near central canal (Link).
   - (*e*) Obliteration of central canal by primitive ependymal cells (Frugoni).

II. Anomalies of cranial nerves.
   - (*a*) Abnormal thinness of trunks (Eisenlohr, hypoglossus, vagus and accessorius roots) (Liefman, both abducens).
   - (*b*) Primitive fibers without degeneration (Oppenheim, II, in both hypoglossi) (Eisenlohr, in hypoglossus, accessorius, vagus, facial).
   - (*c*) Slight discoloration of facial nerves and of the anterior roots of some of the spinal nerves (Jolly).

III. Degeneration of fibers of one or more cranial nerves. Sossedorf, Widal-Marinesco, Dejerine and Thomas, Burr and McCarthy, Mayer, Batten and Fletcher, Fajersztayn.

IV. Changes in cells of nuceli in medulla and pons (chromatolysis of Marinesco).

V. Leptomeningitis (Long and Wiki, Osann).

VI. Cyst in anterior lobe of left hemisphere following old hemorrhage (Berkeley).

VII. Homogeneous masses (probably coagulated lymph, Marburg) in the cord, medulla, pons and roots of facial nerves. Where Marchi's fixing fluid has been employed these masses stain black.

VIII. Recent hemorrhages, subpial or in or about nuclei of brain stem (many authors).

Scattered hemorrhages have been the most frequently observed lesion in the nervous system, but these have always been designated as recent and attributed to the suffocative symptoms immediately preceding death. The utter lack of uniformity in the lesions thus tabulated is in itself sufficient to demonstrate that the clinical picture of myasthenia gravis cannot be dependent upon them. As Marburg correctly states, all of the changes recorded in the nervous system have been found either in pathological conditions bearing no relation to myasthenia gravis, or even in apparently normal cases.

Infiltrations in the nervous system have heretofore been recorded only by Buzzard who found small collections of lymphocytic cells in a number of the posterior root ganglia. While we have been able to demonstrate the presence of several lymphorrhages in the medulla, their situation and scarcity seem to indicate that they have no bearing on the bulbar phenomena manifested clinically. Their pathological significance will be discussed subsequently.

In none of the recorded cases have any changes been found in the peripheral nerves. Unfortunately these were not preserved for examination in our case.

## PATHOGENESIS.

The pathological and physiological data at our command are too inconclusive to warrant the formulation of a pathogenetic theory of myasthenia gravis. Many such theories, some of which have already been discussed, have been advanced. Among earlier writers, Oppenheim classifies the disease as a neurosis, possibly based upon a congenital anlage. In support of this view he cites that group of cases in which somatic anomalies or anomalies of the nervous system have been present. Etiological significance has also been ascribed to the toxemia arising either from tumors of thymic or other origin, from coprostasis, from pregnancy or from various antecedent infectious disease. Among more recent writers particular stress has been laid upon disturbances of metabolism. As the result of his investigations along these lines Kaufman con-

cludes that the cause of myasthenia is to be found in insufficiency of the metabolic functions of the liver. Only three cases of our series, however, contain a definite statement as to a diseased condition of this organ (cirrhosis, Raymond and Alquier, Boldt; Banti's disease, Mohr). Sitsen records a case in which the preponderance of polynuclear leucocytes in the capillaries of the muscles and internal organs points to leukemia. General lymphatic hyperplasia was present in this case as well as in that reported by Hoedlmoser. Sitsen includes in this group all those cases in which thymic hypertrophy has been recorded, and suggests that the causative toxic agent of myasthenia may arise in the lymphatic system.

It would consume too much space to discuss in detail all the theories that have been propounded. In general, it may be said that a review of the literature demonstrates the notable inconstancy in the pathaological, anatomical or anamnestic findings upon which they have been founded. Our case does not enable us to throw any additional light upon the question of pathogenesis, but our findings seem to warrant the following conclusions:

1. Neoplasms of thymic origin have been noted too frequently in myasthenia gravis to be ignored as a possible etiological factor in a certain proportion of the cases. In our case an unusual type of tumor, hitherto undescribed in this disease, is present.

