

THE CLINICAL HISTORY AND *POST-MORTEM* EXAMINATION OF FIVE CASES OF MYAS- THENIA GRAVIS.

BY E. FARQUHAR BUZZARD, M.D., M.R.C.P.,
*Assistant Physician to the National Hospital for the Paralysed and Epileptic,
to the Royal Free Hospital, and to the Belgrave Hospital for Children.*

With Five Figures.

IN a paper which was read before the Pathological Society of London I have already given a short summary of the histological findings in the five cases of myasthenia gravis which form the subject of this communication, but it appears to me desirable that a full account of these cases should be placed on record, inasmuch as they present features which are not only of pathological but of clinical interest.

The object of the present paper may therefore be regarded as two-fold. In the first place it will draw attention to some striking clinical phenomena occasionally occurring in this disease, and in the second place it will serve to propagate the view, which my experience has caused me to hold, that there are constant morbid changes associated with myasthenia gravis.

My best thanks are due to Dr. T. Buzzard, Dr. Ormerod, Dr. Head, and Dr. Wall, for their kind permission to make use of the clinical notes on the cases under their care.

Case 1.—A. J., aged 41, was admitted into the National Hospital under the care of Dr. T. Buzzard on November 3, 1903. His family history was too vague to be of importance.

His previous health had been good; but at 16 he contracted gonorrhœa, followed by no evidence of a sore or of secondary syphilitic symptoms. In 1892 he injured left eye and suffered from monocular diplopia for eight years. Moderate drinker of beer; no spirits. Occupation for twenty-one years had been that of a stone-grainer. Married nineteen years; fourteen children, of whom six died in infancy and one was stillborn.

PLATE I.

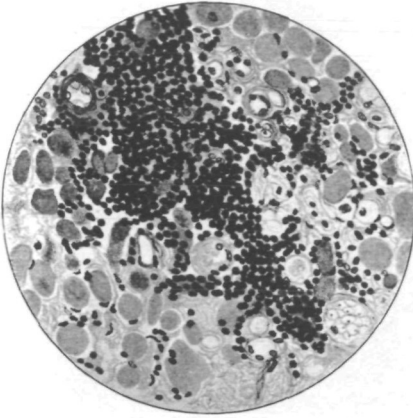


FIG. 1.

Section of inferior rectus muscle of Case 1, typical of lymphorrhages in ocular muscles.

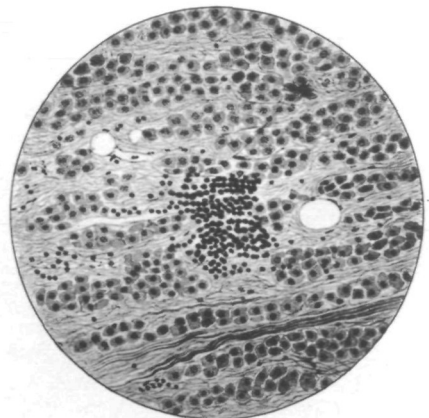


FIG. 2.

Section of adrenal gland in Case 4. A small lymphorrhage in the cortex of the gland.

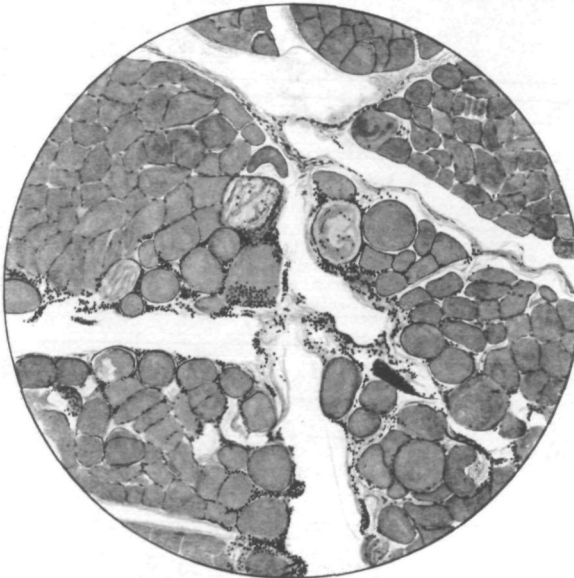


FIG. 3.

Section from triceps muscle of Case 5, showing marked changes in muscle fibres, some of which have been invaded by the cellular exudation.

Present illness.—For three or four years the patient had been obliged to lift his upper eyelids with his fingers when reading for any length of time. In other respects he had been well until March, 1902, when he noticed a feeling of heaviness in the right leg, which became easily tired. A month later he experienced an aching pain, first of all in the right foot, then in the left shoulder, and later all over the body, which would come on after he had been up for a couple of hours and remain until he turned in for the night. More recently he had been unable to walk more than fifty yards, after his work, without resting. For two or three months he had noticed a difficulty in swallowing, the bolus of food lying at the back of the throat and tending to get into the nasal passages. During the same period saliva would collect in his mouth and shortness of breath and difficulty in articulation would come on rapidly after a short conversation. At times his voice failed altogether, and his speech became unintelligible. He had lost two stone in weight during the previous year.

Condition on admission.—The patient was spare, but muscular, somewhat pale and tired-looking, and his movements sluggish and feeble. His forehead was almost constantly wrinkled in the effort to overcome the ptosis of both upper eyelids. As a witness he was bright and intelligent, answering questions readily and clearly. His appetite was good and he slept well.

With the exception that his heart sounds were somewhat feeble, all the internal viscera appeared to be healthy. There was no evidence of glandular enlargement in the mediastinum or elsewhere.

The examination of the blood showed 3,496,000 red corpuscles and 8,000 white corpuscles per cubic millimetre; Hæmoglobin 60 per cent. There were no abnormal forms of red or white cells, and the different varieties of the latter were present in the usual relative proportions.

Smell, taste, and hearing were perfect.

Sight $\frac{6}{60}$ with both eyes. Visual fields were normal. The fundus of each eye was healthy in appearance.

All ocular movements were very limited in range, the horizontal being restricted to about one-sixth and the vertical to about one-quarter inch.

The axes of the eyes were parallel and diplopia was not complained of. Pupillary reaction to light and accommodation was healthy. Marked ptosis was present on both sides. No nystagmus was observed.

Fifth nerve.—All movements of the jaw were performed with

fair power. Opening and shutting the mouth was repeated 594 times before the patient was tired. On the other hand 45 momentary applications of a mild faradic current wore out the contractility of the left masseter. There was no alteration of sensibility in the skin of the face.

Seventh nerve.—All facial muscles were more feeble than normal, but the orbiculares palpebrarum and oris markedly so. The orbicularis palpebræ did not contract to a faradic current. The left zygomatics were exhausted by 50 applications.

The ninth and tenth nerves.—Deglutition was always difficult, even with the softest food, fragments of which were very apt to pass into the nose.

Liquids were swallowed more easily. Phonation tired rapidly, and might be absent altogether in the evening.

The palate was flaccid and moved very little, either on phonation or on reflex stimulation.

Twelfth nerve.—The tongue movements were fairly good, and it was not noticeably wasted. It was protruded ninety-one times before being tired.

The neck.—Patient could not raise his head from the pillow. When sitting up the head would fall forwards unless supported.

Upper extremities.—Movements performed by the muscles of the shoulder girdle were all feeble. The biceps was still more feeble, while extension of the forearm by the triceps could scarcely be carried out. Wrist movements were rather better, but both grasps were poor. All movements of the fingers could be made, but were easily resisted. There was no wasting of any muscle.

Trunk.—Patient could not sit up even with the help of his hands, but the abdominal muscles could be felt to contract in the effort. When in the sitting position the back assumed a round kyphosis, which could not be voluntarily straightened.

Respiration was partly thoracic and partly diaphragmatic, but shallow in type.

Lower extremities.—All muscles were well developed and their power much better than that of the muscles of the upper extremities. Extension of the right ankle was the weakest movement. The gait was good and no dragging of feet was noticed.

The co-ordination of all limbs was normal, and the sense of position accurate. No tremors were observed. Romberg's sign was not present.

Sensory system.—Aching pains in various parts were complained of, especially after movement. Attacks of sharp pain

occasionally affected the inner side of his arms and his back. There was relatively diminished sensibility to light touches and to pricks over the ulnar aspects of the arms.

Reflexes.—The Jaw-jerk was present. Triceps and supinator-jerks were not elicited. Knee- and ankle-jerks were brisk. Epigastric, hypogastric and cremasteric reflexes were present. Plantar reflexes were of flexor type. The knee-jerk was not exhausted by 300 consecutive stimulations.

Electrical reactions.—To galvanism all muscles reacted normally. To faradism the following muscles reacted well at first, but were exhausted by varying numbers of applications.

Left sternomastoid	...	46	...	Right	50.
„ trapezius	...	14	...	„	14.
„ supraspinatus	...	16	...	„	31.
„ deltoid	...	52	...	„	56.
„ extensor digitorum	114	...	„		96.

January 29, 1904.—The patient has been suffering greatly with shooting pains, chiefly in the lower extremities, and from one or two attacks of respiratory failure, in which he was markedly cyanosed. The right knee-jerk is now much diminished and exhausted by six taps. The left is exhausted by twelve taps.

January 31.—Much weaker lately. Yesterday the temperature rose to 102° without obvious cause. Occasional profuse sweats are noticed.

The special senses are unaffected.

The patient has still marked ptosis which varies considerably, and is generally more marked in the evening than in the morning. There are practically no vertical or outward movements of the eyeballs, and inward movements are very limited. A week ago the only movement possible was a slight degree of conjugate movement to the left. Pupils react well. Chewing food causes rapid exhaustion of the jaw muscles. All facial movements are very feeble. He cannot fully close the eyes or whistle. The face is very expressionless. In smiling the mouth is merely elongated and its angles slightly raised. The muscles do not appear to be wasted. Fluid tends to run away from the corners of the mouth, and solid food collects between the teeth and cheeks. Regurgitation of fluids through the nostrils takes place occasionally. Swallowing of solids on some days is very difficult, and attended by choking and coughing. Articulation and phonation are easily exhausted.

The tongue is large and flabby, and all movements are readily tired on repetition.

There is no wasting of the muscles of the extremities, but they are flabby and toneless.

Movements of the neck are fairly good, but he is unable to hold his head erect for any length of time when sitting up. Patient cannot extend the upper limbs in front of him for more than a minute, and the left fails before the right. The grasps are feeble, but the relative strength of the movements varies considerably from day to day.

Respiration is chiefly diaphragmatic, and during the attacks of dyspnoea from which the patient occasionally suffers, the thoracic movements are very feeble and shallow. The act of coughing is poorly performed. No special weakness of abdominal or spinal muscles is observed.

