STUDIES ON AMEBOID MOTION AND SECRETION OF MOTOR END-PLATES

VII. Experimental Pathology of the Secretory Mechanism of Motor End-Plates in Thermal Shock *

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In reference to the shock of heat stroke, Moon [1] made the following statements (page 366): "The mechanism by which heat stroke causes circulatory death is not known, but many believe it to be through effects upon the central nervous system. Neither is it known whether disturbances in the central nervous system, either organic or functional, affect the circulation through the sympathetic system or through some other route. But it is evident that the same cycle [in the production of shock], whose effects have been seen in numerous other conditions, is operative here."

After years of study of the problem of shock, Cannon [2] clearly stated the unsolved problem of the onset of shock as follows (pages 140 and xi, respectively): "The mode of action of the initiating agent in secondary shock is thus left unsatisfactorily explained." "The reader should understand from the beginning that the mystery of the onset of shock has not been definitely cleared away despite a considerable increase in our knowledge of it, and that there still remains much work to be done before we shall have elucidated all the factors which play a rôle in its establishment." This is particularly true of the rôle of the pathologic motor end-plates in both primary and secondary shock. Cannon and his colleagues did not use morphologic methods in the study of shock. Moon and his associates did employ anatomic methods but did not study the changes in the motor end-plates.

The present study is an attempt to reveal, by the methods of experimental morphology, gold impregnation, and teasing of the innervation of muscle tissue, (1) the nature of the normal mechanism of secretion in motor end-plates of skeletal muscle; and (2) the rôle of this exaggerated secretion in the structural exhaustion of the motor end-plates and alteration of muscle structure and function in the pathologic mechanism of shock produced by heat.

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Materials and Methods

The preconception of the histologists, that there is a well defined and constant line of demarcation between nerve and muscle, determined the selection of histologic technics employed in the past in the study of the neuromuscular apparatus. The gold impregnation and teasing method had been replaced by some histologists for those in which silver and methylene blue were used. The granules of Kühne were poorly portrayed by silver and methylene blue but were clearly defined with gold. When there was variation in the intensity of impregnation of the axons and granules with the uncontrolled gold solutions, the method was discarded as unreliable. The fact that impregnation with gold and teasing whole mounts of muscle fibers revealed both the variations in the total morphologic structure and variations of intensity of impregnation of motor end-plates stamped this method as superior to any other. When normal and abnormal tissues were subjected simultaneously to the same solutions, the variations were clearly visualized and could be evaluated.

These changes in form and quantity of nervous substances were, therefore, intrinsic to the tissues and were not due to extrinsic variables in the gold technic. The apparent unreliability and real variations of results misled histologists, and resulted in their discarding a technic that contained the clue to the function of the motor end-plates. Technicians were hunting for a standardized result. The motor end-plates could not be standardized with a constant and fixed structural pattern any more than the cross striations of muscle could be arbitrarily classified with a fixed number of constant sarcomeres. The tissues may be overstained or understained with gold, but under controlled conditions this is avoided, or may be detected and evaluated.

The minute differences of structure and the variable affinity of the neuromuscular apparatus for gold used under the conditions in which comparisons were made, revealed these important facts about the motor end-plate: (1) The pleomorphism is due to ameboid motion; (2) The quantitative variation of granules is due to a secretory mechanism by which the terminal axons of the end-plate are attenuated or depleted by their direct transformation into granules discharged into the myoplasm of the muscle fiber. It was an error, therefore, to consider the junction of nerve and muscle as possessing a fixed structure when, in reality, the relationship was one of elusive continuity rather than that of a deceptive discontinuity. It was no less an error to discard the best method available because of variations of morphologic results, which portrayed the secretory mechanism of the motor end-plates.

The revelation of the gland-like nature of the structure of the motor end-plates is dependent upon the methods selected to demonstrate the polarity of the secretory mechanism of the neuromuscular apparatus. There are several methods commonly used for the microscopic study of the motor end-plates, *viz.*, the silver, the methylene blue, and the gold method. The authors of current histologic textbooks and manuals of technic claim that the gold method is uncertain and unreliable. There is considerable variation of opinion as to which method is most accurate. Experience counts for much in accuracy. The gold method may be easily mastered: our freshmen medical students use it with good effect as a routine laboratory procedure. Impregnation with silver and *intra vitam* staining with methylene blue do not visualize the granules of Kühne as well as does impregnation with gold chloride. Attempts to study the end-plates in living muscle are now in process in our laboratories. This is a difficult problem because of the similarity of the refractive index of living nerve endings and muscle. There appears to be a more specific affinity of the axoplasm and its discharged granules for gold than for any other substance used thus far in the staining or impregnation of the end-plates. *In vitro*, gold chloride forms a specific precipitate with both choline and acetylcholine.

Teasing is better than sectioning for the preservation of the polarity of the secretory mechanism of the motor end-plates. By the teasing method significant changes in the epilemmal axon, hypolemmal ramifications, granules of Kühne, and in the cross striations of muscle may be observed as a whole, simultaneously and in relationship one to another. This structural relationship may be photographed. This total anatomic relationship of nerve and muscle is obscured, if not destroyed, by sectioning the muscle. Gold impregnation and muscle teasing are old methods and therefore are discredited in the minds of a few investigators who possess inadequate experience with them. For the purposes of this study, nevertheless, these methods are superior to any other neurologic technic. The nuclei may be counterstained. The Bielschowsky [3] and Boeke [4] silver and sectioning methods are good for clear visualization of the nuclei and of the variable neurofibrils formed by the streamlining of protoplasmic flow in the axis cylinder. These methods were used as a check against the gold chloride method of impregnation and teasing of muscle. The Spielmeyer technic was used to detect demyelination of the peripheral innervation of muscle and staining with scharlach R for acute fatty degeneration of nerve fibers.

White rats (*Mus norvegicus*) were subjected to shock due to scalding by the method of Prinzmetal, Hechter, Margoles, and Feigen.[5] This method possessed the following features: the degree of trauma

was objectively controlled and reproducible; the method was simple and fast, so that a sufficient number of animals yielded results of statistical significance; finally, the shock-producing procedure resembled a type of trauma which produces shock in man.

