urinary infection is reasonably common in the community, but few patients in the acute attack enter the practice of a hospital. Strict criteria of diagnosis can be established, using the facilities available in any clinical laboratory. Given these facilities, treatment can be standardized, and its short-term success or failure can be established. Finally, the long-term result will become apparent only after many years, during which the patient will have no symptoms that would make repeated visits to a hospital for follow-up seem reasonable; but his family doctor could check his blood-pressure and examine his urine without any particular disturbance.

REFERENCES

- Fairbrother, R. W. (1959). *A Text-book of Bacteriology*, 8th ed. Heinemann, London.
- Grollman, E. F., and Grollman, A. (1959). *J. clin. Invest.*, **38**, 749.
- Himsworth, H. P. (1949). *Lancet*, **1**, 465.
- James, U. (1959). *Lancet*, **2**, 1001.
- Merrill, J. P. (1955). *The Treatment of Renal Failure*. Grune and Stratton, New York.
- Oliver, J. (1950). *Amer. J. Med.*, **9**, 88.
- Parsons, F. M., and McCracken, B. H. (1959). *Brit. med. J.*, **1**, 740.
- Platt, R. (1952). *Ibid.*, **1**, 1313.
- (1959). *Lancet*, **1**, 159.
- Rosenheim, M. L., and Spencer, A. G. (1956). *Ibid.*, **2**, 313.
- Sarre, H. (1959). *Nierenkrankheiten*. Stuttgart.
- Stanbury, S. W. (1957). *Brit. med. Bull.*, **13**, 57.
- Stevenson, G. C., Jacobs, R. C., Ross, M. W., Collins, W. F., and Randt, C. T. (1959). *Amer. J. Physiol.*, **197**, 141.
- Winsbury-White, H. P. (1959). *Brit. med. J.*, **1**, 1001.

THE INNERVATION OF SKELETAL MUSCLE*

BY

RUTH E. M. BOWDEN, D.Sc., M.B., B.S.

Professor of Anatomy, Royal Free Hospital School of Medicine, London

[WITH SPECIAL PLATE]

Although our knowledge of the pattern of innervation of skeletal muscle and its functional significance is still incomplete, there is much that throws light on the problem of control of postural and so-called volitional movement. In this brief review attention will be confined to the nerve-supply of mammalian striated muscles and to the connexions that these neurones make in the central nervous system.

The Motor Unit

The smallest functional unit in a muscle is the motor unit, which consists of a single anterior horn cell, all its processes and all the muscle fibres supplied by it.^{1,2} It follows that the strength of contraction depends, in part, upon the size of these motor units as well as on the number brought into activity.³ Recent estimates of the average number of muscle fibres in human motor units range from 5–9 for extrinsic ocular muscles⁴ to 1,600–1,900 for one of the calf muscles.⁵ The endings of the motor nerves lose their myelin sheaths as they pierce the sarcolemma and break up into fine branches which rest in the shallow troughs that form the sub-neural apparatus.⁶ These troughs are lined by structures which are rich in cholinesterase,⁷ the enzyme that destroys acetylcholine, which is the chemical transmitter of the nerve impulse across the neuromuscular junction (Special Plate, Figs 1 and 2). The motor end-plates may be confined to a localized band or be scattered throughout the substance of a muscle. In some muscles

—for example, the extrinsic ocular and facial muscles—more than one motor ending can be seen on a single fibre; and these end-plates are sometimes supplied by nerve fibres which approach from different directions.^{8,9} Since motor nerve fibres not only branch in the main nerve trunks³ and muscles,¹⁰ but also may form intramuscular plexuses (Special Plate, Figs. 3 and 4), histological preparations of healthy muscles do not give reliable evidence about the parent neurones of the divergent fibres. For larger muscles in which the physical difficulty of examining long fibres throughout their length is increased, there is only scant reference to histological evidence of multiple endings on a single fibre, but electrophysiological experiments have shown that large motor nerve fibres may innervate individual muscle fibres at two or more places.^{11–13,17} These multiple endings may be derived from the branches of a single neurone or from several neurones. The muscle fibres of a unit may be in a compact bundle or they may be separated widely from each other and give rise to a diffuse motor unit.^{8,10,14–17}