Patient cannot raise either extended leg from the bed, nor can he extend the knees against gravity. Other movements of the lower limbs are relatively stronger. There is no inco-ordination, tremor or fibrillation observed in any limb.

All voluntary muscles are easily exhausted by rapid repetition of action, and there is analogous exhaustion of many of the weaker muscles by rapidly repeated faradic shocks. For instance, the biceps on each side is completely exhausted by sixty shocks, and the triceps by thirty stimulations. On the other hand, the pectoralis major was not completely put out of action by one hundred faradic shocks. Even when the muscles are completely inactive to faradism they respond briskly to galvanism. An effort to exhaust the muscles by direct mechanical stimuli was not successful.

Subjective sensations are divided by the patient into three classes: (1) Dull aching pains, chiefly in shoulders and back of neck; (2) a general tired feeling and a sensation of tightness and stiffness about the knees; (3) shooting pains of a sharp stinging character which dart from place to place in the lower limbs.

On testing there is considerable relative anaesthesia and analgesia along the ulnar borders of the arms extending over the ulnar half of each little finger. On the trunk the sensory loss involves a definite area between the second costal cartilage and a line about 1 in. below the nipples. There is also a slight degree of analgesia on the peripheral parts of both lower extremities. Muscle pain sense is also reduced in the legs, but there is no loss of sense of position in any limb.

Reflexes are in the condition mentioned in the previous notes.

The sphincters are unaffected.

April 11.—His condition remained unaltered until about ten day sago, when it became considerably worse. On some days the patient has scarcely been able to swallow at all, even his breakfast, and respiration has been difficult and associated with cough. Only a little pale mucus is expectorated after great effort, owing to the feeble nature of the cough. No abnormal physical signs are detected in the lungs. The urine is normal. The ptosis and ophthalmoplegia are much as before, but the pupils are smaller and react rather sluggishly to light. Mastication and jaw movements are very poor; towards evening the lower jaw drops, and has to be supported by the hands during conversation. There is some anaesthesia and analgesia over the central part of the face, including the nose.

Articulation and phonation are feeble.

The arms are much more weak; the patient can extend neither in front of him. Full closure of the fist is impossible. Abdominal muscles are definitely affected. The lower limbs are much as before, but more easily exhausted.

Subjective sensations remain as before, except that the shooting pains are more severe.

Analgesia is more intense and extensive than at the time of the last note. The ulnar half of each arm and both little and ring fingers are affected. On the trunk there is almost complete analgesia between the second costal cartilage and a level about an inch above the umbilicus. Analgesia is also more extensive on the lower limbs.

There is complete loss of sensibility to cotton wool on the whole of the upper extremities excepting a narrow strip along the radial border and thumb. The same condition obtains from the second costal cartilage to the umbilicus, and to a less extent below that level.

On the legs there is almost complete loss to the same test, but this fades off above the knees. The reflexes are as before, except that the abdominal and epigastric are not now obtained.

The fingers are now pointed and the skin over them thin, shiny and glossy.

The patient grew worse and had several attacks of respiratory failure, in one of which he died on April 26, 1904.

The autopsy was performed ten hours after death, when *rigor mortis* was well marked. The body was poorly nourished, but not emaciated. Nothing abnormal to the naked eye was observed in the course of removing the brain,

spinal cord, and various nerves and muscles. The left eyeball was removed with the optic nerve and ocular muscles attached.

The thoracic organs were healthy in appearance, and only slight traces of the thymus gland could be detected in the fatty tissue of the superior mediastinum. The thyroid gland was well developed. The spleen was natural except for the presence of two small calcareous lumps in its substance. The pancreas, liver and kidneys were normal. The adrenal bodies were not obviously diseased. There were no enlarged peritoneal glands. Both scrotal sacs contained hydroceles with clear fluid—the testicles were free from disease.

MICROSCOPICAL.

Ocular muscles.—The muscles attached to the left eyeball were hardened in formalin and cut, some in paraffin, but the majority in celloidin, which gave much the better results. Longitudinal and transverse sections were made of each muscle. Most of the sections were stained by hæmatoxylin and eosin, but a few were stained by the Weigert-Pal method. It is unnecessary to detail the changes found in each muscle, as they were more or less the same, and the inferior rectus may be taken as a type of the others. Transverse sections across the body of this muscle, stained by the logwood-eosin method, presented unusual appearances, even with a low power, owing to the presence of three or four darkly-stained clumps of cells. These clumps were of various sizes, the largest measuring about .2 mm. by .15 mm. Under higher powers it was seen that these unusual appearances were due to the presence of a large number of cells, indistinguishable from the ordinary lymphocytes of the blood, lying scattered between the muscle fibres, nerve bundles and blood-vessels. Since these cell-clumps are characteristic and present in many parts of the body in this disease, I have proposed, for the sake of brevity, to denote them by the term “lymphorrhage.” This name is chosen for two reasons. In the first place the cells are, as has been said above, indistinguishable from lymphocytes

by their size, and by the fact that the nucleus is generally round or slightly oval and surrounded by an extremely narrow belt of protoplasm. In the second place they have infiltrated the tissues in the same way as red blood corpuscles do in the case of a capillary hæmorrhage, and are not, as a rule, associated with obvious changes in the surrounding structures, inflammatory or otherwise (Plate I., fig. 1).

In longitudinal sections similar lymphorrhages were met with, and some of these measured as much as .3 mm. in length. Here, again, the cells were seen to lie in the spaces between the muscle fibres and not to invade them.

Every now and then a capillary vessel was observed running through the cells, generally empty but occasionally containing red corpuscles. Passing from the consideration of these lymphorrhages the condition of the muscle fibres next claims our attention. A careful comparison of the fibres in this case was made with those in similarly prepared sections from a normal ocular muscle, with rather indefinite results owing to the great difficulty in forming an opinion. It may be stated generally that the large majority of fibres were of normal size and appearance, but that possibly there was a greater variety in calibre than is seen in the healthy muscle. There is certainly not any marked increase of nuclei nor proliferation of connective tissue.

No abnormality could be detected in the nerve bundles or in the blood-vessels.

The sections stained by the Weigert-Pal method gave a beautiful picture of nerve fibres apparently well myelinated as far as their muscular connections.

Cardiac muscle.—The preparations of cardiac muscle stained by logwood and eosin were of perfectly normal character and free from any lymphorrhages.

Skeletal muscles.—Portions of the biceps femoris, vastus internus, tibialis anticus, and triceps muscles, were hardened in formalin and cut in paraffin and celloidin. A large number of sections were stained by the logwood-eosin method and examined.

Some longitudinal sections of the vastus internus showed fairly numerous lymphorrhages differing little from those seen in the ocular muscles. Some of them, however, were rather more extensive, from .5 to 1 mm. in length. The cells lay quite free between the fibres, and there was no evidence of reaction in the latter. The sections taken from the other muscles did not present lymphorrhages, but it is hardly necessary to say that this fact does not signify an absence of lymphorrhage from the muscles.

Here, again, it was obligatory to investigate carefully the muscle fibres. In longitudinal sections the transverse striation was generally well marked and the fibres appeared healthy. In transverse sections it was noticed that a certain proportion of the fibres differed from their neighbours in two respects. In a transverse section of a normal skeletal muscle the fibres present polygonal shapes and fit together in a mosaic-like pattern. In the sections under consideration a number of fibres were rendered conspicuous by their rounded and non-angular contour and sometimes by their greater size. The same fibres were often still further differentiated by the fact that their protoplasm was more homogeneous and of a paler and more yellow hue than that of their healthy neighbours. Such variations from the common type are occasionally met with in presumably normal muscles, but are not nearly so numerous as in the sections obtained from this case and, as we shall see later, from other cases of myasthenia gravis. In all other respects the muscles appeared to be healthy, and sections stained by Busch's method showed no evidence of fatty change.

Cranial nerves.—A portion of the left trigeminal nerve close to its origin from the pons was stained in Busch's fluid, teased and examined microscopically. Not a single degenerated fibre was found. A portion of the oculomotor nerve, close to its central origin, and one of its muscular branches were treated in the same way and with the same result.

The right trigeminal nerve was stained by Busch's method and cut in celloidin; the sections showed no degeneration.

The ventral half of the crural region of the brain-stem, including the outgoing third nerves, was also examined by the Busch method with negative results.

A muscular branch of the oculomotor nerve was stained by the Weigert-Pal method and the fibres presented a perfectly healthy appearance.

The left optic nerve was cut longitudinally and transversely, and sections of it stained by Weigert-Pal and by logwood and eosin. Nothing abnormal was detected.

Spinal nerves.—A short length of the left ulnar nerve, taken from the region of the elbow, was stained by Busch's method and teased. No evidence of degeneration was observed in any of the fibres.

Another portion of the same nerve was embedded in paraffin and stained with logwood and eosin, but nothing abnormal was seen in the sections.

A piece of the anterior crural nerve was stained by Busch's method and cut in celloidin. No degeneration was found. Transverse sections of the sciatic nerve were stained by logwood and eosin and appeared to be healthy in all respects.

Spinal nerve roots.—The first dorsal anterior and posterior roots of one side were teased in Busch's fluid, but no pathological changes were detected. The posterior root of the opposite side with the ganglion attached was cut and stained with logwood and eosin. The root fibres were healthy in appearance, but owing to faulty fixation I do not feel inclined to express any opinion on the condition of the ganglion cells. In this ganglion and in several others from the dorsal and lumbar regions there were present a few small collections of lymphocytes scattered between the cells. As far as I could judge they were similar to the lymphorhages in other tissues, although generally smaller.

Central nervous system.—The Busch, Weigert-Pal, Nissl and logwood-eosin methods were employed for the examination of the central nervous system after it had been hardened in 5 per cent. formalin. The parts examined included the left motor cortex, the oculomotor region of the brain-stem, the pons, medulla and various levels of the

cord. With the exception of a few recent capillary hæmorrhages in the gray matter of the cervical cord the results were entirely of a negative character. Not a suggestion of early tabetic changes could be detected by the Weigert-Pal or Busch methods and the ganglion cells generally were of healthy character, as portrayed by Nissl's stain.

Liver.—Sections of this organ showed small scattered patches of fatty degeneration. Here and there were seen a few collections of lymphocytic cells resembling the lymphorrhages seen in the muscles. These appeared to be associated in most cases with a small intralobular capillary and sometimes a few of the neighbouring hepatic cells had undergone degenerative changes. In other respects the sections appeared healthy.

Adrenal bodies.—Sections from these glands revealed perfectly normal structures except for the presence of a few lymphorrhages. One or two larger ones were situated in the medullary part of the gland and a few smaller ones in between the cell groups of the cortex. It was noticed that the neighbouring capillaries were often engorged.

Pancreas.—Microscopical examination of this organ revealed no abnormal features.