The method consisted in immersing the entire body surface, except the head and neck, of either etherized or nonetherized rats, for definite periods of time in a water bath set at different water temperatures. The degree of trauma was a function of the duration of exposure and of the temperature of the bath.

Two hundred rats, average weight 200 gm., were subjected to immersion for 10 seconds at 75° C. The animals were not allowed access to food or water after immersion. At 30-minute intervals the gastrocnemius muscles were excised from 40 of the most prostrated animals, prepared by the gold chloride technic,[6] and teased. Preparations were stained for the study of the myelin sheaths of the epilemmal axons.

Fifty rats were subjected to a temperature of 90° C. The mean survival time was 75 seconds. After immersion 10 of the most prostrated animals were selected at 15-second intervals and their gastrocnemius muscles were excised. The muscles were immediately subjected to the gold technic.

At different time-intervals after the rats were immersed at 75° C. for 10 seconds the temperature of the skin decreased and hemoconcentration was evident, as well as dyspnea. Great muscular weakness and flaccid paralysis were present in later stages. Rats subjected to 90° C. for 10 seconds became spastic at once and exhibited extensor rigidity preceded by muscular twitchings. This pathologic functional response of immediate spasticity of the muscles was exhibited, likewise, by 20 rats immersed in water at 90° C. for 1 second. The temperature of the muscle of these animals varied from 37.8° to 42.4° C.

Twenty rats, average weight 200 gm., were used as controls. The gastrocnemius muscles were excised 15 minutes after the intraperitoneal injection of nembutal, 4 mg. per kg. These relatively normal control muscles were run through the same solutions concurrently for the same periods of time as those muscles excised from the scalded animals. The histologic variations of the motor end-plates are due, therefore, to factors intrinsic to the muscle, and not to uncontrolled accidental variations of technic extrinsic to the muscle. The simple and easily reproducible experiments under controlled conditions herein outlined may be used as classroom demonstrations of the secretory mechanism of the motor end-plates in skeletal muscle.

Since photographic evidence is the only acceptable means of over-

coming the current confusion about the true structure of the motor end-plates in shock, an apparent abundance of illustrations is presented. On the other hand, all that has been written on this subject for over a century has convinced no one. This photographic series constitutes objective evidence which any one may easily observe and as easily evaluate. Thus a permanent atlas is at hand to serve anyone as a point of departure for future experiments on the pleomorphism of the neuromuscular apparatus.

Small variations from the normal, standard intensity of the impregnation with gold may be attributed by some critics to faulty technic of overstaining or understaining and not to any irregularity in the quantity and structure of the chrysophilic axonic substances in the end-plate itself. Since normal and abnormal tissues were subjected concurrently to the same concentrations of solutions and for the same periods of time, these differences are due to variations in the quantity of the axonic substances in the motor end-plates themselves. These minute differences in the quantity of Kühne's granules, and variations in the form and structure of the hypolemmal axons of the motor end-plates, offer real footholds for scientific advance in the anatomy, physiology, and pathology of the neuromuscular apparatus.

Experimental Observations

I. The Pathologic Physiology of Muscle in Thermal Shock

There were variations not only in the time of onset but also in the type of the convulsions leading to muscular rigor in primary thermal shock. Certain animals had typical, severe, clonic spasms characterized by extensor rigidity. Some animals were thrown into a single, violent, tonic convulsion and remained in this condition. When rats were immersed for 1 second at 90° C., the convulsive movements frequently began with twitching and then vigorous shaking or shivering of the body. The typical clonic convulsion was followed by tetanic spasms of extensor rigidity of the entire body that preceded the death of the animal. Some animals experienced dyspnea and gasped for air during the time just prior to the clonic convulsion. Respirations were at first rapid, 150 to 200 per minute, and either gradually or suddenly became progressively slower until they reached 15 to 35 per minute.

The short time-exposures, by dipping the animals (except the head) for 1 to 10 seconds in water 75 to 90° C., were insufficient for the direct effect of heat to be transmitted to muscle by conduction. Some heat may have been transmitted through the blood stream. But when the skin was in contact with water at a temperature of 75° to 90° C., the

underlying gastrocnemius muscle in 24 animals had a temperature that varied from 37.8° to 42.4° C. The muscle rigor, therefore, was not the direct effect of heat on muscle producing heat rigor by protein coagulation. The clonic and tonic convulsions or cramps of the muscles were produced by reflex nervous action on the neuromuscular apparatus, arising from the initial sensory impulses generated by the caloric stimuli on the skin surface, reflected from the spinal cord through the motor innervation. The violent motor impulses transmitted to the neuromuscular apparatus were coincident in time with a massive transmission of axonic material into the end-plate and a torrential flow of the hypersecreted nervous substance away from the end-plate out into and between the muscle fibers. There was a corresponding and coincidental decrease in the diameters of the axons of the medullated branches of the sciatic nerve to the gastrocnemius muscle.

At autopsy the subcutaneous vessels were found enlarged, hyperemic, and densely packed with clumps of coagulated red blood cells. The intramuscular capillaries and venules, likewise, were enlarged in many places and in a condition of active hyperemia in those animals that were in thermal shock for 1 to 8 hours. Perivascular edema and packing of the minute vessels of the muscle with red blood cells were late manifestations of shock by heat. The muscles of those animals dissected within 10 to 30 seconds after the primary heat stimulus to the skin had the explosive pathologic changes in the motor end-plates, and not in the capillary bed of the muscles. The muscles in rigor produced by the reflex action of heat frequently did not respond to either direct or indirect mechanical or electric stimulation, but there was individual variation in the response. Many muscles in strong tonic contraction or tetanic spasm induced by the reflex action of heat did not manifest irritable retraction when transversely severed. Such muscles frequently had extensive axonorrhea or a discharge of the axonic nervous substance in the muscle. Many of the spastic muscle fibers were disorganized and in a condition of acute granular, hyaline, or Zenker's degeneration. During the late stages of thermal shock the muscles were frequently in a condition of flaccid paralysis. Such muscles had a dissolution of many of the motor end-plates and the nerve fibers terminating in them. There was a loss of the gold-staining substance in the motor end-plates that extended progressively in a centripetal direction in the epilemmal axons. This resulted in a local loss of many motor innervations of muscle fibers at the peripheral myoneural junction, and flaccid paralysis or muscle weakness. There was good correlation between abnormal structure and function of the neuromuscular appara-

tus. In the early stages of spastic palsy reflexly induced by heat, there was extensive secretion of nervous substance manifested by the gold-staining axonic material discharged into the muscle. In the later stages of thermal shock the animals were frequently in a condition of flaccid palsy. Many muscles from such animals had a structural loss of innervation at the junction between nerve and muscle. The pathologic function manifested by the skeletal muscle, therefore, was highly variable and was dependent upon the strength and duration of the stimulus, upon the time interval after onset of the stimulus, and upon the individual resistance of the animals to thermal shock.