Whatever the spatial arrangement of the motor units within the muscle belly, however, there is anatomical and physiological evidence that the motor nerve cells supplying individual muscles are grouped together in the brain-stem and spinal cord, where they form nuclei.^{18–26} Sharrard²³ reconstructed the lumbar and sacral segments to scale from serial sections of three normal spinal cords and of seven from patients who died at intervals ranging from three months to eight years after the onset of anterior poliomyelitis. The reconstructions took no account of the dendrites and axons, but gave the relationships between the bodies of the anterior horn cells. By correlating the histological and clinical observations it was possible to demonstrate the arrangement of the nuclei supplying individual muscles. These nuclei varied in size; some occupied several segments of the cord, while others were confined to a single segment, and functionally related nuclei were anatomically related to each other. Thus the nuclei supplying the tibialis anterior and posterior muscles were contiguous. Both these muscles invert the foot; the former dorsiflexes the ankle-joint and the latter plantar-flexes it.

The lower motor neurones which activate the motor units form the “final common pathway”²⁷ between the central nervous system and the muscles, and once they degenerate there is no longer any effector pathway between the central nervous system and the muscle fibres. Anterior horn cells have many dendrites which lie inside and outside the grey matter of the cord^{28,29} and these processes account for the greater part of the total surface area of the cells,³⁰ thus increasing the area for contact with the “end feet,” or *boutons terminaux*, of other neurones. It is through these *boutons* that neurones from other levels of the nervous system exert their influence on the lower motor neurone. It has been estimated that about 80% of the surface of an anterior horn cell is related to the *boutons*,³¹ at least 2,000 of which may rest on the surface of a single large cell in the cat.^{29,31,32} This does not necessarily mean that there are synaptic connexions with 2,000 other neurones, for the nerve terminals branch, and many of the *boutons* might be derived from one parent cell. The *boutons* vary in size, but even with electron microscopy it has not proved possible to distinguish

*A paper read to the Section of Anatomy and Physiology at the Annual Meeting of the British Medical Association, Birmingham, 1958.

between the excitatory and inhibitory endings that physiological evidence has shown to exist³²⁻³⁴

Conduction of Impulses

Muscles are not only activated and influenced by the central nervous system, but they are also a source of incoming sensory stimuli. In a so-called motor nerve, for example, supplying a limb or trunk muscle, at least 30-40% of the fibres are sensory in function and have their cell bodies in the dorsal root ganglia of the segmental nerves.¹⁻³ The diameter of these afferent fibres ranges from 1μ to 20μ ,^{3,35} and the spectrum of fibre sizes has three peaks—Group I ($12-20\mu$), Group II ($4-12\mu$), and Group III ($1-4\mu$).^{35,36} The rate of conduction of impulses varies from 1 to 125 metres per second; and the full extent of the range is stressed when the rate of conduction is given as about $2\frac{1}{2}$ miles (3.6 km.) per hour for fibres of the smallest diameter and 280 miles (450 km.) per hour for those of the largest diameter.

The endings of afferent fibres in muscle vary enormously in structure. The simplest are very fine, non-myelinated nerve fibres with no specific endings. Some run in perivascular plexuses (Special Plate, Fig. 5), others are found in connective tissue, and it has been suggested that these are pain fibres.^{37,38} More complex encapsulated Pacinian corpuscles (found also in skin and the mesentery) are described. These clearly are not specific to muscle; indeed, they are hard to find,^{37,39} but when found they are related to deep fascia, to aponeuroses, and to intramuscular vessels and nerves (Special Plate, Fig. 6); they are supplied by large, fast-conducting nerve fibres. In the mesentery they have been found to respond to mechanical stimuli,⁴⁰ but their function in muscles has yet to be analysed.

The third variety of sensory ending is presumably stimulated by contraction of single muscle fibres. Large-, medium-, and small-diameter nerve fibres form claw-like endings, spirals (Special Plate, Figs. 7, 8, 9), and basket-like networks round individual muscle fibres. These forms of sensory ending have been found in extrinsic ocular muscles⁴¹ and those of the face^{9,42} and larynx.⁴³

More is known about the fourth and fifth types of sensory end-organ, which constitute built-in automatic damping-down and alerting mechanisms in striated muscles.⁴⁴ Golgi tendon organs are inhibitory in function,^{45,46} and are arranged in series with the muscle fibres^{2,46} and are close to the insertions of the spindles which constitute the alerting mechanism.³⁷ In tendon organs the terminal branches of large, fast-conducting nerve fibres lie at the musculo-tendinous junctions, and the spray of endings constitutes either the whole or part of a sensory unit (Special Plate, Fig. 10). The size of these units and their relation to individual motor units are unknown at present. The frequency with which the tendon organs fire off impulses is a measure of the tension developed within the muscle either by active contraction or by passive stretch.⁴⁷ Through a reflex pathway in which there is an interposed connecting neurone these organs exert an inhibitory effect upon the anterior horn cells which innervate their own and functionally related muscles.^{45,48}