Kidneys.—As far as the glomeruli and tubules were concerned these organs seemed to be healthy. Now and then there appeared to be an unusual number of small round cells lying between the convoluted tubules. The aspect produced was different from that of the lymphorrhage in other organs because the cells were not lying together in rounded clumps but spread out between the tubules. It is difficult to express an opinion as to the abnormality of this appearance, and I prefer to leave the question open.

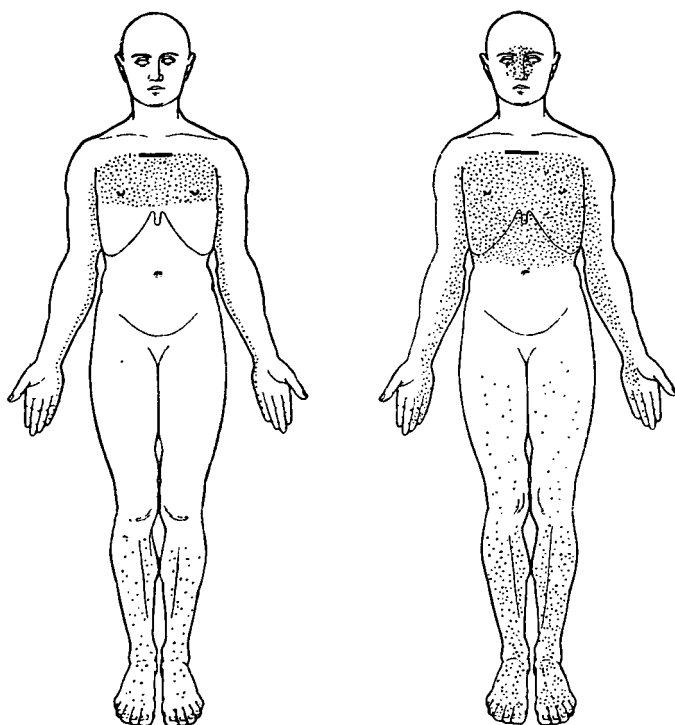
Testicle.—Sections of this organ presented no unnatural feature.

The thyroid gland, pituitary body and spleen were all healthy as regards their histological appearance.

Thymus.—Report by Dr. Dudgeon. The fibrous tissue in which the scanty islets of thymus tissue are to be seen consists of very dense tissue without any nuclear marking

in places. The cortex of the gland cannot be distinguished from the medulla. Many of the concentric corpuscles are very large and calcified in great part.

Case 2.—A Russian Polish woman, aged 28, was admitted to the National Hospital on October 8, 1902, under the care of Dr. Ormerod.



Analgesia, January 31, 1904.

Analgesia, April 11, 1904.

Family history.—Mother died of consumption. Father is alive and healthy. Five brothers and sisters are alive and healthy. There is no history of any similar condition in any relation.

Previous health.—Health was good with the exception of measles until the onset of present illness. Married eight years, but has never been pregnant. Husband is now 50 years of age and had children from his first wife. Patient's food has been of the ordinary character, and she has abstained from alcohol for some years.

Present illness.—Seven months ago patient began to feel pain in the shoulders, the arms and the legs and a sensation of pins and needles in the tips of her fingers. The pains were sharp and intermittent in character and were worse in wet weather. About the same time she complained of weakness in the arms, hands and legs. She continued for a month in this condition doing her housework, but always suffering and becoming weaker as the day went on.

Six months ago she experienced a sudden difficulty in talking during a conversation with a friend; she felt her mouth become stiff and her tongue immobile. About the same date she began to see double and to have a certain amount of dysphagia. The pains and weakness in the limbs continued and during the last few months her symptoms have become considerably worse. Lately she has found it difficult to prevent food coming back from her mouth through the lips, but has had no regurgitation through her nostrils.

Condition on admission.—Both upper eyelids droop and the lower lip is somewhat everted. Around the lips the skin is studded with beads of perspiration and the whole face is slightly flushed and pink in colour.

In smiling there is no elevation of the corners of the mouth, only a widening of the oral fissure and increased eversion of the lower lip. In voluntary movements of the face the action is slow and badly maintained. The patient is unable to whistle, but can blow out her cheeks. The attempt to close the eyes causes a movement of the feeblest character, especially on the right side. Elevation of the eyebrows is equally deficient.

The ocular movements are briskly and fully performed at first, but soon become partially exhausted. There is no nystagmus and at the present time no strabismus.

Opening and closing the jaws is well performed at first, but after twenty repetitions the observer can place his finger between the teeth and allow the patient to bite with impunity. The tongue movements are good at first attempts, but tire easily. The tongue itself is somewhat peculiar owing to its flabbiness, and to the presence of three linear grooves on its dorsal surface, one median and two about half way between the midline and the lateral edges.

The palate moves well on phonation and in response to stimulation, both sides being raised equally. Only on one occasion has the patient had any regurgitation of fluid through the nose.

Speech is normal. Articulation begins well, but soon tires. After frequent repetition the word "grub" becomes "grum," and by this time the patient is unable to blow out the cheeks without air escaping.

The pupils react to light and on accommodation, and this reaction was not exhausted by frequent stimulation or effort.

The muscles of the limbs exhibit diminished power generally, and this defect becomes much more marked on exertion, not only in the muscles exerted but in those of other parts. It was noticeable too that, after the limbs had been in a state of activity for a short time the ptosis of the eyelids would become more severe. The respiratory movements were of normal type and depth.

Sensation.—The patient complains of pain of two kinds: (1) general aching and stiffness, especially after exertion; (2) sharp intermittent pains as described above. On testing, cutaneous sensibility appeared to be perfect, except in a small area over the left shoulder, where there was relative anæsthesia and analgesia. It should be mentioned that the testing of sensation in this patient was unsatisfactory owing to her mental attitude.

Reflexes.—All deep reflexes were brisk and not exhausted by repeated stimulation. The corneal and abdominal reflexes were brisk, and plantar responses of the flexor type.

The sphincters performed their function in a normal manner.

Electrical.—The extensors of the left wrist were stimulated by repeated faradic shocks and completely exhausted in three minutes. At this moment very little voluntary power was left in the muscles, but a galvanic current produced a normal contraction with K.C.C. greater than A.C.C.

The left facial muscles were exhausted in ninety seconds, and on asking the patient to show her teeth no movement was obtained on that side of the face.

December 10, 1902.—General condition has improved, but strength varies much from day to day. The pains continue at times, and are not associated with any rise of temperature, but appear to coincide with increased weakness. There is now paresis of the right external rectus muscle and diplopia on looking to the right. The other movements are much as before.

Heart and lungs are healthy. There is no enlargement of thyroid, and the abdomen is normal on examination.

January 20, 1903.—Last night patient complained of great pain in her left leg. To-day she says that leg is weaker than the other, and this appears to be the case on examination.

There is no sensory loss.

There is dulness on percussion over the upper part of the sternum, and for about half an inch on either side of it. There is no tracheal tugging, and nothing to be felt in the episternal notch.

September 25.—Patient went to a convalescent home in June, and improved considerably during the first few weeks she was there. Five weeks ago she experienced a relapse, especially in swallowing and articulation. Since that time she has become gradually weaker and can now only swallow fluids and only talk for a very short time. She has suffered from sharp pains in the face, throat and neck. During the last ten days she has been unable to walk alone, and has had difficulty in breathing when lying down.

Physical examination reveals much the same as before, only the paresis is much more marked in the limbs and respiratory musculature. The knee-jerks can now be easily exhausted by repeated taps.

November 6.—The patient remained in practically the same condition, with variations, until to-day. This morning she seemed somewhat better than usual, but at 2 p.m. had a sudden attack of respiratory failure. When seen she was lying in bed with face, lips and extremities very cyanosed, and making feeble, shallow, gasping attempts at respiration. After artificial respiration had been performed, and a hypodermic injection of strychnine given, the patient recovered, but several attacks of the same character followed in rapid succession, and death took place at 3 p.m.

The autopsy was made four and a half hours after death, before *rigor mortis* had developed. The central nervous system, its meninges and enveloping bones, were all perfectly natural and healthy to the naked eye. The examination was limited owing to the wishes of the relatives, and only a few muscles and nerves were procured for microscopical examination.

The thoracic and abdominal organs were examined and removed through an abdominal incision. The heart and lungs were healthy. Lying in the superior mediastinum and loosely attached by its anterior surface to the posterior aspect of the manubrium sterni was a large thymus gland the vertical length of which measured $3\frac{1}{2}$ ins. and the breadth

about $2\frac{3}{4}$ ins. at its broadest level. Its shape was roughly that of a pear with a narrow stalk above and a bilobar gland below. The weight of the organ was 41 grammes, and its consistence was firm throughout. The glandular substance was surrounded by a small amount of fat which could be readily stripped off its surface.

The thyroid gland was felt in its usual situation and appeared to be natural in size, shape and consistence. It was not removed.

All the abdominal and pelvic organs were healthy except for a small cyst attached to the right ovary.

The various organs and tissues removed were hardened in 5 per cent. formalin.

After hardening the thymus was again examined and a section made through the middle of its broadest part. There was no evidence of necrosis or of malignant disease and the appearances suggested a simple hypertrophy of the gland.

MICROSCOPICAL.

Central nervous system.—The Busch, Weigert-Pal, Nissl and logwood-eosin methods were utilised for the purpose of examining sections from the motor cortex, brain-stem, medulla and spinal cord, but the results in all cases were negative so far as the discovery of any pathological changes was concerned.

Peripheral nerves.—Sections from the ulnar and sciatic nerves were stained by the Busch and Weigert-Pal methods with similar results.

Skeletal muscles.—Portions of the trapezius, deltoid, triceps and erector spinæ muscles were examined microscopically after embedding in paraffin or celloidin. Only a very few lymphorrhages were found and these were of small size. Numerous fibres, sometimes singly and sometimes in groups, were seen in transverse sections to be rounded in outline, often slightly swollen, and to react quite differently to protoplasmic staining reagents. With eosin or fuchsin the sarcoplasm assumed a pale and sometimes a rather bright yellow hue, the contrast to the pink colour

of the normal fibres being a striking one. Sections stained by Busch's fluid also revealed the presence of these fibres which then assumed a darker brown colour than their neighbours.

Whether the stain used was eosin or Busch the homogeneity of the plasma was equally noticeable and longitudinal sections displayed the same features.

Cardiac muscle.—Sections from the left ventricular wall were stained with logwood and eosin and presented two points of interest. There were fairly numerous small lymphorrhages of a definite character, generally closely associated with capillary vessels. Except for the fact that the cells were not clumped so closely together, these generally resembled the lymphorrhages seen in other muscles. The second point to be noted was seen in a series of four sections which displayed a capillary blood-vessel engorged with blood and surrounded by a serous exudation of considerable extent. This exudation contained numerous lymphocytes but practically no polymorphonuclear cells and no red corpuscles.