Muscles reflexly manifesting a state of tonic spasm, rigor, or cramp due to the application of heat superficially applied to the end-organs of sensory nerves in the skin, presented two important problems: (1) Was the tonic spasm of muscle, induced by the nervous reflex to heat applied to the skin, caused solely by the transmission of immaterial trains of waves of electric energy constituting the nervous impulse to muscle? If so, morphologic methods are impotent to answer this question except by indirect evidence detected in alterations of the structure of the cross striations.[7] (2) Was the tonic spasm of muscle, induced by the nervous reflex to heat applied to the skin, associated in time with the transmission of a real material substance from nerve to muscle? If so, then morphologic methods are competent to reveal histologically this nervous substance discharged from nerve endings into muscle. The morphologic evidence herein presented demonstrates conclusively that there is a substantial transfer of nervous material from the nerve ending to muscle associated with functional activity.

The gross manifestations following shock produced by heat were comparable to those previously described for the viscera. The blood vessels of the gastrointestinal tract were pale, collapsed, and bloodless. The liver had blood vessels packed with red blood cells. Upon sectioning the liver, there was little or no bleeding. The spleen was retracted and failed to bleed upon sectioning, soon after trauma by heat. The kidneys and lungs had active hyperemia and vessels packed with red blood cells. These vascular changes became prominent during the late stages. Muscles were more red than normal ones and they were more friable and softer to teasing. The accumulation of metabolites evidently changed the consistency and elasticity of the fibers. Some paralyzed muscles failed to respond to transection of the spinal cord within 60 seconds after thermal trauma, as well as to direct mechanical cutting, and to direct and indirect stimulation by the galvanic and faradic currents. The rectus abdominis muscle demonstrated well the reflex

stimulation due to thermal shock to the skin by increased visibility of its contours: the lineae alba, semilunaris, and inscriptiones.

There was manifested the so-called bloody tears or chromodachryorrhea in 10 per cent of the rats at various time-intervals after immersion at 75° C. for 10 seconds. This biologic response has been considered the effect of increased amounts of acetylcholine or dacryorrhetin in the circulating blood stream.

II. The Pleomorphism of the Normal Motor End-Plates Compared with that Produced by Magnesium Sulfate and Strychnine

At the entrance of the axis cylinder of the medullated nerve fiber into the muscle fiber, the sheath of Schwann joins with the sarcolemma and the nerve loses its medullary sheath, but the axis cylinder passes into the muscle. The axon, upon entering the muscle fiber, divides dichotomously into a number of ramifications. The nerve plates (*terminaisons en plaque*) have two parts: (1) the ramifications of the axis cylinder, and (2) the variable amount of finely granular substance or sole plate of Kühne. This granular sole is abundant in the dark, retracted endings and is diminished in amount or completely depleted in the light, expanded plates. The axons of the terminal plate divide into many branches resulting in a variety of shapes. There are irregular dilatations and constrictions of the branches, like a string of beads. In the plate-like endings these ramifications are immediately under the sarcolemma. The granular sole is or is not in immediate continuity with the axonic divisions. The nuclei were divided by Ranvier [8] into three groups: (1) nuclei of the granular substance (*noyaux fondamentaux*); (2) nuclei belonging to the ramifications of the nerve (*noyaux de l'arborisation*); and (3) nuclei of the sheath of Schwann covering the terminal axons (*noyaux vaginaux*). It was impossible by morphologic criteria or differential staining to determine whether these nuclei are muscular or nervous in origin. The presumptive evidence was strong that the nuclei of the sole of Kühne were clusters of nuclei of the muscle fiber.

Where the epilemmal axon becomes continuous with the terminal plate-like expansion it divides and extends with further ramification, and thereby greatly increases its secretory surface area. The granular sole of Kühne is formed by the secretion granules of the discharging tips of the divisions of the axon. There is a direct transformation of the terminal axons in muscle into the granular sole of Kühne. The granules are poured out by the axons in arborescent arrangement and become incorporated into the myoplasm of the muscle fiber. Before

1874, Frey [9] (p. 323) made the following pertinent remarks, which have been ignored in recent times: "Now, if, as would appear to be the case, the distribution of the nerve fibre be confined to the immediate mass of the terminal plate, the extremities of the muscle fibre must remain without nervous supply, in that the former is set into the latter at about its middle. But the fleshy matter manifests contractility at the extremities also!"

The intramuscular axons, by progressive diffusion of the secreted granules, become merged throughout the fleshy mass of the muscle fiber. There is, therefore, a real anatomic blending of nerve and muscle by the periodic discharge of nervous material into the myoplasm. By the secretory mechanism of the motor end-plates there is anatomic and chemical continuity, and not discontinuity, as now taught, between nerve and muscle. There is a real, substantial fusion of nerve and muscle through the products of secretion of the nerve endings into muscle. There is, therefore, no constant line of demarcation between nerve and muscle. A search for it is like an attempt to discover a constant location where fresh water ends and salt water begins in the confluence between the Columbia River and the Pacific Ocean. This change depends upon many conditions, *viz.*, rate and quantity of flow, tide, and rate of diffusion.

The concept of Jordan and Speidel [10] that muscle has a structure composed of static membranes called sarcomeres, fixed in number, was an old one which had befuddled investigators of muscle structure for over a century. The changeable form of both motor end-plates and related cross striations invalidated any concept of constancy of structure, or fixation in number, of sarcomeres. The structure of the neuromuscular apparatus was highly variable corresponding to the periodic discharges of nervous substances into muscle. With each discharge the nervous substances blended with the myoplasm and there were concomitant changes of muscle structure as well as of the motor end-plates. The periodic discharges of nervous substances into muscle constituted one factor that determined the variation of internal structure of muscle.