2. While definite proof is still lacking, it seems most probable that the disease is the manifestation of a toxemia of indeterminate origin.

3. The action of the toxic agent is not confined to the muscular system, but the organism is generally effected as evidenced by the widespread presence of lymphocytic infiltrations throughout the body.

4. Although no degenerative changes are demonstrable in either brain or cord, the occurrence of lymphocytic infiltrations in the medulla, observed for the first time in our case, indicates the involvement of the central nervous system in the general toxemia.

5. The changes in the muscle fibers are purely degenerative, the result of the toxemia, and not dependent upon a primary myositis. These degenerative lesions bear no relation to the site of the lymphocytic infiltrations.

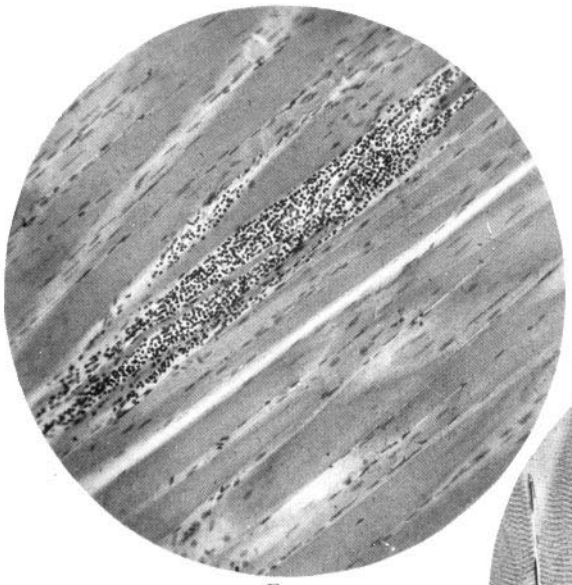
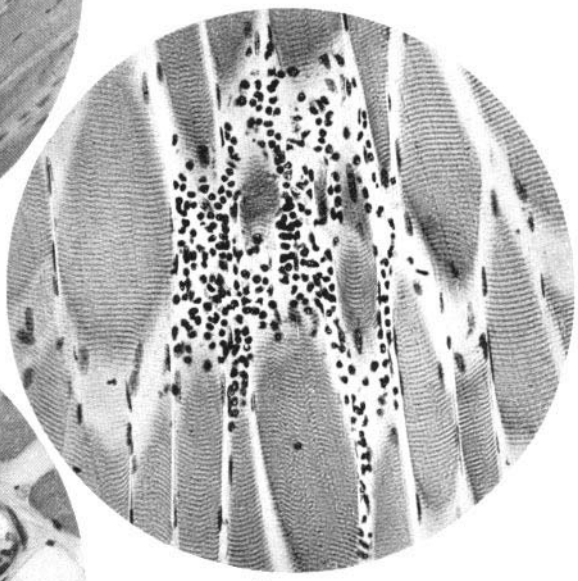


FIG. 1.



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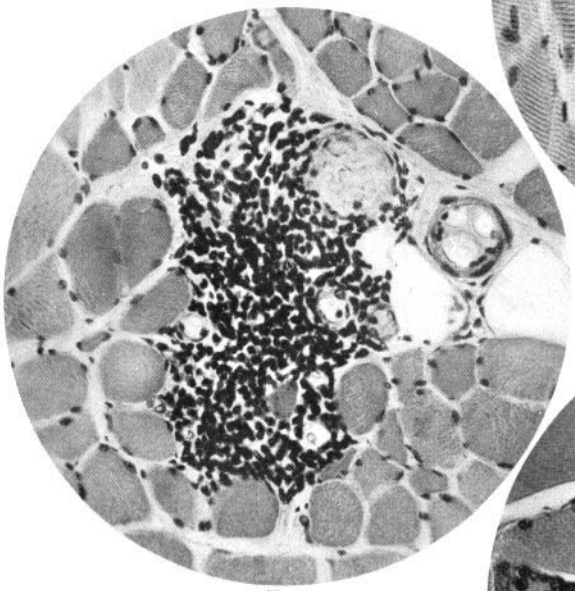