Muscle Spindles

The muscle spindles are encapsulated, vary in complexity, and have both motor and sensory nerves.^{1,37,49,50} In man they have been found in muscles

of the face, larynx, palate, and infrahyoid region, in extrinsic ocular muscles, in the tongue, in the muscles of trunk and limbs, and in the striated upper third of the oesophagus.^{41-43,51-54} So far they have not been found in muscles of the pharynx or the anal and urethral sphincters, which are still being investigated. They may occur singly or in groups,^{39,51,56} and in man are more numerous per unit volume of muscle in the intrinsic muscles of the hand and in muscles of the neck than in the large limb muscles.⁵² They are probably most plentiful in postural muscles, and nearly as numerous in flexors used for delicate movements.⁵⁶ Some indication of the density of the spindle population can be gained from the fact that 47 were found in the inferior rectus and as many as 71 in the superior oblique muscle in man.^{52,55} In the cat 45 spindles were found in the soleus, 57 in the gastrocnemius, and 58 in the tibialis anterior.³⁹

Spindles are fusiform and may even be visible to the naked eye—for example, a single spindle from the vastus medialis in a rabbit measured 3.6 mm.,³⁷ and in the intrinsic muscles of the human hand they ranged from 3 to 12 mm. in length.⁵³ The muscle fibres inside a spindle are known as the intrafusal fibres and are of two distinct sizes. It is suggested that the larger intrafusal fibres are of the fast twitch variety, and that the smaller ones, like red muscle fibres, are slow and tonic in their contractions⁵⁰ (Special Plate, Fig. 14). The largest extend from end to end of the spindle, and may pass right through one into another, forming tandem spindles⁵³; the narrowest fibres are inserted into the capsule.³⁷ The smallest spindles contain one fibre, but as many as twelve have been reported.⁵³ Intrafusal fibres differ from the extrafusal ones in several respects (Special Plate, Figs. 11 and 12): they are usually narrower in diameter, stain differently, are more faintly cross-striated, and have centrally placed nuclei, which, in the larger intrafusal fibres, become so numerous halfway along the length of a spindle that this equatorial region is also known as the "nuclear bag" (Special Plate, Fig. 13). In the nuclear bag the sarcoplasm is much paler and the cross-striation becomes so faint that

DESCRIPTION OF SPECIAL PLATE

FIG. 1.—Motor end-plates in gracilis of rhesus monkey. (Gold chloride stain.* $\times 250$.)

FIG. 2.—Subneural apparatus (marked by arrows) in diaphragm of rat. (Couteaux's modification of Koelle's stain. $\times 110$.)

FIG. 3.—Intramuscular plexus formed by trigeminal and facial nerves in facial muscle of rhesus monkey. (Gold chloride stain. $\times 63$.)

FIG. 4.—Intramuscular plexus in rabbit's interosseus muscle. Note scattered motor end-plates. (Gold chloride stain. $\times 68$.)

FIG. 5.—Perivascular plexus in rabbit's interosseus muscle. *a*=nerve trunk from which a fibre (*b*) enters the plexus. (Gold chloride stain. $\times 68$.)

FIG. 6.—Pacinian corpuscles (P.C.) related to neurovascular bundle in cat's interosseus muscle. *A*=an arteriole. (Gold chloride stain. $\times 30$.)

FIG. 7.—Transverse section of sensory endings (*a*) in medial rectus muscle of man. (Romanes's silver stain. $\times 200$.)

FIGS. 8 and 9.—Longitudinal section of spiral sensory endings in medial rectus muscle of man. (Romanes's silver stain. $\times 200$.)

FIG. 10.—Golgi tendon organ in cat's interosseus muscle. (Gold chloride stain. $\times 68$. Preparation by Miss B. Higgs, B.Sc.)

*For details of gold chloride stain see *J. Anat. (Lond.)*, 1956, 90, 217.