Cannon [11] asked what standard we used to control our experiments in order to evaluate the normal from the pathologic changes in the motor end-plates. This was a pertinent question for the reason that characteristic changes were obtained by different local and general anesthetic agents, states of nutrition, and mechanical means employed prior to excising the muscle for microscopic study. The so-called normal had wide limits of variation. The motor end-plates quickly dis-

appeared during rigor mortis. Because of the normal sensitivity and pleomorphism of the motor end-plates, the problem was comparable to the study of the various complex forms of the waves that compose breakers along a diversified coastline. In this study we designated as standard or relatively normal (Figs. 1, 6, 23, 24, 25, and 27 to 32) those variations of form observed in the neuromuscular apparatus from muscles excised 15 minutes after the intraperitoneal injection of nembutal, 4 mg. per kg.

The relatively normal trees (Figs. 1 and 6) of motor end-plates have 10 to 20 per cent of the motor end-plates in a state of retraction and 80 to 90 per cent in a state of expansion in a differential count of 5,000 motor nerve endings, in 20 gastrocnemius muscles excised from 10 rats. The normal retracted endings surrounded by the granular sole varied from 20 to 40 μ in length. The expanded end-plates with a decreased quantity of the granular sole varied from 40 to 70 μ in length.

The cross striations were finer, closer together, and increased in number in relation to the expanded rather than to the retracted motor end-plates. If the motor end-plates did not influence the cross striations of muscle (and these cross striations are constant structures according to Jordan's [12] "sine qua non" for identification) the following questions are pertinent:

1. If the sarcomeres are constant in number in relation to each motor end-plate and in each muscle fiber, why do the expanded plates have finer striations, and more of the closely spaced striations, than are related to the retracted end-plates?

2. If the sarcomeres are constant in number in relation to each motor end-plate, would one not expect the striations to be spread farther apart in relation to the expanded plates and to lie closer together in relation to the retracted plates? The reverse relationship, however, was found.

3. If the sarcomeres are constant in number in a muscle fiber, how are they maintained when the discharge of nerve substance in muscle blends with the myoplasm?

4. Why are the cross striations frequently absent in relation to some motor end-plates?

There was, therefore, sufficient reason for the inclusion of those changes of end-plates excised from muscles in a state of flaccid paralysis 2 hours after the intraperitoneal injection of magnesium sulfate (Fig. 4), 2 gm. per kg. The retracted end-plates composed 25 to 35 per cent of the total of 5,000 end-plates counted in 20 gastrocnemius muscles from 10 animals. This proportion of retracted motor end-

plates (Fig. 4) was in contrast to that (Fig. 5) of expanded end-plates in the rigorous gastrocnemius muscle excised during an initial convulsion 10 minutes after the intraperitoneal injection of 0.5 cc. of 1:1000 strychnine sulfate. The expanded end-plates, with a diminution or complete depletion of the granular sole of Kühne, composed 95 to 98 per cent of 5,000 end-plates counted in 20 gastrocnemius muscles from 10 animals. There were numerous pseudopod-like, elongated branches in the motor end-plates during the early stage of expansion caused by strychnine.

This neoformative influence upon the ramifications and increase of surface area by ameboid expansion of the motor end-plates favored the secretory discharge of a fine spray of neuronic granules into muscle during the early period following strychnine stimulation. The chemical effect of strychnine stimulation had a morphologic expression in the structural changes of the motor end-plates and cross striations in the skeletal muscle fibers. The clear-cut photographic evidence of pleomorphism of the neuromuscular apparatus after nembutal, magnesium sulfate, or strychnine sulfate served as relatively normal and abnormal variations of changes of structure and as a base line of reference for evaluating the deviations produced by thermal shock.

The dark, anisotropic cross striations were coarser, and were separated by wider, light, isotropic bands in the flaccid muscle (Fig. 4) excised 2 hours after the injection of magnesium sulfate, than were those after the use of strychnine (Fig. 5). The latter were finer and more closely spaced than the former. This change of pattern was not due to the simple mechanical approximation and remotion of a constant number of sarcomeres in a "shuttle-like shift," like the opening and closing of the constant folds of an accordion. These changes in the cross striations were the structural expressions of changes in mechanical energy and chemical composition and concentration which are part of the ceaseless reactions of metabolism that underlie the variable tonicity, heat production, and mechanical activity of the muscular furnaces and internal combustion engines of motion of the living organism.

III. The Histopathology of the Neuromuscular Apparatus in Thermal Shock

1. *Achrysophilia and Hypochrysophilia of Motor End-Plates.* Muscles excised from rats 2 hours or more after immersion in water, except the head and neck, 75° C. for 10 seconds, had the majority of the motor end-plates (3,765 of 5,000 counted) completely liquefied (Figs.

3, 49, 68, 69, 70, 72, and 74). This final result leading to explosive disappearance of the motor endings was likewise related in many places (Figs. 68 to 70, and 74) to an acute granular degeneration and hyalinization of the cross striations of the muscle fiber. These changes of the hypolemmal axons of the motor end-plates were likewise accompanied by different degrees of depletion ending in complete exhaustion (Fig. 74), achrysophilia, and hypochrysophilia, of the substance with an affinity for gold in the epilemmal axons.

The liquefaction of the motor endings resulted in structural loss of innervation at the neural junction. Progressive hypochrysophilia to achrysophilia were those final conditions of exhaustion in which the axonic materials of the motor end-plate were discharged and dispersed in the myoplasm.

In some locations (Figs. 68 to 70), where the motor end-plates had disappeared, the clusters of dark, rounded, pyknotic nuclei, 6 to 15 in number, were clearly revealed by counterstaining with hemalum after gold impregnation. These nuclei of the depleted sole of Kühne appeared to belong to the myoplasm. They frequently were made visible without a counterstain when lactic acid was injected locally in the muscle. Lactic acid caused a rapid disappearance of the motor end-plates and paralysis due to the peripheral local loss of innervation in the muscle.