Unstripped muscles.—Sections of the œsophageal wall showed no changes in the unstripped muscles.

Adrenal bodies.—Histologically these organs were healthy looking, except for the presence of lymphorrhages, which were numerous. They were found in the medullary part, in the cortex, and in the loose connective tissue of the capsule. One unusually large one in the lower layers of the cortex was traced through a number of serial sections and in each had a diameter of about half a millimetre. This one obscured and probably destroyed a considerable amount of the glandular structure, but many of the smaller ones caused little or no reaction in the neighbouring cells.

Liver.—A few sections of this organ stained by logwood and eosin showed the presence of a few lymphorrhages, the best marked of which lay in the centre of a lobule and measured not more than $\cdot 15$ by $\cdot 25$ of a millimetre. In other respects the sections were natural.

Kidney.—No lymphorrhages or other abnormal appearances were observed.

Spleen.—Healthy, the follicles being particularly well marked.

The pancreas, the pituitary body, and a bronchial gland were examined microscopically with negative results.

The thymus.—(Report by Dr. L. S. Dudgeon.) The gland presents a normal appearance under a low power of the microscope, and there is no evidence of fibrosis. The cortex and medulla are clearly differentiated, and the cellular constituents are of normal structure. There is, however, a point of great interest in the fact that, although the gland is enlarged and the structure is of normal appearance, yet there is a complete absence of eosinophile cells, such as are met with in the large thymus glands of children and young animals. These cells, which are often present in very large numbers along the septa and around the blood-vessels, are entirely wanting. The only condition in which I have found these cells to be few in number or absent, if the gland is enlarged, is in cases of hypertrophy of the adult gland. Many of the Hassall's corpuscles are degenerated. One or two of these contain calcareous masses which fill almost the entire corpuscle. Hyaline degeneration is also extremely well marked, and some of the cells have quite a clear centre surrounded by only a few cells at the periphery. Numerous hæmorrhages are present in the gland tissue and the small blood-vessels are very congested, a condition which is often associated with death from diseases accompanied by increase in intrathoracic pressure in young children.

Case 3.—N. S., aged 37, was admitted into the London Hospital, under the care of Dr. Head, on February 3, 1904.

Family history.—Her father is alive and healthy at over 60 years of age. Her mother is 59 years old and in good health except for varicose ulcers. Three sisters and two brothers are alive and well. Five brothers and sisters died before reaching 3 years of age; cause unknown. One brother died at 19, of diabetes. No history was obtained of any nervous disease in the family.

Previous health and habits.—Patient enjoyed good health, except for the ailments of childhood, until September, 1902, when she was laid up for a fortnight with inflammation of the lungs. She drinks about five small cups of tea daily, and never any alcohol.

Present illness.—At the beginning of October, 1903, the patient complained of some headache and vague pains, and noticed some “stiffness” of the eyelids on waking in the morning. During the following week she experienced double vision, and had to give up work. Drooping of the right eyelid was then noticed, as well as some difficulty in articulation. Improvement set in and continued until about a week after Christmas, when she appeared to catch cold. Articulation became more difficult, her lower jaw seemed to drop, and her head tended to fall forward. In spite of rest in bed her symptoms became worse, and towards the end of January dysphagia was observed.

Condition on admission.—The patient's complexion was rather sallow, but there was no abnormal pallor of the mucous membranes and no cyanosis. The facial aspect was peculiar owing to the bilateral ptosis and dropping of the lower jaw. Speech was a little indistinct, and in talking the lower jaw was supported by the patient's hand.

Vision was good and the optic discs and fundi healthy in appearance. The sense of smell was perfect.

The amount of ptosis varied; at times the upper eyelid covered the eyeball, but at others she was able to expose the lower half of the cornea. All external ocular movements were abolished, but the pupils were equal and reacted briskly to light and accommodation.

Sensation over the face was normal, but all movements of the jaw were markedly paretic.

The facial movements were so diminished as to render the physiognomy expressionless and flat. The orbiculares palpebrarum and oris were almost completely paralysed.

Hearing and taste were normal.

The palate moved quickly on phonation, but the movement was of small range and poorly maintained. Phonation was feeble and whispering in character.

The tongue showed no obvious atrophy, but was small and convex on the dorsal surface when protruded. After twelve attempts protrusion was so limited that the tip did not pass the teeth. A minute's rest sufficed to restore the original mobility.

The muscles of the trunk and limbs presented no wasting, no tremors, no fibrillary twitchings, and no spasticity.

The head fell forward unless supported, but, when support was given, lateral movements were freely performed. The sternomastoids responded briskly to the faradic current, but fifty short

PLATE II.

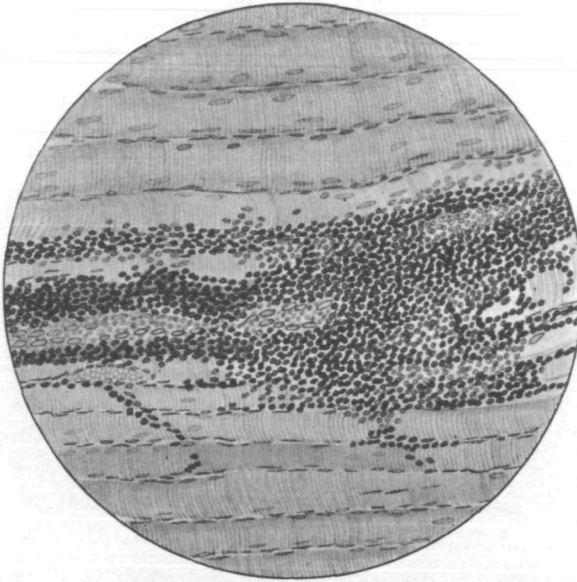


FIG. 1.

Section from the rectus abdominis muscle in Case 3, cut longitudinally and stained by logwood and eosin. Large focus of lymphocytes, healthy muscle fibres and, in the midst of the focus, a capillary vessel represented by a layer of endothelial cells.

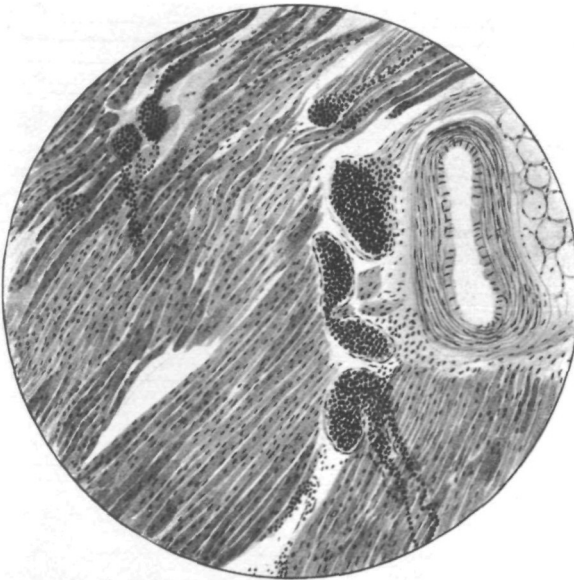


FIG. 2.

Section from cardiac muscle in Case 3, stained by logwood and eosin. Many of the cells are here contained in capillary vessels lined by endothelial cells.

applications were sufficient to abolish the response. The response to galvanism was not interfered with.

The limb movements were carried out with fair power and co-ordination. The patient had only recently noticed any undue fatigue after walking.

Sensation everywhere was perfectly natural.

The knee-jerks were equal and brisk, and there was no ankle clonus. Plantar stimulation gave flexor responses on both sides.

The spine, sphincters and respiratory system were normal.

The heart was normal, pulse good, moderate tension, arterial wall not felt.

March 18, 1904.—Patient seems much worse, and muscular weakness is more marked.

She had two choking fits yesterday and one in the night.

April 15.—(Note by Dr. Head.) On the whole she is better, and has been up on a couch. The speech is distinctly nasal, and she holds her jaw with her hand when talking in order to bring the lips together. She cannot completely lift the eyelids nor close the eyes firmly. Profound ocular paralysis is present, especially in the left eye, where upward, external, and downward movements are impossible. There is slight power of internal movement. Slight degrees of upward, downward, and external movements are possible in the right eye, and internal deviation is about equal to that of the left. Pupils react normally. She cannot close her jaws, nor can she push her lower jaw forward or to either side. Movements of face can be made at command. The tongue can be protruded through the lips but not many times in succession. Palate movements are weak. Head tends to fall forward on the chest. Arm and leg movements are good. Sterno-mastoids still show the myasthenic reaction. Knee- and wrist-jerks are brisk and equal. Plantars give a flexor response. There is no sphincter trouble.

June 29.—Dr. F. Buzzard saw the case with Dr. Head. There is no impairment of resonance over the upper part of the sternum. There are no glandular enlargements. Thyroid region appears normal. The temporal muscles are definitely wasted.

July 1.—Differential count of white blood corpuscles made by Dr. Grünbaum.

Six hundred cells classified. Neutrophile polymorphonuclear, 73 per cent. ; lymphocytes, 19 per cent. ; hyaline, 4·25 per cent. ; eosinophile, 3·25 per cent. ; basophile, ·5 per cent.

July 11.—Knee- and wrist-jerks cannot be exhausted by frequent taps. The patient's condition remained much the same

although she lost weight and wasted considerably, until September 23, when she had some severe choking fits, became very dyspnoëic, and died.

The autopsy was made twenty-four hours after death and *rigor mortis* was present. The body was somewhat emaciated. Neither the brain nor the spinal cord showed any change to the naked eye. The region of the thymus gland was occupied by fatty tissue. The thyroid weighed 20·5 grammes and was of natural consistence and appearance. Pancreas weighed 2 ozs. and seemed normal. Spleen was firm, and weighed $8\frac{1}{2}$ ozs. Kidneys were healthy except for a small yellow nodule in one pyramid, the size of a pin's head. Adrenals presented a few small fibrous nodules but were otherwise normal. The liver weighed 2 lbs. 9 ozs. and seemed healthy. The heart was natural except for a small yellow atheromatous patch on the ventricular flap of the mitral valve. The lungs contained air throughout, except the base of the left lower lobe which was plum-coloured and sank in water. The right ovary was cystic. The muscles had a healthy appearance.

MICROSCOPICAL.

Central nervous system.—The Nissl and logwood-eosin methods were used for the examination of the motor cortex, the oculo-motor, facial and hypoglossal nuclei and the ganglion cells of the cord. The large majority of cells in all these regions were of a perfectly healthy type, and if a few were slightly swollen and pale there was certainly nothing like a true chromatolysis or atrophy to be seen. Weigert-Pal specimens of the motor cortex, the brain-stem and spinal cord were remarkable only for their normal appearance. Sections stained by Busch's method from the same regions must also be passed as normal, although a few isolated black dots were scattered about in the white matter. No lymphorrhages were seen in the brain or spinal cord.