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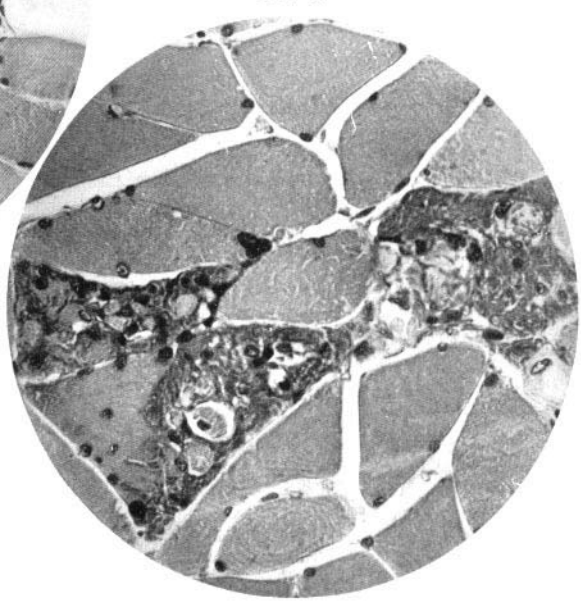

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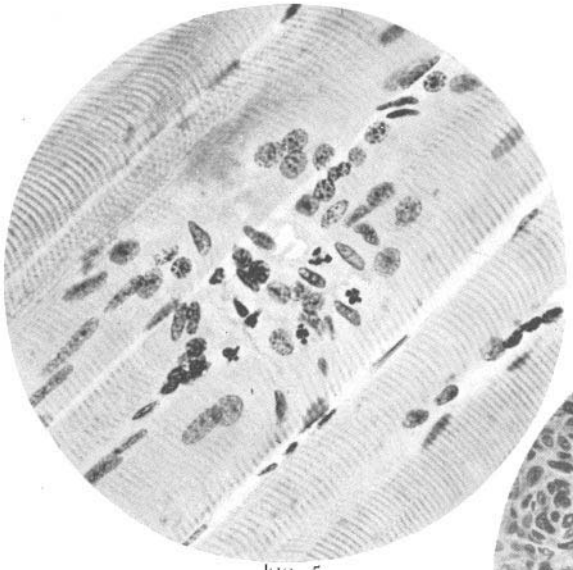

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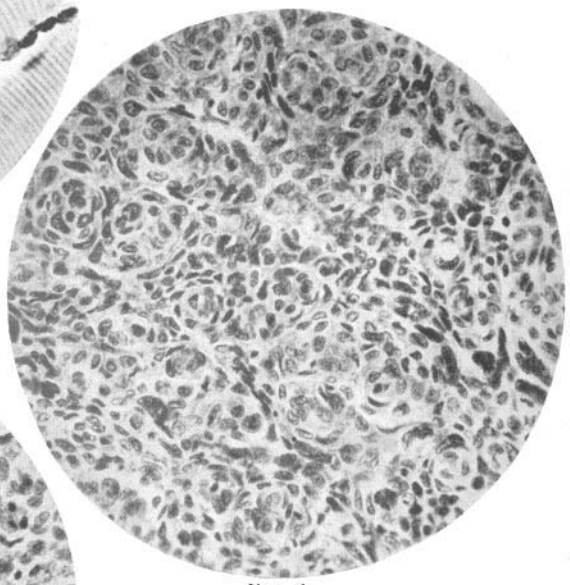