2. *Hyperchrysophilia of the Motor End-Plates.* The first morphologic result of heat applied to the skin was reflexly produced by an augmentation and overflow of the quantity of substance in the motor end-plates which had an affinity for gold (Figs. 2, 7, and 50 to 62). This increased blackening of the motor end-plates was not due to overstaining. The normal and abnormal muscles were run through the same technical procedures at the same time. This increased affinity of the end-plates for gold, due to the transmission of increased amounts of substances from the epilemmal into the hypolemmal axons, was accompanied by variations in the structure of the axons proximad to the plate. There were variations in the size of the swellings and constrictions in the moniliform patterns of the epilemmal axons. The changes in structure observed were compatible with increased conduction distally of nerve substances into the terminal axons of the motor end-plates.

3. *Axonorrhea of the Motor End-Plates.* The second result of the reflex activity of heat applied to the skin was an abnormal discharge and projection (Figs. 8 to 22, and 50 to 67) of the nervous axonic substances into the myoplasm of the muscle fiber.

The best time to observe this short-lived phase in the secretory cycle

of the motor end-plates was within 10 to 30 seconds after the rat was immersed in water, except the head and neck, for 1 to 10 seconds at 90° C. The gastrocnemius muscle was in a reflex state of spasm or rigor and had a muscle temperature of 37.8° to 42.4° C. The initial effect of heat applied to the skin for short durations on the form of the motor end-plates was via the nervous reflex arc and not by direct conduction from skin to muscle. The muscle was excised immediately and processed at once for gold impregnation. This period in motor end-plate discharge was both tenuous and ephemeral. The quantity of discharge was more copious after reflex action due to heat stimulation (Figs. 2, 7, and 50 to 62) of sensory nerves in the skin, however, than it was in the normal (Figs. 1, 6, 23, 24, 25, 27 to 38, 71 and 73) controls.

This discharged axonic material in the muscle fiber was either densely opaque with gold impregnation or cross-striated. Its cross striations were or were not in alignment with those of the muscle fiber. There were various stages in the projection, diffusion, and dissolution of the neuronic substances secreted into the myoplasm of the muscle fiber. The cross striations of the muscle offered no obstacle to the projection and diffusion of the axonic substances discharged from the motor end-plates. These cross striations, therefore, were not rigid membranes or hard and fast partitions. The easy projection of axonic substances and streamlining of the cross striations were morphologic evidences that render untenable the theory that the muscle fiber is divided into a constant number of compartments or sarcomeres by rigid partitions. There was good correlation of abnormal muscle structure and function by the morphologic presence of the nervous discharge of inclusion masses of Kühne's granules into the myoplasm and the spasm of muscle reflexly induced by heat.

The discharged nervous secretion into the myoplasm had an increased affinity (hyperchrysophilia) for gold and was in continuous relationship with the motor end-plate or projected as discrete masses throughout the muscle fiber. The arrangement of the discharged secretion in juxtaposition to the motor end-plate was unipolar (Figs. 50 to 55), bipolar (Figs. 58 and 59), or multipolar (Figs. 8, 10, 61, and 62). The form of the nervous substance secreted into the myoplasm was likewise variable, namely: (1) as discrete granules (Figs. 12 and 63); (2) as vacuoles (Fig. 64); (3) as short or long fusiform and irregular masses (Figs. 65 to 67); and (4) as short or long, Indian-club or arrow-shaped projections (Figs. 10 and 11). The axonic masses projected away from the nerve terminal were usually within the myoplasm but some were found external to the sarcolemma of the muscle

fiber. In such conditions the motor end-plates were missing and the epilemmal axons terminated external to the sarcolemma of the muscle fiber.

The axonic material descended from the epilemmal axons into the hypolemmal axons and discharged between and away from the branches of the end-plate. This discharged secretion formed either a small (Fig. 40) or a large hub (Fig. 41) in the end-plate. This central mass of Kühne's granules formed, at times, a ring with a thick rim (Fig. 42) from which the mass or masses of discharged nervous substance extended into the myoplasm. The hypolemmal axons of the motor end-plate became attenuated as they were transformed into the granules of Kühne (Figs. 44, 47, and 48). This transformation of axons into granules was well advanced in some places (Figs. 48 and 49). The periodic internal structure of the muscle was replaced by a diffuse arrangement of granules (Fig. 49).

These masses of discharged nervous secretion into the muscle underwent progressive decrease in size and incorporation into the colloidal substance of the myoplasm of the muscle fiber. It was clearly evident, therefore, that there was no fixed boundary or line of demarcation between the junction of nerve and muscle. The substantial secretion from the motor nerve ending became incorporated into the explosive mixture that forms the active muscle.

There were many examples of so-called ultraterminal branches (Figs. 18 to 22) of the motor end-plates in the very early periods after shock due to scalding. The term "ultraterminal" was applied to an unmyelinated branch which arises from the ramifications of the axonic terminals of the motor end-plates. These ultraterminal branches terminated in rudimentary swellings in the same or in neighboring muscle fibers. Both types of terminals have been observed. They were the product of overstimulation due to multiple causes. They were frequently found in the very early stages of primary shock due to scalding of the skin of rats. They represented an early stage in the explosive projection of axonic secretory material from the motor end-plates due to reflex overstimulation. They were found under various conditions of anoxia. At another instant of time the projected material became disconnected from its point of origin in the axonic branches of the motor end-plates. These projected secretory masses of axonic material then became discrete bodies of inclusions in the myoplasm of the muscle fiber. This stage of axonic inclusion masses in muscle was a very temporary one. The nervous material discharged into muscle soon underwent dissolution. The accumulation of acids and other metabo-

lites in muscle due to overstimulation and anoxia causes a delay in the the dissolution of acetylcholine deposited physiologically at the synapses, according to Gesell and co-workers.[13]

The end-plates showing these sequences of changes of their hypolemmal axons following the reflex activity of scalding the skin—(1) hyperchrysophilia, (2) axonorrhea, (3) hypochrysophilia, (4) achrysophilia, and (5) centripetal degeneration or depletion of the epilemmal axons—were intermingled with relatively normal end-plates. Large quantities of muscle tissue were teased in order to reveal the relative proportion of the pathologic changes of the end-plates. Certain axons of a motor tree manifested excessive pathologic changes; others remained relatively normal in the same or neighboring trees of innervation.