RUTH E. M. BOWDEN: INNERVATION OF SKELETAL MUSCLE

RUTH E. M. BOWDEN: INNERVATION OF SKELETAL MUSCLE

in some histological preparations it appears to be lost. In the narrowest fibres the nuclei form a chain in the equatorial region.⁵⁰

The capsule may consist of a single layer of connective tissue or of several layers (Special Plate, Figs. 14 and 15). It has been suggested that the more numerous the layers of the capsule the greater its protective function, but it is possible that this layering is a means of grading the response or of reducing the sensitivity of the sensory endings.⁵² Since the spindles lie in parallel with the muscle fibres, they are extended when the muscles lengthen and are relaxed when they shorten; but as the intrafusal fibres have a motor nerve supply their tension can be altered by contraction of the intrafusal fibres themselves.

Innervation of Muscle Spindles

The pattern of innervation of the spindles is still being studied, but certain facts are well established. There are several motor end-plates on each pole of an intrafusal fibre^{37 53} (Special Plate, Fig. 16), and the nerve fibres which supply them are slow-conducting (20–44 metres per second) gamma fibres of 3–8 μ in diameter.^{57 58} These arise from the small cells of the anterior horns of the cord, leave by the anterior roots of spinal nerves, and constitute about one-third of the total number of motor fibres destined for skeletal muscle.^{3 17} The small motor fibres branch and therefore form spindle motor units (Special Plate, Fig. 17). A single nerve fibre and its branches may supply each pole of one intrafusal fibre, and also may innervate other fibres of the same and different spindles.^{37 39} It is also known that the fibres of a single spindle may be innervated by more than one spinal segment.³⁹ One pole of a spindle may receive additional larger, and therefore more rapidly conducting, motor fibres^{37 47 53 56} (Special Plate, Fig. 19).

DESCRIPTION OF SPECIAL PLATE

FIG. 11.—Part of muscle spindle in cat's interosseus muscle. Note the narrower and more darkly staining intrafusal muscle fibres. M.F.=the fine motor nerve fibre supplying two motor end-plates on a single muscle fibre; S.E.=the sensory endings supplied by a thick nerve fibre. (Gold chloride stain. $\times 68$. Preparation by Miss B. Higgs, B.Sc.)

FIG. 12.—Longitudinal section of sartorius muscle of rhesus monkey, showing the polar region of a spindle with narrow, more palely staining muscle fibres. (Romanes's silver stain. $\times 100$.)

FIG. 13.—The nuclear bag or equatorial region (a) of the same spindle as Fig. 12. Note b, the thick sensory nerve fibre forming part of the annulo-spiral ending. ($\times 182$.)

FIG. 14.—Transverse section of medial rectus muscle (man). Note a, the single layer of the sheath of a muscle spindle with seven intrafusal fibres of large and small diameter. (Romanes's silver stain. $\times 200$.)

FIG. 15.—Transverse section of cat's soleus. Note layering of capsule (a) of spindle. (van Gieson's stain. $\times 152$.)

FIG. 16.—Multiple motor end-plates (marked by arrows) on intrafusal muscle fibres in rabbit's interosseus muscle. (Gold chloride stain. $\times 178$.)

FIG. 17.—Gamma motor fibre (3.8 μ) dividing at a in the spindle shown in Figs. 12 and 13. Four branches could be found by focusing up and down; only three show in the plane of the photograph. ($\times 200$.)

FIG. 18.—Elaborate annulo-spiral ending in large spindle in rabbit's tibialis anterior. (Gold chloride stain. $\times 173$.)

FIG. 19.—Spindle in rabbit's interosseus muscle. Note (a) simple annulo-spiral ending; (b) medium-sized motor fibre ending at c. (Gold chloride stain. $\times 100$.)

FIG. 20.—Part of a spindle in sartorius muscle of rhesus monkey. Note (a) an intramuscular nerve trunk supplying extrafusal motor end-plates (b) with medium-sized fibres and (c) the large-diameter fibres forming the annulo-spiral endings. (Gold chloride stain. $\times 200$.)

However, this is denied by some workers,⁵⁸ and the significance of the observation is obscure. Although the motor supply of both intrafusal and extrafusal fibres may run in the same intramuscular nerve trunk (Special Plate, Fig. 20), there is some doubt whether one axon ever supplies both types of muscle fibre.