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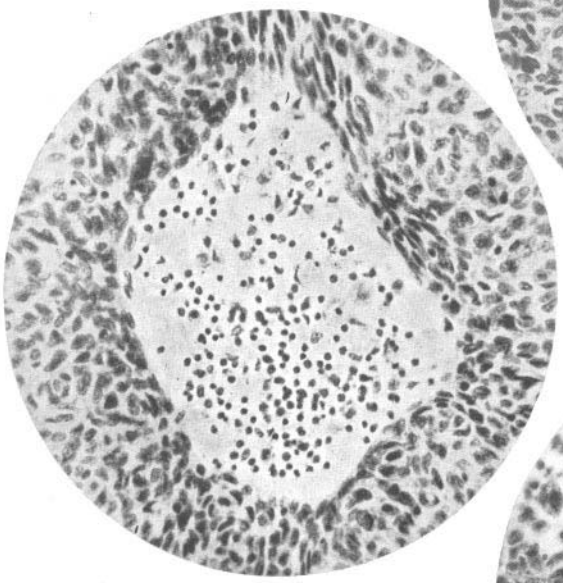

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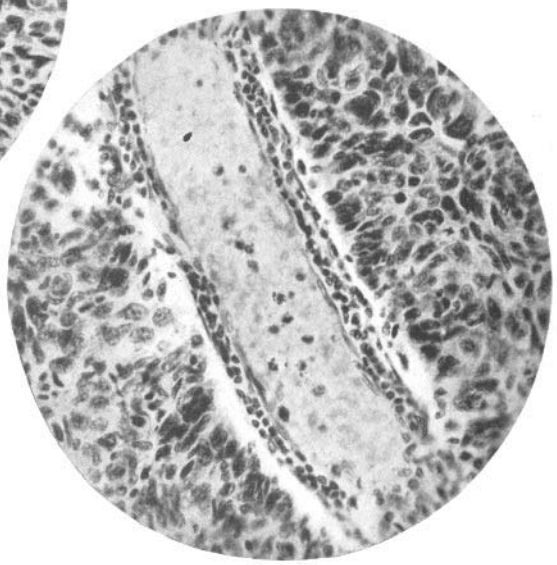

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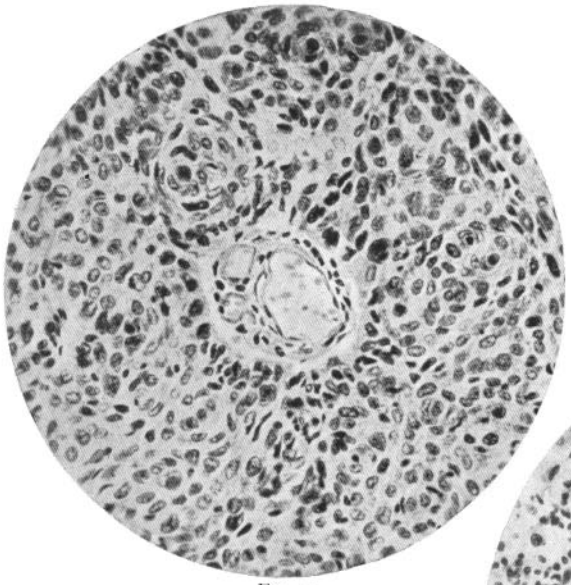

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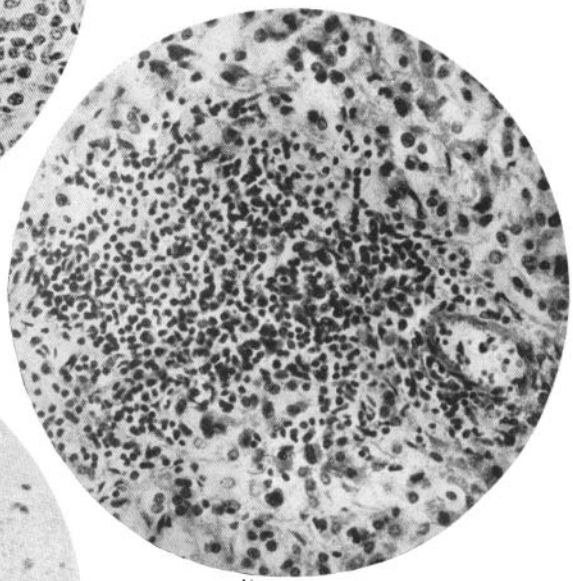

FIG. 10.