4. *The Centripetal Depletion of the Epilemmal Axons.* The gastrocnemius muscle (Fig. 74) was excised 2 hours after the entire body of the rat, except the head and neck, had been immersed for 10 seconds in water at 75° C. There was complete disappearance of the motor end-plates (achrysophilia) and diminution of the capacity of the granular epilemmal axons for gold impregnation (hypochrysophilia). The depletion of these axons extended in a centripetal direction and away from the site of the granules that occupied the previous site of the motor end-plates. Thermal shock, therefore, produced a structural exhaustion of both the epilemmal axons, that extended proximally for variable distances, and hypolemmal axons of the motor end-plates.

5. *The Pathologic Changes in the Muscle Fibers.* The time of appearance of spastic and flaccid paralysis depended upon individual resistance of the rats, upon the temperature of the water, and duration of immersion. The time interval after traumatic scalding was likewise a factor in the degree of intensity of pathologic changes in the muscle fibers. During the early period after scalding the cross striations in many places were replaced diffusely by granules (Figs. 49 and 74) arranged especially in close relationship to the motor end-plates. The muscles, whose irritability was reduced or lost, had Zenker's waxy degeneration localized in some fibers. There was increased visibility of pyknotic nuclei in certain muscle fibers. There was a loss of the differential types of fibers in the majority of the muscles examined microscopically. There was little alteration of the intramuscular capillaries during the very early periods, 10 to 60 seconds after scalding. These capillaries were dilated and packed with clumps of red blood cells in many places within the muscles 2 hours after the heat stimulus (75° C. for 10 seconds) was applied to the skin. During the early stages the lesions of the muscles were dominant in the neuromuscular apparatus.

During the late stage hyperemia, perivascular edema, and leukocytic infiltration were prominent findings.

By counterstaining with hemalum there were found clusters of dark, pyknotic, rounded nuclei, 6 to 15 (Figs. 68 to 70) in number, that were related to the sole plate. These nuclei appeared to be modified muscle nuclei. Within the cluster of nuclei of the depleted motor end-plates there was granulation, in some places, of the cross striations of the muscle fiber. These morphologic changes were comparable to those produced by the injection of lactic acid locally in the zone of innervation of the muscle. The epilemmal axons frequently ended in bulbous expansions (Figs. 68 to 70) and had complete depletion of their motor end-plates. The function of these sole plate nuclei is under investigation.

Discussion

The prevailing static concept of the relation of the motor end-plate to the striped muscle fiber is one of a mechanical penetration and crude apposition, of discreteness and separateness of two vitally united structures. This may be one effect of the cell theory based upon the concept that the muscle cell and nervous cell are completely discrete structures in all of their parts. The dynamic interrelationship of muscle and nerve is an acceptable point of view to account for the periodic discharge of nervous substances into muscle. This results in a blending of the neuromyoplasm in a functional dynamic unit.

The initial mixture of nerve and muscle working-substances quickly forms a compound of complex colloidal neuromyoplasm. The nervous discharge may be a fine spray or a flood of secreted substances. A complex explosive mixture of the nerve and muscle substances, like a mixture of mercury fulminate and black powder, becomes thoroughly commingled until the nerve substance is nondetectable as such in the neuromyoplasm. The periodic mild and strong chemical reactions produced by the explosive mixture in an elongated capillary strand of nerve and muscle substances, confined in one fiber, are reflected in either regular and ordered cross striations or irregular and completely disordered arrangements of the internal structure of the cross striations.

The cross striations of living, nerve-intact muscle, therefore, are the mechanical products and structural expressions of capillary chemism enclosed in an elongated capillary system of neuromyoplasm. During life there is a ceaseless replacement of one system of cross striations by another. There are variations of amplitude and of combinations of one system of periodic bands with another. There may be mathematical additions and subtractions of constructive and destructive interfer-

ences, respectively, of these various systems of longitudinal pressure waves, which are expressed in the variable internal structure of skeletal muscle. Any concept that attempts to simplify the internal structure of muscle, for descriptive purposes, by postulating constancy of sarcomeres and alphabetical symbols, does not conform to easily reproducible facts obtained by experimental morphology. This static concept of structure has hindered the correlation of the anatomy and physiology of nerve and muscle for over a century.

The cross striations are the structural expression of periodic pressure waves composed of alternate zones of condensation and rarefaction that accompany the periodic explosive chemical changes in the capillary skeletal muscle fiber. This fiber, therefore, is dual in nature: (1) Its chemical composition undergoes reversible and irreversible quantitative and qualitative changes that are periodic or aperiodic; and (2) the chemical reactions confined in capillary spaces are accompanied by the physical explosive energy of internal compression waves. These align the protoplasmic colloidal mixture of the skeletal neuromuscular fiber into longitudinal waves of alternate zones of compression and rarefaction. This spectrum of internal compression may be used to estimate both the intensity and speed of chemical reactions and of the physical internal pressure which is synchronous with the explosive chemical reaction. The revelation of the secret of the transformation of the chemical energy of muscle into mechanical work lies in the field of morphology correlated with that of chemistry, physiology, and pathology. The attached myoneural capillary fiber gives direction to the explosive action of the muscle protoplasm roughly analogous to the direction given by the gun barrel to the explosive action of its gun powder, but the gun barrel, the skeletal muscle fiber, is closed at both ends.

Thermal shock produces pyknotic changes of the nuclei of the granular sole of Kühne. The functions of these nuclei are unknown. Do they contribute to the synthesis of the hypothetical transmitter substance—acetylcholine? Do they aid in the manufacture of choline esterase? The combined methods of morphology and that used by Stoerk and Morpeth [14] in the estimation of choline esterase activity in skeletal muscle may aid in finding the answers to these questions.

The so-called bloody tears or chromodacryorrhea was considered by Tashiro and Stix [15] as the biologic effect of acetylcholine or dacryorrhetin. Dacryorrhetin was found in an extract of muscle and considered a product of muscle metabolism. There appeared to be a correlation between the abnormal changes in the harderian glands of the lacrymal

apparatus and those of the neuromuscular apparatus in thermal shock in the rats. Additional experimental work was suggested by this interrelationship.