Peripheral nerves.—Sections stained by the Weigert-Pal and Busch methods were made from the trigeminal, sciatic and ulnar nerves, but these presented no evidence of

pathological change. Other sections stained by the log-wood-eosin method showed no obvious abnormality.

External ocular muscles.—The appearances presented by sections of these muscles were practically identical with those found in Case 1. Lymphorrhages were unusually small but fairly numerous and were unassociated with any other changes either in the muscular, nervous, or connective tissue elements.

Skeletal muscles.—Portions of many of these muscles were examined, but only in a few were lymphorrhages observed. Excellent examples, however, were obtained in the rectus abdominis, and one of these in longitudinal section is represented in Plate II., fig. 1. This one measures about .7 mm. in length and .25 mm. in its greatest breadth. An empty capillary, represented by its endothelial lining, was seen to traverse the centre of the mass of lymphocytes and the neighbouring fibres appeared to be perfectly healthy.

Apart from the presence of lymphorrhages only a few sections showed any other pathological conditions and these were much the same as have been described in Cases 1 and 2, but perhaps in a few instances of greater intensity. Rounded, swollen fibres with hyaline and homogeneous sarcoplasm were present, but in some the change had gone a step further, and alterations in the refractive properties of the central portions of the fibre, with pericentral vacuolation, or central nucleation and vacuolation, were occasionally observed and reminded one of the earliest stages of certain forms of muscular atrophy. With these exceptions, and they were comparatively rare, the muscles presented a very healthy appearance.

Cardiac muscle.—Attention must be drawn to the condition seen in Plate II., fig. 2, which pictures a capillary vessel crowded with white blood corpuscles, chiefly of the lymphocytic variety and unaccompanied by any red corpuscles. Some of these cells had escaped into the neighbouring tissues, but the specimen is unique in my series, and important in that it suggests the condition which precedes the production of a lymphorrhage.

No changes were observed in the heart muscle fibres themselves.

Liver.—The changes found in this organ were rather difficult to describe. Scattered here and there in the midst of healthy hepatic tissue were small areas from which the liver cells had disappeared and were replaced by necrotic *débris*, together with a number of small round cells, some of which had the appearance of lymphocytes and others had irregularly-shaped nuclei.

Dilated spaces containing a few cellular elements were occasionally seen in the substance of Glisson's capsule. As far as size, distribution and general appearances are concerned they were compatible with what may be supposed to be the ultimate remains of lymphorrhages, and the presence of the small cells, some of which may also be undergoing degenerative changes, lends some support to this view. At the same time I think it wiser to abstain from expressing any decided view as to their origin.

The greater part of the liver tissue appeared to be healthy, both microscopically and macroscopically.

Adrenal bodies.—In the case of these organs there could be no doubt as to the presence of lymphorrhages, which were numerous and in some cases of considerable size. They occurred in most instances in the inner or central parts of the cortex, although the medullary region was not spared entirely. Beyond the mechanical destruction of the glandular cells in the immediate neighbourhood, the adrenal tissue did not appear to be affected by their presence and would pass muster as healthy.

The spleen, pancreas and kidneys.—These viscera presented no pathological changes on microscopical examination.

The thyroid gland.—Dr. Chalmers Watson who kindly examined the slides prepared from this gland reports that there were: (1) Distinct interstitial fibrosis; (2) numerous areas of cellular infiltration resembling small abscesses (lymphorrhages); (3) a large area of colloid degeneration of the fibrous stroma in one part; (4) proliferation of the epithelium with formation of new vesicles in some regions; and (5) enlargement of spaces as seen in simple goitre.

Thymus gland.—Dr. Dudgeon reports that only islets of gland tissues could be seen scattered throughout dense connective and adipose tissue. In some places the adipose tissue was surrounded by glandular structure. The cortex could not be distinguished from the medulla and some endothelial proliferation was present. The concentric corpuscles were mostly in good condition, but some had undergone both granular and calcareous degeneration. No eosinophile cells were seen.

Case 4.—H. B., a schoolmaster, aged 40, was admitted to the National Hospital in October, 1899, under the care of Dr. T. Buzzard, and the following account is reproduced from the *British Medical Journal* of March 3, 1900, in which the clinical features of this case, along with another, were published.

Family history.—The patient's mother died of phthisis. His father, who is alive, aged 63, has suffered from muscular rheumatism. The grandparents on both sides are long-lived. The patient had four brothers and sisters, of whom a brother three years younger than himself is alive and strong; a sister died of scarlatina, two died in infancy. He has three children, aged 14, 10 and 8, all of whom are fairly strong, and there have been no deaths, no miscarriages. No similar condition to the patient's is known to exist among his relations. There is a rheumatic tendency in his father's family. A paternal uncle died in a lunatic asylum; a paternal aunt, aged 60, of "creeping paralysis."

Personal history.—Although never robust he was quite healthy till 1892. Twenty-eight years ago he had scarlatina, otherwise he has never had a day's illness until the present trouble. Syphilis can with certainty be excluded. There is no history of injury. He has not had a distinct attack of influenza. He is a total abstainer from alcohol, and not a heavy smoker. His work as a schoolmaster is hard and involves much speaking. His recreations have been chiefly of a sedentary nature, although he is fond of walking. He has had considerable worry during the last year or two.

Present illness.—Until 1892 he enjoyed good health. He then began to take a cold bath every morning, and is disposed to attribute his illness to this. About Christmas, 1892, after sawing wood, his little and ring fingers felt weak, but speedily recovered. The weakness recurred after playing the organ, and his right index finger would occasionally drop. In 1893 he occasionally

saw double, and this trouble recurred in 1894. About this time his voice, after speaking a few minutes, would acquire a nasal character. His right eyelid, too, tended to droop. This weakness in fingers and eyelids occasionally recurred, but not in a very marked form, during the three following years. In the summer of 1897 he felt weakness in the lips and tongue, and spoke through his nose. After speaking some time the voice would become feeble. He again saw double. In the vacation he walked eight or ten miles a day without fatigue for several days. After this his right thigh became weak. He found that he had frequently to stop and rest it for a few minutes, after which he could go on walking. He had never noticed this difficulty before. In the winter of 1897-98 both arms and hands were easily fatigued, and the right leg felt weak. In July, 1898, his speech was again affected, especially in the evenings. He walked sixteen miles in one day during the vacation, and although he found difficulty in accomplishing the last few miles, this was due rather to trouble with his breathing than with his legs. At times he would suffer from palpitation, which was new to him. In October, 1898, whilst suffering from catarrh, he had difficulty in coughing and clearing his throat, and also in swallowing. This cold seems to have pulled him down very much, and he has never recovered the strength which he had before. In January, 1899, his right arm was so weak that he could not brush his hair or write upon the blackboard, but after two days' rest he was able to move the arm quite well. At this time there was dull, aching pain in the right arm and leg, especially after exertion, but also sometimes whilst lying still in bed. At Easter, 1899, he again had ptosis of the right lid, which has persisted in varying degree since. In June he gave up work. Diplopia and masticatory difficulty were then his chief troubles, but from time to time he would also suffer from dyspnoea, especially after exertion or emotion. From August he again improved, but was subject to recurrences of all his troubles, especially in very hot or cold weather. After a considerable rest his symptoms almost entirely disappeared.

Condition on admission (October, 1899).—His face is somewhat expressionless, and there is right-sided ptosis. Intelligence is not impaired. After speaking a little his speech becomes slower, laboured, and indistinct, and the voice is nasal in character and gradually fails. He describes the lips and tongue as feeling tired. It is noticeable that the chest expands less and less with each succeeding breath. The change in speech would appear to depend

upon weakness of the respiratory muscles as well as those of articulation. Diplopia is only present on extreme lateral deviation to the right, and then only if the eyes are maintained for some considerable time in this position. The optic discs are normal. Hearing, taste, smell, and the viscera are unaffected. The ptosis is more marked in the evening, and is present to a slight extent also in the left eyelid; it is not always present. Two days after admission, when examined in the morning before rising, instead of ptosis there was actually retraction of the upper lids, so that a portion of the sclerotic was exposed above the cornea. Directly this condition was remarked upon the lid began to droop, illustrating what he says is one of the most characteristic features of his complaint, namely, that when his attention is drawn to any particular symptom, it will become exaggerated. He cannot voluntarily open his eyes widely, but when interested in conversation the lid moves upwards to a greater extent than he is capable of producing by any act of the will.

Ophthalmological examination.—Mr. Gunn, during his examination, remarked this incident, and attributed it to the action of Müller's muscle. Not only is he unable to open his eyes widely, but if he looks steadily upwards at an object held above his line of vision, the upper lids gradually droop lower and lower until the eyes are almost closed. Mr. Gunn reports: "Downward movement and convergence are good; upward movement defective; both external recti are weak. The pupils are equal, of moderate size, and react perfectly to light and on convergence; they dilate upon appealing to the patient's emotions, and occasionally upon mental concentration after prolonged convergence they show a great tendency to oscillatory movements."

Laryngological examination.—Sir Felix Semon, who was so good as to examine the palate and larynx, reports as follows: "The condition of the motor movements of the palate corresponds to what has been observed in the other voluntary muscles upon voluntary exertion. At first the palate is fairly well and symmetrically raised on phonating the letter A; gradually, however, as he repeats phonating, the movements become less and less marked, and finally hardly any raising of the palate is observed.

"On laryngoscopic examination, at first the larynx appears perfectly normal, except perhaps that on deep inspiration the vocal cords do not separate quite as much as in the ordinary condition; but as the patient, previous to the commencement of the examination, complained spontaneously of the shortness

of breath, this might have been due to his general inability to take a long breath. Closure of the glottis on phonation was, and remained, perfect; on repeating his endeavours at breathing deeply, the glottis certainly finally opened less than at first. It is very probable, however, that this phenomenon was only part and parcel of the general exhaustion."

Muscular System.—He is quite unable to raise the eyebrows and wrinkle the forehead, and can only frown slightly. He can close his eyes, but cannot screw them up firmly. He can whistle and show his teeth, but movement of the upper lip is feeble. Contraction of masseters, temporals and pterygoids is feeble. He says that the jaw will frequently drop, the muscles apparently being unable to support it. The masticatory muscles become tired in the act of eating. The lips feel weak after talking, and at night saliva will dribble from his mouth. Occasionally he feels twitching sensations about the face, though no movements have been noticed, but he is awakened sometimes by a champing movement of the lower jaw. There is at present no difficulty in swallowing. The tongue is protruded straight, promptly, and to its full extent. It is symmetrical, and the movements are good, but easily exhausted.