The sensory fibres have their cells of origin in the dorsal root ganglia of the segmental nerves, and their peripheral endings are either at or near the equatorial region. The most elaborate annulo-spiral or primary endings are formed by the largest myelinated fibres (12–20 μ diameter), which are wound round the equator of the intrafusal fibres (Special Plate, Figs. 18 and 20). Other more diffuse flower-spray or secondary endings are formed by medium-sized fibres, and there may be one, two, or none in the spindle. When annulo-spiral and flower-spray endings are found together the latter lie to the side of the nuclear bag.^{37 50} Both types of ending are stimulated by deformation due to a change in the shape of the contractile intrafusal fibres.

A constant stream of impulses, of frequencies ranging from 10 to 60 per second, are transmitted by the γ motor fibres to the intrafusal fibres. These contract, and, while they add nothing to the tension of the muscle as a whole, they prime the sensory endings to fire off when a critical level of distortion is reached. When stimulated effectively the large fibres conduct impulses back to the spinal cord through the dorsal roots at rates ranging from 60 to 125 metres per second (216–450 km. or 135–280 miles per hour). The central processes of these nerves end directly on the anterior horn cells supplying their own and functionally related muscles. These sensory fibres constitute the afferent arc of the stretch reflex. There is the minimum synaptic delay, since there is no internuncial or connector neurone in this reflex pathway. By means of a branch working through an internuncial neurone these same afferent fibres inhibit the contraction of their antagonistic muscles.^{33 45 59} The activity of spindles is not only enhanced by activity within muscles, but also by impulses carried to the anterior horn cells from higher levels of the central nervous system.^{60–62} It is damped down or inhibited by the cut-out mechanism provided by the Golgi tendon organs⁴⁵ as well as by inhibitory impulses from other levels of the nervous system.^{61 62}

Sensory Supply of Trunk and Limb Muscles

The sensory supply of trunk and limb muscles provides the afferent arc of a spinal reflex pathway for the adjustment of the activity of the lower motor neurones. The precise afferent pathways for muscles supplied by cranial nerves are not yet known, but it is clear that these lower motor neurones in the brain-stem as well as those in the spinal cord are under the influence of higher levels of the nervous system. However, careful search has so far failed to demonstrate any afferent projection pathway from the muscles to the cerebral cortex. This, at first sight, is surprising in the light of the many movements which require delicate gradation of muscular activity. On the other hand, the capsules of joints have a rich sensory innervation, and a projection pathway from joints to cerebral cortex has been found in cats.^{63–65} Therefore, since the position of joints is signalled to the cortex, and this position, in any movement, is the result of muscular activity, there is, in effect, an indirect cortical representation of the muscles.

Grateful thanks are due to the National Foundation for Infantile Paralysis Inc.; to my colleague Dr. Charles

Downman for helpful criticism; to Mr. William Matthews for technical assistance; to Miss F. Ellis, Miss J. Cherry, and Messrs. J. M. Crane and V. Willmott for the photography; and to the Editor of the *Journal of Anatomy* for permission to use Fig. 20.