From a very early period, the nature of the terminals of nerve in striped muscle has occupied the attention of anatomists and physiologists. Before the use of the microscope, conjecture alone was possible. It was supposed that the terminal twigs of a nerve broke up into finer and finer branches which became finally fused with the muscle. The nerve fiber was considered a conduit for the transmission of a vital spirit which in some manner was delivered to the organ activated by nerves.

That the nerve fuses and commingles with muscle by the discharge of some ephemeral and tenuous substance through the secretory mechanism of the motor end-plates is nearer the truth than anatomists have realized since the introduction of the microscope. The termination of nerve in muscle is one of a fusion, a commingling of their respective substances and not one of cellular separation by partitions, like watertight compartments. There is thus established a morphologic and functional continuity and dynamic unity of the organization of nerve and muscle.

The intact living muscle fiber with its blood supply and attachments should be looked upon as a morphologic and functional whole composed of neuromyoplasm. This applies to both red and white muscle fibers. This unit may have periodic changes in its internal structure of longitudinal and cross striations corresponding to changes of function and nutrition. The inconstant longitudinal striations are evanescent mechanical products of streamlining produced by metabolism and the mechanical tension and pressure due to changes of function and nutrition. The specious division of the muscle fiber into stable contractile myofibrils and constant, intermediate, nutritional sarcoplasm does not conform to the facts. Some muscle fibers have well defined longitudinal striations and granular sarcoplasm; other neighboring fibers in the same muscle do not possess longitudinal myofibrils. These morphologic differences are correlated with different levels of metabolism and functional activity. One type readily transforms into the other, but both stages perform their tonic, thermal, and contractile functions. The muscle fiber is activated as a whole throughout its neuromyoplasm. No adequate evidence has been presented to support the assumption that the ephemeral, longitudinal myofibrils of the muscle fiber are the only structures capable of contraction in the

muscle fiber. The neuromyoplasm of the skeletal muscle fiber, with or without a sarcolemma, functions as a whole; it may or may not be cross striated; it may or may not be longitudinally striated into ephemeral myofibrils.

The histologic characteristics of the dorsal deep component of the sternocleidomastoid muscle in the rat are those of a specific red muscle fiber. Its fibers are smaller in diameter on the average and more granular than the easily separated, ventral, superficial part of the muscle. The inclusion of pigmented granules of myohemoglobin evidently acts as a storage of oxygen for the intrinsic respiration and metabolism of the deep part of the muscle.

The red pigment of hemoglobin compounds is found in the larval blood-worms inhabiting the warm springs of the Yellowstone National Park. Brues [16] and Leitch [17] have studied experimentally the rôle of hemoglobin in the larval blood-worms of the dipteric insect, Chironomus. They came to the conclusion that the function of hemoglobin in the blood-worm and snail in thermal springs consists in making available, by the power of binding oxygen chemically, a quantity of oxygen sufficient for the needs of the animal at oxygen tensions so low that the necessary amount is not supplied by physical solution. There is a dearth of dissolved oxygen in thermal waters which renders respiration difficult for purely aquatic animals. Hemoglobin is characteristic of many mud-inhabiting invertebrates that live where oxygen is present in only very small amounts. The larvae of Chironomus, by the presence of hemoglobin, are thus able to live under relatively anaërobic conditions and, furthermore, an increased alkalinity serves in some way to increase the resistance of these animals, according to Packard,[18] to a lack of oxygen.

The presence of a muscle pigment of hemoglobin would give a local supply of oxygen within the muscle where there was a decrease of the availability of oxygen. Whether or not white muscle could be transformed into red muscle by elevations in temperature, much as Huggins and co-workers [19] have found that increase of temperature transforms yellow into red bone marrow, is a problem under investigation. Each red or white muscle fiber, respectively, functions as a unit and is composed of the chemical fusion of nerve and muscle substances to form the neuromyoplasm. The structural changes in both types of muscle fibers are correlated with different levels of functional activity. There are, however, physiologic differences between red and white muscle fibers that have not been completely correlated with structure.

Summary

1. Whole-mount specimens of the gastrocnemius muscle and the motor end-plates from 250 rats subjected to thermal shock produced by water immersion (except the head and neck) at 75° to 90° C. for 1 to 10 seconds; were studied by the gold and teasing method; the gastrocnemius muscles were excised from 20 rats 15 minutes after light nembutal anesthesia and used as controls. The muscles were excised from within 10 seconds to 3 hours after the thermal trauma. The muscles from the control series and the traumatic series were divided into groups and run through the gold technic together. Exact comparison of the quantity and quality of the gold impregnation in the relatively normal control series and in the traumatized series was made by this method.

2. There was individual variation in resistance of the rats to primary thermal shock. Some of the animals, immediately upon immersion, had severe clonic spasms and paroxysms, or convulsions that resulted in tonic extensor rigidity. Others manifested mild twitching at first, and then strong, shivering, fascicular movements of the muscles. After 1 to 3 hours many of the rats had flaccid paralysis of one or more extremities. There was variation in the transition from violent muscular movements and from a spastic to a flaccid state of the muscles, as well as in the degree and extent of loss of muscle motion. These functional changes were dependent upon: (1) individual resistance of the animals; (2) duration of immersion; (3) degree of temperature; and (4) time interval after onset of the violent heat trauma.

3. The temperature of the muscles varied from 37.8° to 42.4° C., immediately after immersion of 24 rats. There was very little direct conduction of heat, therefore, from the skin to the spastic skeletal muscle. It was concluded, therefore, that the initial and variable pathologic function of muscle in immediate response to cutaneous scalding was produced by violent impulses transmitted through the neuromuscular apparatus. Some of these muscles, during the early stage of heat shock, failed to respond to both direct and indirect electric stimulation. This likewise applied to certain flaccid muscles in the late stage of shock. There were variations of response of the muscles in both a generalized and localized manner.

4. The majority of the motor end-plates had disappeared in 75 per cent of the muscles examined within 1 to 3 hours. The ordinary sequence of histologic changes, intermingled with normal appearances, in the motor end-plates were as follows:

(a) Hyperchrysophilia or increased intensity of gold impregnation

due to increased quantity of axonic material transmitted to the motor end-plate.