The muscular power of this patient is subject to great diurnal variations. Towards evening he often sits with his hands clasped behind his neck supporting his head, as though the neck were weak. There is a tendency for the head to fall backwards. He cannot sit up for very long without feeling the back weak. He cannot sit up in bed without using his hands. He has some difficulty in turning in bed.

The rapidity with which the respiratory muscles are fatigued is demonstrated when he reads. Respiration is abdominal in type. During respiration there is almost no thoracic expansion, the difference in circumference of the chest between extreme voluntary inspiration and expiration amounting to less than half an inch. No weakness of the diaphragm can be detected.

The movements of the upper extremities are feeble, the right more so than the left; the dynamometer grasp, right 45, left 50 (average man 160). The ready way in which the muscles of the hand become fatigued is demonstrated by asking him to button and unbutton his waistcoat repeatedly. As regards his writing, he begins to write rapidly, forming his letters well. After a few lines the writing becomes slower and laboured, and the letters are not so well formed. Finally he comes to a stop, more or less suddenly, unable to write further. After a minute or two's rest he is able to write again as well as at first.

He can raise his arms above his head, but cannot maintain them in this position for more than half a minute. They gradually fall; he feels as if heavy weights were attached to them. Again, after a short rest he performs the movement quite well. If requested to lift his arms quickly above his head several times in succession he will do this, but at each effort the arms are lifted less high, and after doing this seven or eight times they cannot be lifted at all, but hang by his sides. After a rest of from thirty to sixty seconds they can be lifted nearly as high as they were at first. All movements of the lower extremities are well and powerfully performed, but the right leg especially is easily fatigued. There is no muscular atrophy, nor are there any fibrillary twitchings. The muscles respond fairly well to direct stimulation with a percussion hammer and no diminution in the activity of the response results from repeated blows.

Sensation.—A dull aching in the neck, back, arms, and right leg, occurring particularly after exertion, but also when lying in bed, is sometimes present. No disturbances of cutaneous sensibility can be ascertained.

Reflexes.—The arm-jerks are present, feeble. The knee-jerks are present and equal, usually a little more active than the average. The patella-jerk is not depressed. Repeated attempts were made to determine whether the knee-jerk diminished after frequent tapping. On one occasion the tendon was tapped continuously for a quarter of an hour, but at the end of that time quite as good a knee-jerk was obtained as at first. No ankle clonus is present. No abdominal reflex was obtained. The plantar reflex is present, with sluggish flexor response.

Sphincters.—The bowels are regular. There is no trouble in commencing micturition, and the stream is well maintained.

Cranium and spinal column.—There is no abnormality. The gait is natural. After walking several times up and down the ward nothing abnormal is noticed. No vasomotor or trophic changes have been discovered.

Of great importance and interest are the results obtained by electrical examination. The muscles respond to faradism in varying degree on different occasions. For instance, if an electrode be placed upon the motor point of the biceps a prompt and good contraction is obtained, except when the muscle has been fatigued by voluntary exertion. The initial contraction in certain muscles is very much poorer than in others, and some muscles tire very much more easily than others. As the result of faradic stimulation, voluntary power of contracting the muscle stimulated

is much diminished and a feeling of fatigue induced. As regards galvanism, after repeated stimulation the muscular contractions become less, but the muscle cannot be tired to the same extent as is the case with the faradic current. No polar change can be demonstrated.

This patient left the hospital in the early part of 1900, but remained more or less in the same condition for the next few years. During the year 1903 he was hardly able to walk from one room to another, and always went out in a bath-chair. Every few weeks he would suffer from severe paroxysms of dyspnoea, and he ultimately died of respiratory failure on January 24, 1904. Owing to the kindness of Dr. Morrow, of Enfield, I was able to perform an autopsy twenty-two hours after death at the patient's house.

The body was extremely emaciated, but the muscles, though poor in size, preserved their natural contour and presented no evidence of local atrophy.

The brain and spinal cord with their meninges and vessels appeared normal to the naked eye. Portions of only a few of the larger muscles and nerves were removed for the examination, and unfortunately the ocular muscles were not among this number.

The heart, lungs, spleen, liver and kidneys showed no signs of disease. The pancreas had undergone *post-mortem* digestion.

The stomach and intestines were normal, and one or two spleniculi were found attached to the mesentery.

The thyroid was natural in size and appearance.

The thymus gland was rather unusually well developed, weighing 9.5 grammes after the adjacent fatty tissue had been stripped off.

MICROSCOPICAL NERVOUS SYSTEM.

The cells of the motor cortex were in excellent condition, and the same remark applies to those of the bulbar nuclei. A few small recent hæmorrhages were seen in the floor of the fourth ventricle. A careful examination of the cells of the cord was made, and it was thought that they appeared smaller than the normal on the average, but the difference was slight if present, and in other respects they lacked none of the healthy characteristics. A few capillary hæmorrhages

were noted in the gray matter of the anterior horns, but these were quite recent and associated with considerable congestion of the vessels.

The Weigert-Pal and Busch methods showed no alteration in myelinated fibres either in the central or peripheral nervous system, and sections of the cord and sciatic and ulnar nerves stained by logwood and eosin showed no pathological conditions.

Muscular system.—Owing to the circumstances under which the *post-mortem* examination was made only a few small pieces of muscle were investigated microscopically, and these came from the erectores spinæ, the left pronator radii teres and the left biceps femoris. In the sections examined, only one or two small lymphorrhages were found and the fibres as a whole were of healthy size and appearance. A certain number, however, were present in which a rounded swollen contour and homogeneous sarcoplasm were noted. No changes were detected in the vessels, connective tissue, or muscle spindles.

Spleen.—There was no thickening of sheath or septa and the relation of the pulp to the fibrous constituents was about normal. Malpighian bodies plentiful and well marked. A spleniculus was also cut and the sections presented similar appearances.

Pancreas.—This organ had undergone so much digestion that it was of no use from an histological point of view. In the loose areolar tissue surrounding the pancreas masses of lymphoid tissue were seen under the microscope having an appearance similar to the islets of thymus remains, but containing no Hassall's bodies. Some of the vessels in this tissue were closely surrounded by clusters of lymphocytes, and some had their lumina blocked with the same kind of cells.

Adrenals.—Numerous small lymphorrhages were seen in the sections of otherwise healthy glands. One of these is depicted in Plate I., fig. 2.

Thymus.—Report by Dr. Dudgeon. The gland is large and the cellular constituents are in good condition. The cortex and medulla can be differentiated from each other,

although the distinction is not so well marked as in the case of the normal organ. There is some increase in the fibrous stroma, and adipose tissue has replaced the glandular tissue in several parts. Many of the concentric corpuscles are very large and calcified, while others give evidence of granular degeneration. No eosinophiles are to be seen.

Case 5.—A man, aged 40, was admitted to the London Hospital, under the care of Dr. C. Wall, on February 10, 1905, with the history of a month's illness.

He was a foreman for a mineral water company. His wife was healthy and had had three children and two miscarriages.

He had suffered from "malaria" fourteen years previously, and since that time was subject to incontinence of fæces after taking aperient medicine.

Present illness.—One month ago he noticed such weakness of his neck that he could not hold his head up straight. The eyelids tended to droop, and he was unable to lift his arms above his head. Difficulty with articulation, mastication and deglutition was also observed, as well as considerable trouble in keeping food from collecting between his teeth and cheeks. Articulation would become worse after he had talked for a while, and diplopia was present at times.

Condition on admission.—The heart, lungs, and abdominal viscera appeared healthy on examination.

The optic discs were healthy. There was partial ptosis of both upper eyelids, weakness of the left external rectus and right internal rectus muscles. There was no nystagmus.

He was unable to protrude the tongue beyond the teeth, but no tremor was observed. All the muscles of the neck were parietic and he was incapable of raising his arms above his head.

Romberg's sign was absent. The knee-jerks were present and equal, and the plantars flexor in type.

February 22, 1905.—Patient had an attack of dyspnoea last night, and a bad fit of choking to-day while eating pudding. He can talk but little without becoming exhausted.

Electrical reactions. The myasthenic reaction is present in the trapezius of both sides, in the pectoralis major, the biceps and flexors of wrist on the right side. The triceps and deltoid muscles did not give the reaction, but it was present in the facial muscles, especially on the left side.

February 23.—Diplopia is marked, but the pupils react normally. The left upper eyelid droops more than the right.

The movements of the right eye are good, but there is complete paralysis of the left external rectus.

February 25.—Swallowing is best in the early morning, and becomes more difficult as the day goes on. He has had two more bad choking fits.

February 27.—There is marked improvement in the ptosis, swallowing and dyspnoea, and the double vision is less than it has been for weeks.

The patient's condition varied from day to day until April 6, when he had increasing difficulty in breathing, and was unable to cough up the mucus from his bronchial tubes. On the 7th his respiratory muscles became progressively weaker, and death took place from respiratory failure.

The autopsy I was kindly allowed to make at the London Hospital fifteen hours after death. The body had been frozen and *rigor mortis* was marked. No evidence of local atrophy or general emaciation was found on inspection.

The brain and spinal cord with their coverings appeared healthy to the naked eye. The pituitary body was normal. Portions of several peripheral nerves and of many muscles were kept for microscopical examination, but to the naked eye presented a natural appearance.

Thorax.—Behind the manubrium lay a large mass which on removal weighed 59·4 grammes. The upper part of this mass was firm and adherent to the subjacent vessels, the lower part was not so adherent and was softer and cystic. On cutting into the upper part it was found to be soft and creamy in the centre, and slide smears were prepared of the pus-like material. Closer examination of the lower portion showed that it was a thin-walled multilocular cyst containing a slightly cloudy fluid.

The lungs were healthy except for an old scar at the left apex.

The heart weighed 10 ounces and was free from any evidence of disease.

There were no enlarged bronchial or tracheal glands. The thyroid weighed 13 grammes and was pale in colour, but otherwise natural.

Abdomen.—The liver looked healthy and weighed 3½ lbs.

The spleen weighed $9\frac{1}{2}$ ounces, was firm and showed prominent malpighian bodies.

The kidneys, pancreas, adrenals, stomach, and intestines, were all examined with negative results. The mesenteric glands and Peyer's patches were prominent without being unduly enlarged. A portion of the left femur was removed with the intention of examining the marrow, but it may be stated at once that this proved of negative value owing to the fatty, non-cellular condition of the latter.

MICROSCOPICAL.

Owing to the acute course of the disease in this patient—the whole illness only lasted about three months—it was thought that the examination of the cells of the central nervous system would be of particular interest, and a number of sections, stained by Nissl's method, were prepared from the motor cortex, the oculomotor and bulbar regions, and from various levels of the spinal cord. After a careful investigation of these it was impossible to state that any definite pathological changes were present, although a certain number of anterior horn cells were somewhat deficient in tigroid. On the other hand, the oculomotor nuclei would pass as typical examples of healthy cells possessing abundant tigroid and central nucleation.