REFERENCES

- ¹ Sherrington, C. S., *J. Physiol. (Lond.)*, 1894, **17**, 211.
- ² Denny-Brown, D., *Proc. roy. Soc. B*, 1929, **104**, 252.
- ³ Eccles, J. C., and Sherrington, C. S., *ibid.*, 1930, **106**, 326.
- ⁴ Torre, M., *Schweiz. Arch. Neurol. Psychiat.*, 1953, **72**, 362.
- ⁵ Feinstein, B., Lindegård, B., Nyman, E., and Wohlfart, G., *Acta anat. (Basel)*, 1954, **23**, 127.
- ⁶ Couteaux, R., Thesis for Doctorate of University of Paris. Thérien Frères, Montreal, 1947.
- ⁷ Koelle, G. B., and Friedenwald, J. S., *Proc. Soc. exp. Biol. (N.Y.)*, 1949, **70**, 617.
- ⁸ Feindel, W., Hinshaw, J. R., and Weddell, G., *J. Anat. (Lond.)*, 1952, **86**, 35.
- ⁹ Bowden, R. E. M., and Mahran, Z. Y., *ibid.*, 1956, **90**, 217.
- ¹⁰ Cooper, S., *J. Physiol. (Lond.)*, 1929, **67**, 1.
- ¹¹ Agduhr, E., *Anat. Anz.*, 1919, **52**, 273.
- ¹² Jarcho, L. W., Eyzaguirre, C., Berman, B., and Lilienthal, J. L., *jun.*, *Amer. J. Physiol.*, 1952, **168**, 446.
- ¹³ Hunt, C. C., and Kuffler, S. W., *J. Physiol. (Lond.)*, 1954, **126**, 293.
- ¹⁴ Sherrington, C. S., *ibid.*, 1892, **13**, 621.
- ¹⁵ Adrian, E. D., *ibid.*, 1925, **60**, 301.
- ¹⁶ van Harreveld, A., *Arch. néerl. Physiol.*, 1948, **28**, 408.
- ¹⁷ Kuffler, S. W., Hunt, C. C., and Quilliam, J. P., *J. Neurophysiol.*, 1951, **14**, 29.
- ¹⁸ Romanes, G. J., *J. Anat. (Lond.)*, 1941, **75**, 145.
- ¹⁹ — *ibid.*, 1941, **76**, 112.
- ²⁰ — *ibid.*, 1942, **77**, 1.
- ²¹ — *ibid.*, 1945, **79**, 145.
- ²² — *J. comp. Neurol.*, 1951, **94**, 313.
- ²³ Sharrard, W. J. W., *J. Bone Jt Surg.*, 1955, **37B**, 540.
- ²⁴ Sprague, J. M., *Amer. J. Anat.*, 1948, **82**, 1.
- ²⁵ Walls, E. W., *Lancet*, 1940, **1**, 123.
- ²⁶ Warwick, R., *J. comp. Neurol.*, 1953, **98**, 449.
- ²⁷ Sherrington, C. S., *Report of the 74th Meeting of the British Association, Cambridge, 1904*, p. 728.
- ²⁸ Hoff, E. C., *Proc. roy. Soc. B*, 1932, **111**, 175.
- ²⁹ Barr, M. L., *J. Anat. (Lond.)*, 1939, **74**, 1.
- ³⁰ Aitken, J. T., *ibid.*, 1955, **89**, 571.
- ³¹ Wyckoff, R. W. G., and Young, J. Z., *Proc. roy. Soc. B*, 1956, **144**, 440.
- ³² Young, J. Z., *Progress in Neurobiology*, ed. J. A. Kappers, p. 81. Elsevier Publishing Co., Amsterdam, London, and New York, 1956.
- ³³ Lloyd, D. P. C., *J. Neurophysiol.*, 1946, **9**, 421.
- ³⁴ Eccles, J. C., *Harvey Lect.*, 1955-1956, **51**, 1.
- ³⁵ Lloyd, D. P. C., and Chang, H. T., *J. Neurophysiol.*, 1948, **11**, 199.
- ³⁶ Rexed, B., and Therman, P. O., *ibid.*, 1948, **11**, 133.
- ³⁷ Barker, D., *Quart. J. micr. Sci.*, 1948, **89**, 143.
- ³⁸ Hunt, C. C., *J. gen. Physiol.*, 1954, **38**, 117.
- ³⁹ Hagbarth, K. E., and Wohlfart, G., *Acta anat. (Basel)*, 1952, **15**, 85.
- ⁴⁰ Gray, J. A. B., and Malcolm, J. L., *Proc. roy. Soc. B*, 1950, **137**, 96.
- ⁴¹ Daniel, P., *J. Anat. (Lond.)*, 1946, **80**, 189.
- ⁴² Kadanoff, D., *Z. Mikr. anat. Forsch.*, 1956, **62**, 1.
- ⁴³ Lucas Keene, M. F., *J. Anat. (Lond.)*, 1957, **91**, 590; and personal communication.
- ⁴⁴ Liddell, E. G. T., *Proc. roy. Soc. Med.*, 1954, **47**, 600.
- ⁴⁵ Granit, R., *J. Neurophysiol.*, 1950, **13**, 351.
- ⁴⁶ Fulton, J. F., and Pi-Suñer, J., *Amer. J. Physiol.*, 1928, **83**, 554.
- ⁴⁷ Matthews, B. H. C., *J. Physiol. (Lond.)*, 1933, **78**, 1.
- ⁴⁸ Eccles, J. C., Fatt, P., and Landgren, S., *J. Neurophysiol.*, 1956, **19**, 75.
- ⁴⁹ Tower, S. S., *Brain*, 1932, **55**, 77.
- ⁵⁰ Boyd, I. A., *J. Physiol. (Lond.)*, 1958, **140**, 14 P.
- ⁵¹ Cooper, S., *ibid.*, 1953, **122**, 193.
- ⁵² — and Daniel, P. M., *Brain*, 1949, **72**, 1.
- ⁵³ — *J. Physiol. (Lond.)*, 1956, **133**, 1 P.
- ⁵⁴ Slawik, F. F., *Anat. Anz.*, 1942, **93**, 133.
- ⁵⁵ Merrillees, N. C. R., Sunderland, S., and Hayhow, W., *Anat. Rec.*, 1950, **108**, 23.
- ⁵⁶ Cooper, S., personal communication.
- ⁵⁷ Leksell, L., *Acta physiol. scand.*, 1945, **10**, Suppl. 31.
- ⁵⁸ Hunt, C. C., and Kuffler, S. W., *J. Physiol. (Lond.)*, 1951, **113**, 283.
- ⁵⁹ Eccles, J. C., Eccles, R. M., and Lundberg, A., *ibid.*, 1957, **137**, 22.
- ⁶⁰ Granit, R., Job, C., and Kaada, B. R., *Acta physiol. scand.*, 1953, **27**, 161.
- ⁶¹ Eldred, E., Granit, R., and Merton, P. A., *J. Physiol. (Lond.)*, 1953, **122**, 498.
- ⁶² Granit, R., and Kaada, B. R., *Acta physiol. scand.*, 1953, **27**, 130.
- ⁶³ Mountcastle, V. B., *J. Neurophysiol.*, 1957, **20**, 408.
- ⁶⁴ — Davies, P. W., and Berman, A. L., *ibid.*, 1957, **20**, 374.
- ⁶⁵ Boyd, I. A., *J. Physiol. (Lond.)*, 1954, **124**, 476.