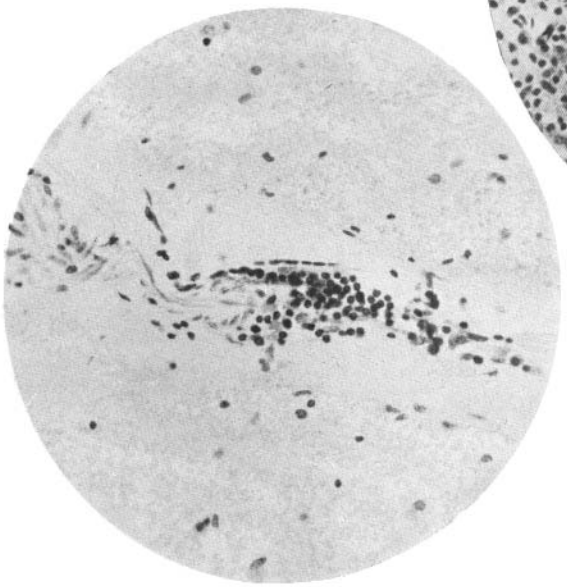

FIG. 11.

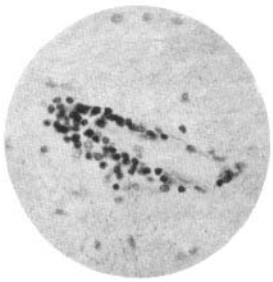

FIG. 12.

6. A study of our specimens seems to show that the lymphoid cells, wherever present in the tissues, are derived from perivascular lymph spaces.

In conclusion we desire to express our thanks to Dr. I. Strauss for his valuable assistance in the study of the nervous system.

EXPLANATION OF PLATES XXI–XXIII

FIG. 1. A long band of lymphocytic infiltration in the rectus muscle. × 125.

FIG. 2. Section of the psoas muscle showing the usual type of lymphocytic infiltration. × 250.

FIG. 3. A cross section of the deltoid muscle with several small capillaries surrounded by a dense infiltration. × 250.

FIG. 4. A cross section of the longus colli muscle showing granular degeneration, vacuolated cells and proliferation of muscle nuclei. × 500.

FIG. 5. From a section of the psoas muscle, showing proliferation of the sarcolemma cells, and five cells with pyknotic nuclear changes. × 500.

FIG. 6. From a section of the thymus tumor, showing the general type of growth and numerous concentric bodies. × 250.

FIG. 7. A section of the thymus tumor showing a dilated lymph sinus filled with large, faintly-staining cells and small lymphocytic cells. The tumor cells are seen springing from the endothelium of the sinus. × 250.

FIG. 8. Longitudinal section of a capillary in the thymus tumor. The capillary wall is outlined by a dense collection of lymphocytes situated in the perivascular lymph space and bounded on either side by endothelium. The tumor cells have slightly shrunken away from the outer layer of endothelium. × 250.

FIG. 9. Transverse section of capillaries in the thymus tumor. Just outside of the vascular endothelium is a mantle of lymphocytic cells in the perivascular lymph space. The tumor cells have retracted and show a radial arrangement. × 250.

FIG. 10. A section of the adrenal showing a large area of lymphocytic infiltration near a small artery. × 250.

FIG. 11. Longitudinal section of a capillary in the gray matter near the tenth nucleus, showing lymphocytic infiltration in the perivascular lymph space. × 250.

FIG. 12. Transverse sections of two capillaries in the outer part of the pyramidal tract ventral to the olivary body, showing the same lesion as Fig. 11.

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*Note.*—Since the completion of the above paper, Chvostek (*Wiener klinische Wochenschr.,* 1908, xxi, 37) has advanced the theory that myasthenia gravis is dependent upon hypersecretion of the parathyroid glands. He bases his hypothesis upon the purely theoretical grounds that both tetany and myasthenia affect the neuromuscular system but are diametrically opposed in their clinical manifestations, and, since tetany arises from hyposecretion of the parathyroid glands, myasthenia must arise from a hypersecretion of these bodies. This theory cannot be accepted without further investigation along these lines.