Serial sections of a cervical posterior root ganglion were stained by the same method and presented an entirely normal appearance.

As in the preceding cases neither the Weigert-Pal nor the Busch methods were successful in revealing any morbid condition in the central nervous system or in the peripheral nerves. Several of the latter were teased, but no abnormal fibres were seen.

Muscular system.—The ocular muscles contained several small and one or two larger lymphorrhages which differed in no particular from those seen in other cases.

The skeletal muscles, from a number of which sections were cut and stained, presented some features peculiar to this case and deserving of special mention.

Lymphorrhages of the usual type and of varying size

were found in a small proportion of the sections examined and were not always confined to the muscle fibres, as in one or two instances they occurred in the fibrous sheath of the muscle. In addition to the ordinary lymphorrhages a condition was found in a number of serial sections taken from a portion of the triceps muscle which is represented in Plate I., fig. 3. A cellular condition is associated in this instance with marked changes, in the form of swelling and protoplasmic disintegration, in the neighbouring muscle fibres. This reaction to the cellular exudation is unique among my specimens and is rendered more interesting by the fact that an examination of the cellular elements of the exudation showed that they differed from the cells usually seen in lymphorrhages. Some of the cells were probably true polymorphonuclear leucocytes but the nature of many of the others could not be definitely ascertained. Their size was very much that of lymphocytes, although some were larger, but they presented more clear protoplasm and contained nuclei which in many instances appeared to be undergoing division into two or four parts. Owing to the fact that they lay thickly together in celloidin sections accurate examination of their characters was impossible, and these facts can only be recorded without any attempt being made to define their true significance. It will be noticed that some of the altered muscle fibres were actually invaded by the cells, a condition which does not apparently obtain in the ordinary type of lymphorrhage.

In the neighbourhood of a small lymphorrhage, in another section, some of the fibres presented an appearance which is occasionally seen in conditions of very early muscular atrophy of toxic origin. In transverse section the fibre is rounded and in the centre is a dark core surrounded by a concentric ring of lighter hue; as far as can be ascertained the appearance is produced by an alteration in the refractive properties of the central and pericentric portions of the plasma, and not to the presence of nuclear elements on the one hand and of disintegration on the other.

In longitudinal sections evidence of early atrophy was also forthcoming here and there in the form of localised

swelling in a fibre and marked proliferation of the sarcolemma nuclei.

While attention is necessarily drawn to the morbid conditions discovered, it must be clearly understood that in this case, as in the others of my series, the large majority of fibres could not in any way be differentiated from those of healthy muscle.

Liver.—In otherwise normal sections a few well-marked lymphorrhages were seen, generally situated round and about the biliary ducts or blood-vessels.

Adrenals.—Microscopical preparations of these organs contained only one or two doubtful lymphorrhages of minute size, and the only feature of note was the intense congestion of all the blood-vessels associated with pallor of the gland cell nuclei.

Pancreas.—The histological appearances of this organ were of a healthy character.

Thyroid.—No lymphorrhages were found and no other abnormal features noted.

Thymus.—The examination of this organ included the preparation of : (1) smears from the semi-fluid matter contained in the centre of the upper solid portion, and from the liquid contained in the cystic portion of the gland ; and (2) sections of the upper portion and of the multilocular cysts. These were stained by logwood and eosin, by Jenner's stain and by Leishman's stain.

The more solid part of the organ consisted of closely packed masses of ordinary thymus gland cells separated by dense bands of connective tissue ; it contained no traces of Hassall's bodies. In the smears taken from this part the prevailing cell was of the lymphatic type, but there were also a considerable number of eosinophile cells of large size. The cystic portion resembled the solid part except for the fact that the dense masses of cells were replaced by a thin fluid containing similar cells in much smaller numbers. Owing to the pressure of this fluid the cyst walls appeared to have a definite lining membrane, but this was not of true cellular structure. In the midst of the fibrous strands composing the cyst walls many lymphocytic cells were entangled,

sometimes in large clumps, and a fair number of eosinophile cells were also observed. One or two doubtful remnants of concentric corpuscles were noted.

Pituitary body.—Sections showed no abnormality beyond some slight colloid degeneration in the glandular part of the body.

CLINICAL SUMMARY.

The five cases here recorded, although varying very considerably in their duration, all presented the typical motor phenomena which we associate with myasthenia gravis, and each one exhibited the bulbar symptoms which at one time gave the name “asthenic bulbar palsy” to the disease. The disorders of motion are now so well known that it is unnecessary to dwell upon them here, and attention will be at once directed to certain other disorders presented by some of my cases which are more rare and less well recognised.

SENSORY PHENOMENA.

In that excellent monograph on myasthenia published by Campbell and Bramwell (3) in 1900, the sensory side of the disease is dismissed in the few words “there are no sensory symptoms.” In the five years which have elapsed since those words were written, a large number of cases of myasthenia have been recognised, carefully investigated and recorded, with the result that that statement no longer holds good. Subjective pains and paræsthesiæ of various kinds have been mentioned in connection with a number of cases, but as far as I am aware no case of the disease has presented such startling disorders of cutaneous sensibility as were found in Case 1 of this series. A reference to the charts will show that the relative analgesia and anæsthesia in this patient was progressively distributed over those areas of skin which nearly always show the same changes in cases of tabes dorsalis. When the reader remembers that these changes were associated in this patient with “lightning” pains, with absent arm-jerks, and with diminished knee-jerks, he will not be surprised to learn that the

possibility and even the probability of myasthenia being combined with early tabes was entertained during life.

The negative results obtained in a careful search for microscopical evidence of the latter disease, allow us to draw one of two alternative conclusions. The sensory disturbances are occasional, if rare, symptoms of the morbid process which we designate by the name "myasthenia," or the patient had a "functional tabes," by which is meant the disease in that early stage where the disorder of function precedes the anatomical lesion, if such a stage actually exists.

The second of these two alternative propositions is one which it is impossible to support with any material evidence at the present time, but the first may be considered in the light of contrast with other cases. Case 2 complained of intermittent sharp pains similar in character to those described by Case 1, and had in addition a small patch of relative analgesia and anæsthesia during a period of the time she was under observation. Senator (7) describes a case in which there was anæsthesia of the chin, and Burr (2) has mentioned the presence of some very interesting visual disturbances in one of the cases which he has reported. It can hardly be denied, therefore, that sensory phenomena may take a prominent place in the symptomatology of the disease, and their presence can no longer be held to be sufficient to throw doubt upon the diagnosis.

The explanation of their occurrence is a most difficult problem, but hardly more so than that of the motor phenomena. Some reference to this subject will be made in discussing the question of pathogenesis.

In this connection it may be interesting to mention that an undoubted case of myasthenia which was under my observation for two or three years, presented unmistakable evidence of mental changes which varied in intensity from time to time. Melancholia with delusions of persecution and some suicidal tendencies were very marked for short periods, and I have in my possession letters from the patient which illustrate well the morbid condition of his mind. Unfortunately I was unable to obtain an autopsy at his

death. This experience again makes one hesitate to accept the dictum of Hun (4) that "mental abnormalities play no part in this disease."

MUSCULAR ATROPHY.

The occurrence of localised muscular wasting in myasthenia has been doubted, but recent records favour the view that it is certainly present in some cases. The tongue is a favourite site for atrophic change, and in Dr. Head's case there was definite wasting of the temporal muscles. Although I have never had the opportunity of examining histologically any markedly wasted muscle in this disease, I am satisfied from clinical observations that such wasting does occur in some instances.

MORBID ANATOMY.

In studying the records of cases of myasthenia which have been examined after death, it is found that in a large number the results have been negative, or variable and trifling, but that in a smaller number, and these belong to recent years, attention has been drawn to the existence of changes in the thymus gland and to the presence of lymphocytic deposits in the muscles. A considerable variety of thymus changes have been described, including so-called thymus tumours (possibly lymphosarcomata) and different degrees of thymus enlargement, and the view has been held that the lymphoid tissue found in the muscles has been of the nature of metastases. My cases show that abnormalities of the thymus are *not constant* features in this disease, and therefore that the lymphocytic deposits, which occur independently of them, are probably not in any way a secondary condition. On the other hand my experience affords reasonable grounds for believing that lymphorrhages are constantly present in the muscles or other organs in cases of myasthenia. That they existed in all five of my cases was only established by a diligent search through some thousands of sections, and for that reason it would be unwise to assume that they were absent from the cases of other observers who had not been led to conduct a similar

Careful investigation with the same object. Moreover, it is interesting to note that since their presence was first described their occurrence has been reported in an increasing number of cases. I would suggest that this number will be still greater when it is realised that a persistent thymus or a mediastinal tumour is not a necessary concomitant of the lymphorrhages. An exhaustive examination of all the muscles is too laborious a task for any investigator to undertake, but it is fairly easy thoroughly to search the ocular muscles and a number of selected samples from various skeletal muscles. The presence of lymphorrhages in other organs, described here for the first time, renders the undertaking still less formidable.

Although the occurrence of a thymus gland of unusual size or with pathological features is not, as we have seen, a constant factor, yet its frequency is so considerable that it will be impossible to disregard it in discussing the pathogenesis of the disease.

Out of my five cases one presented a very large thymus gland which had undergone changes partly proliferative and partly degenerative in nature, another exhibited considerable simple hypertrophy of the gland, a third a minor degree of the same change, while in the two remaining patients were found only those islets of lymphoid tissue which are commonly present in the adult human being.

Lymphorrhages were present in varying numbers in all five cases, but were by no means confined to the muscles. In several cases they were seen in the heart, liver, adrenals and thyroid gland. A considerable increase of round cells in parts of the kidney of at least one case was evident, but it was difficult to say whether the condition was identical with the lymphorrhages of other organs. In one instance (Case 1) there were scattered small foci of lymphocytes around vessels in the substance of several posterior root ganglia, and these I believe, after some hesitation, to be small lymphorrhages.

What is the origin and what is the fate of a lymphorrhage? To these questions I find it impossible to give a definite answer. The impressions gained from examining

a large number of these cell deposits inclines one to the view that they arise in some way from the capillary blood-vessels, and this feeling is strengthened by the fact that no evidence of any lymphatic disease has been forthcoming. At the same time we are shaken in our belief by the absence of blood changes during life and by the knowledge that the lymphocytes are not the most migratory of blood cells.

Certain appearances which would seem to give some support to the view that lymphorrhages are of vascular origin have been described in the preceding records of the cases but may be referred to again in this place.