METABOLIC AND ENDOCRINE ASPECTS OF DIABETIC NEPHROPATHY

BY

M. NAGY EL MAHALLAWY, M.D.

Assistant Professor of Medicine

MOHAMED SADEK SABOUR, M.D., M.R.C.P.Ed.*

Clinical Demonstrator of Medicine

LAILA MOHAMED OSMAN, D.Cl.Sc.

Resident in Clinical Laboratories

AND

SAMIR HANNA SADEK, D.Cl.Sc.

Clinical Demonstrator of Clinical Chemistry

From the Departments of General Medicine and Renal Clinic, and Clinical Pathology, Abbassia Faculty of Medicine, Ein-Shams University, Cairo, Egypt

In the past few years various metabolic and endocrine disturbances have been described in association with the specific vascular lesions of diabetes—namely, retinopathy and nephropathy. It is claimed that many of these disturbances have a pathogenic relationship with the development of the vascular complications.

Becker (1952) gave evidence of excessive adrenal cortical function in diabetics with retinopathy and Kimmelstiel-Wilson (K.W.) lesions. He noted an apparent relationship between the lipoid-laden vacuolated cells in the zona fasciculata of the adrenal cortex and the K.W. lesions in the kidney. A picture similar to early diabetic retinopathy and the K.W. lesion could be produced in alloxan-diabetic rabbits by the injection of corticotrophin or cortisone. Becker, Allen, *et al.* (1954), Becker, Maengwyn-Davies *et al.* (1954), and Maengwyn-Davies (1956) gave further evidence of excessive production of adrenal glucocorticoids in patients with diabetic retinopathy.

Becker *et al.* (1953) also reported a disturbance of vitamin B₁₂ metabolism in patients with diabetic retinopathy. Using the vitamin B₁₂ excretion test, they found that diabetics with retinopathy cannot retain the vitamin, while those with no retinopathy retain most of the given dose. However, Field *et al.* (1957) could not find a definite relationship between the development of degenerative complications of diabetes and the excretion patterns of the B vitamins.

A disturbed carbohydrate metabolism has been found in patients with clinically evident K.W. syndrome. Thus, Berkman *et al.* (1953, 1954), in a study of the serum polysaccharides in diabetics and non-diabetics, reported an increase in the total serum polysaccharides in diabetics with degenerative vascular complications, the highest level being observed in those with clinically evident nephropathy (Adlersberg *et al.*, 1956). It is not clear whether this increase is due to the renal impairment and is thus the result of the diabetic nephropathy, or whether it precedes the nephropathy and provokes the pathological lesions in the kidneys.

Mann *et al.* (1949) have noted hypercholesterolaemia in association with diabetic glomerulosclerosis. Later,

*Part of a thesis submitted by M. S. Sabour for the degree of Doctor in Medicine.