In the first place the close association of the lymphocytic exudation with a small blood-vessel has been noted repeatedly. In Plate II., fig. 2, a capillary vessel is seen to be engorged at one point with white corpuscles, some of which have escaped into the surrounding tissues. In Case 2 attention has been directed to a cardiac blood-vessel full of red corpuscles, but surrounded by a mixed serous and lymphocytic exudation. A somewhat similar condition was seen in the liver sections of Case 3, in which dilated spaces containing amorphous *débris* and a few white cells were found in parts of Glisson's capsule. It would be premature to argue dogmatically from those preparations, but they certainly seem to throw some light upon the formation of these cellular deposits.

With regard to the fate of the lymphorrhages we can only suppose that they are transitory phenomena, since they are not more numerous, if as numerous, in long-standing cases as in those which run an acute and rapidly fatal course. Does the prevalence of lymphorrhages in a muscle bear any relation to the functional activity of that muscle? The data at my disposal are inadequate for the purpose of forming any opinion on this question.

The possibility that lymphorrhages might occur in other conditions was one which naturally arose, and an effort was made to settle the point by examining sections of muscles obtained from various other diseases of muscular or nervous origin. The ocular muscles from a case of pontine tumour, in which there had been ophthalmoplegia

for many months before death, were investigated with negative results. In a variety of other conditions the skeletal muscles were searched, but in only one instance was there found any appearances resembling the lymphorrhages described above. The case was one of amyotrophic lateral sclerosis which ran a very atypical clinical course, and in which the lymphocytic deposits were associated with extensive and unusual changes in the muscular fibres. In another example of the same disease no lymphorrhages were observed.

Although the lymphorrhages appear to be the most striking of the anatomical changes in myasthenia, yet it is desirable to point out that in every one of my cases some of the muscles have shown abnormal appearances in a small proportion of their fibres. These abnormalities have not always been identical, but they have all been of the character which one associates with an early stage of muscular atrophy, and suggest that they would have resulted in grave muscular degeneration had the morbid process at work been further encouraged. They certainly make the occasional occurrence of true muscular atrophy in this disease by no means surprising.

Attention having been directed to certain positive factors in the morbid anatomy it will be well to emphasise the untrustworthiness of certain negative factors. For instance, there can be little doubt that the methods at our disposal for the examination of the axis cylinders in nerve trunks, and more especially the terminations of neurofibrils in their muscular connections, are inadequate, and it is impossible, therefore, to feel certain that these important structures do not show definite, but hitherto undetected, alterations. At the same time we should expect that permanent structural changes in these tissues would lead to some recognisable reactions, either in the myelin sheaths, or in the neurone cells, and of such there is no evidence.

The discovery of small lymphoid masses resembling thymic islets, except for the absence of Hassall's corpuscles, in the peripancreatic connective tissue of Case 4, makes one regret that more of this tissue in various parts of the body was not examined.

PATHOGENESIS.

Great as has been the increase in our knowledge of myasthenia within recent years, it is undeniable that the pathogenesis of the disease is still far from clear, and it is not my intention to discuss the problems with which we are faced at any length. At the same time it may not be unprofitable to refer to some points which are suggested by the cases just described, as well as to some further points observed in other cases, and to review them in the light of recent theories on muscular and glandular physiology.

A few years ago, Dr. H. D. Singer and I carried out some investigations on two cases of myasthenia in the National Hospital, some results of which I will briefly summarise here.

(a) Biceps humeri. With faradic current, the muscle rapidly ceased to be tetanised, the subsequent contractions being intermittent for a time and then ceasing altogether. By this time voluntary power was much diminished but not lost, the biceps-jerk remained unchanged, the galvanic reaction was brisk, and direct excitability to percussion was as lively as before.

(b) Same muscle. The muscle was rapidly tired out by voluntary action. Diminished faradic excitability was then present. The galvanic reaction, the tendon-jerk and direct excitability were unaltered.

(c) Same muscle. Rapidly repeated galvanic shocks for two minutes produced no diminution in the briskness or size of the response.

(d) Same muscle. Faradism with moderate strength of current was continued until no response was obtained. An increase in the strength of current immediately produced a contraction which was rapidly exhausted.

(e) Same muscle. The tendon-jerk was not diminished by rapid repetition for a considerable time.

(f) Attempts were made to ascertain the effect of exhaustion of one group of muscles upon the activity of another but the results were variable. General clinical observations seem to show, however, that there is a general reduction of power produced by local exhaustion.

(g) The same muscle in another patient, very weak and quickly tired. Tendon-jerk absent. Direct excitability to percussion less than normal.

After exhaustion by faradism there was still further loss of voluntary power. After further exhaustion by voluntary action there was diminished reaction to faradism. Galvanic response good and brisk.

The muscle was exhausted by faradism and then by voluntary action. When it ceased to respond to volition it had regained some response to faradism; galvanic response still good.

The above observations, which were made at a number of different sittings, admit of course, of various interpretations, but they appear to me to suggest certain conclusions. In the first place the exhaustion of a myasthenic muscle is always a relative phenomenon, and bears a definite relation to the nature and probably to the strength of stimulus employed. In the second place the liability to exhaustion is much more pronounced in the case of tetanising stimuli, such as are employed in voluntary action and faradism, than in the case of stimuli producing single sharp contractions such as direct percussion, indirect excitation through the tendon and galvanism.

Thirdly, I would emphasise most strongly the fact that no comparison should be drawn between the phenomena observed in myasthenic muscles and those which we associate with the reaction of degeneration. In the former case a muscle which has lost its response to faradism gives the normal brisk response to the make and break of a galvanic current. In the latter case a muscle, irresponsive to induction currents, gives a slow worm-like contraction on applying or discontinuing the galvanic current.

Jotezko (5) has shown that the slow contraction just mentioned is an idiomuscular phenomenon, and this fact, taken in conjunction with those just mentioned, distinctly contravenes the theory that in myasthenia we have to deal with an exhaustion or liability to exhaustion on the part of the muscular nerve endings.

Botazzi (1) has advanced the view, which is supported by

Jotezko (6), that in muscle there are two contractile substances, a fibrillar and a protoplasmic. The fibrillar contraction is the short sharp response, such as is produced by the make or break of a galvanic current; the protoplasmic contraction is slow and resembles that which is seen in the reaction of degeneration. They can both be produced by the galvanic current, but the protoplasmic reaction requires a stronger stimulus than the fibrillar. After nerve section the muscle tends to return to an embryonic condition, in which the fibrillar substance diminishes and the sarcoplasm relatively increases. Assuming these views to be correct they would help to explain the paradoxical condition observed in the myasthenic reaction, and we might suggest that in the disease under consideration, some agent is at work which reduces the excitability of the protoplasmic more than that of the fibrillar constituents of the muscle.

Going a step further it may be asked, what evidence is there of the presence of a toxic agent of either exogenous or endogenous origin? So far as our knowledge goes there is no good reason for believing that any microbe is the causative agent of the disease; on the other hand the clinical features of myasthenia present many resemblances to those of what are called the internal secretion diseases and especially to Graves' disease and to Addison's disease. With that idea in my mind, the ductless and other glands have been the object of much attention in the histological examination of my cases, but the results have not been illuminating. It is true that several of the glands have been shown to be the site of lymphorrhages but these are so widespread in their occurrence in these cases that their presence can only be regarded as part of a general condition and not as the specific cause of morbid glandular function.

The frequent abnormalities in the thymus are interesting in this connection but their inconstancy is a bar to attaching too much importance to them. At the same time it is well to remember that experimental observations have led to the belief that the thymus has some excito-motor influence when injected into animals.

The fact that the thymus is mainly a lymphatic

structure and that lymphorrhages form a prominent feature of the morbid anatomy of the disease, will doubtless lead to further investigation of the lymphatic system in myasthenia, and in this direction lies our best hope of solving the problem of its pathogenesis.

I have stated above that I was unable to estimate the relation of lymphorrhages to the functional activity of a muscle, but on clinical and anatomical grounds it would seem quite likely that some such relation may exist. The probability that lymphorrhages are temporary phenomena and the fact that muscles are irregularly, variably and sometimes suddenly affected in the course of the disease, suggest that in addition to a general morbid process there may also be local factors influencing its incidence. While admitting this I do not feel inclined to support the view that lymphorrhages exert a deleterious influence on muscular activity by the mechanical effect of their presence or by blocking the local lymph flow. As I have said in a former paper I prefer to regard them as the outward and visible sign of some more subtle—metabolic or chemical—influence which is exerting itself upon the function and in extreme and rare instances, upon the actual structure of muscular and other tissues.

It is necessary to assume that the toxic agent is capable of exerting an influence on the function of other tissues besides muscle in order to account for the sensory, mental, vasomotor and secretory disorders occasionally met with in the disease, but it is impossible to say at the present time whether a disorder of any one of these functions is always associated with the anatomical presence of lymphorrhages in the tissues subserving that function. In this connection I can only point with diffidence to the occurrence of cellular exudations, resembling in their histological features lymphorrhages of other tissues, in the posterior root ganglia of Case 1, the only patient of my series in whom diminution of cutaneous sensibility of root distribution was observed during life.

As a result of my experience and in order to remedy the defects in my own investigation I would advocate more

attention being directed to the condition of the blood, the marrow, the lymphatic system, and last, but not least, to the fatty and connective tissues of the body in cases of this disease which come to *post-mortem* examination.

The conclusions to be drawn from this investigation may be briefly summarised thus :—

Clinical.

(1) That myasthenia gravis is a disease in which the symptoms are not always confined to the motor system, but may include others of sensory, mental or other origin.

Anatomical.

(2) That in all probability it has a definite and constant morbid anatomy constituted by the presence of widely distributed cellular, and sometimes serous, exudations (lymphorrhages) in the tissues and organs of the body.

(3) That slight muscle-fibre changes are frequent and severe muscular atrophy rare occurrences in the disease.

(4) That proliferative and degenerative changes in the thymus gland are frequently but not constantly met with.

Theoretical.

(5) That the symptoms of the disease are best explained by assuming the presence of some toxic, possibly autotoxic, agent which has a special influence on the protoplasmic constituent of voluntary muscle and a less specialised influence on the function of other tissues.

(6) That the relation of this toxin to the incidence of lymphorrhages and to thymic alterations is not clear.

REFERENCES.

- (1) BOTAZZI. *Archiv. of Anat. u. Physiolog.* 1901, S. 377.
- (2) BURR. *Journal of Nerv. and Mental Disease*, 1904, p. 28.
- (3) CAMPBELL & BRAMWELL. *BRAIN*, 1900, p. 277.
- (4) HUN. *Albany Medical Annals*, Jan., 1904, p. 28.
- (5) JOTZKO. *Compt. Rend. Soc. de Biologie*, 1899, p. 384.
- (6) „ *Journal de Neurolog.*, 1904, p. 221.
- (7) SENATOR. *Neurolog. Centralblatt*, 1892, S. 168.