(b) Axonorrhea or the abnormal discharge of the axonic material from the motor end-plates, increased in permeability, into the myoplasm of the muscle fiber. The substantial secretion from the motor end-plates was arranged in a unipolar, bipolar, and multipolar pattern. The pleomorphism of the discharged secretion was manifested as granules, vacuoles, short or long fusiform inclusion masses in the myoplasm, short or long Indian clubs, triangles, or irregular masses that had a greater affinity for gold than the myoplasm. The length of the axonic material secreted into muscle varied from 0.5 to 1000 μ. The nonmedullated projection of axonic material still connected with the motor end-plate has been previously described as an "ultraterminal branch." Such projections were frequently found during the early primary effects due to reflex overstimulation by scalding the skin. The finding of large amounts of inclusion masses of the discharged nervous secretion in the myoplasm was synchronous with the manifestation of rigid spasticity of the muscles. These nervous inclusion masses in the myoplasm were either opaque or cross-striated.

(c) Hypochrysophilia and achrysophilia were evident as a progressive lack of gold impregnation finally leading to the complete absence of gold in the terminal of the nerve. This lack of gold impregnation was due to the complete absence of the terminal axonic structures. These had undergone granular transformation and dispersion in the myoplasm. The final stage was a complete structural exhaustion of the motor end-plates coincident in time with the flaccid paralysis. There was muscle denervation at the myoneural junction produced by complete structural exhaustion. This exhaustion was the result of the sudden axonic transformation into granules which composed the products of the acute hypersecretion into muscle induced by scalding the skin. The abnormal heat stimulus to the skin accelerated the drainage and depletion of the axonic fluid in motor nerves.

(d) The granular exhaustion of the epilemmal axons extended in a centripetal direction. The motor end-plates appeared to be vulnerable chemical fuses between the peripheral nerves and muscles.

5. There were acute changes in the myoplasm in addition to the great quantities of inclusion masses of nervous secretion: granular, hyaline or Zenker's degeneration, and pyknosis of nuclei.

6. During the early stages, 10 to 60 seconds after traumatic scalding of the skin, the dominant change in the muscle was in the neuromuscular apparatus. After 1 hour there were prominent vascular

changes: active hyperemia, packing of the vascular lumina with red blood cells, perivascular edema, and leukocytic infiltration. There was individual variation of the rats in manifesting this usual sequence of pathologic reaction to the abnormal motor impulses generated by the reflex response to burns.

7. Ten per cent of the rats subjected to immersion in water, 75° C. for 10 seconds, manifested the so-called bloody tears or chromodacryorrhea of the harderian glands. It has been established previously that this biologic response was produced by acetylcholine or by the breakdown products of muscle metabolism called dacryorrhetin. There appeared to be a correlation in the isolated changes in the neuromuscular apparatus and in the harderian gland in the rat.

8. The nerve-intact skeletal muscle fiber should be considered as a functional and morphologic unit composed of neuromyoplasm; it may or may not possess a sarcolemma; it may or may not have cross striations; it may or may not be longitudinally striated or subdivided into myofibrils. The variable cross striations are structural expressions of the changeable mechanical energy of explosive pressure that accompanies the capillary chemistry of metabolism. The ephemeral longitudinal striations are streamlining products of the periodic changes of metabolism and of the mechanical tension and pressure accompanying muscle function. The cross and longitudinal striations are changeable and not constant structures. The myofibril, therefore, cannot be considered the constant specific structure that subserves the contractile function. It is a mechanical, structural effect and not the definite morphologic cause or sole protoplasmic substratum underlying muscle contraction.

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DESCRIPTION OF PLATES

The photomicrographs of Figures 1 to 71 are from teased whole muscle fibers (gastrocnemius muscle) and motor end-plates of the white rat (*Mus norvegicus*). These teased preparations of motor end-plates in skeletal muscle were previously prepared by the gold technic. The photographs were made as direct contact prints from the negatives which were exposed through the microscope and not subjected to subsequent enlargement. These photographs, therefore, may be readily compared with those of the the white rat and the chameleon previously published.[6] In the plates, "epa." designates the epilemmal axon; "hya.," the hypolemmal axon; and "Kg.," masses of extra-axonic Kühne's granules. There has been no retouching of either negatives or prints.

PLATE 36

FIGS. 1 to 3. Sprays of axons of medullated nerve fibers and motor end-plates of the white rat (*Mus norvegicus*) in the relatively normal gastrocnemius muscle excised 15 minutes after the intraperitoneal injection of nembutal, 4 mg. per kg. (Fig. 1); muscle excised 30 seconds after immersion of rat at 90° C. for 10 seconds (Fig. 2); muscle excised 2 hours after immersion of rat at 75° C. for 10 seconds (Fig. 3). In the relatively normal muscle (Fig. 1) there is a variation in the type of muscle fibers and in the sizes of the motor end-plates. Some motor end-plates in the retracted condition are surrounded by a dense accumulation of Kühne's granules. The light, expanded end-plates have a diminution or complete absence of the surrounding granules of Kühne. The first morphologic effect of the heat stimulus applied to the skin was hyperchrysophilia (Fig. 2), increased intensity of gold impregnation of the enlarged motor end-plates. This was due to the increased accumulation of nervous material in the end-plate prior to discharge into the muscle. In some locations the discharged nervous secretion is evident in the muscle fiber. The epilemmal axons (Fig. 2) manifest beginning exhaustion of their substance. The complete dissolution of the motor end-plates (Fig. 3), and the centripetal depletion of the epilemmal axons of gold-impregnated substance are the last events in a whole series of changes that occur in the peripheral denervation of muscle at the myoneural junction subsequent to the shock stimulus produced by heat applied to the skin. The neuromuscular apparatus, therefore, manifests in thermal shock the following sequence of changes: (1) hyperchrysophilia of the enlarged end-plates; (2) axonorrhea, or abnormal discharge of nervous secretion into muscle from the abnormally permeable motor end-plates; (3) hypochrysophilia; (4) achrysophilia; and (5) depletion of the gold-impregnated material in the epilemmal axon in a centripetal direction. One clearly evident result of the reflex action of heat applied to the skin is the loss of the dark type of muscle fiber (Figs. 2 and 3) due to simultaneous contractions of the great majority of these fibers. The fractional contraction of normal muscle is structurally expressed by the presence of dark and light muscle fibers (Fig. 1). × 150.

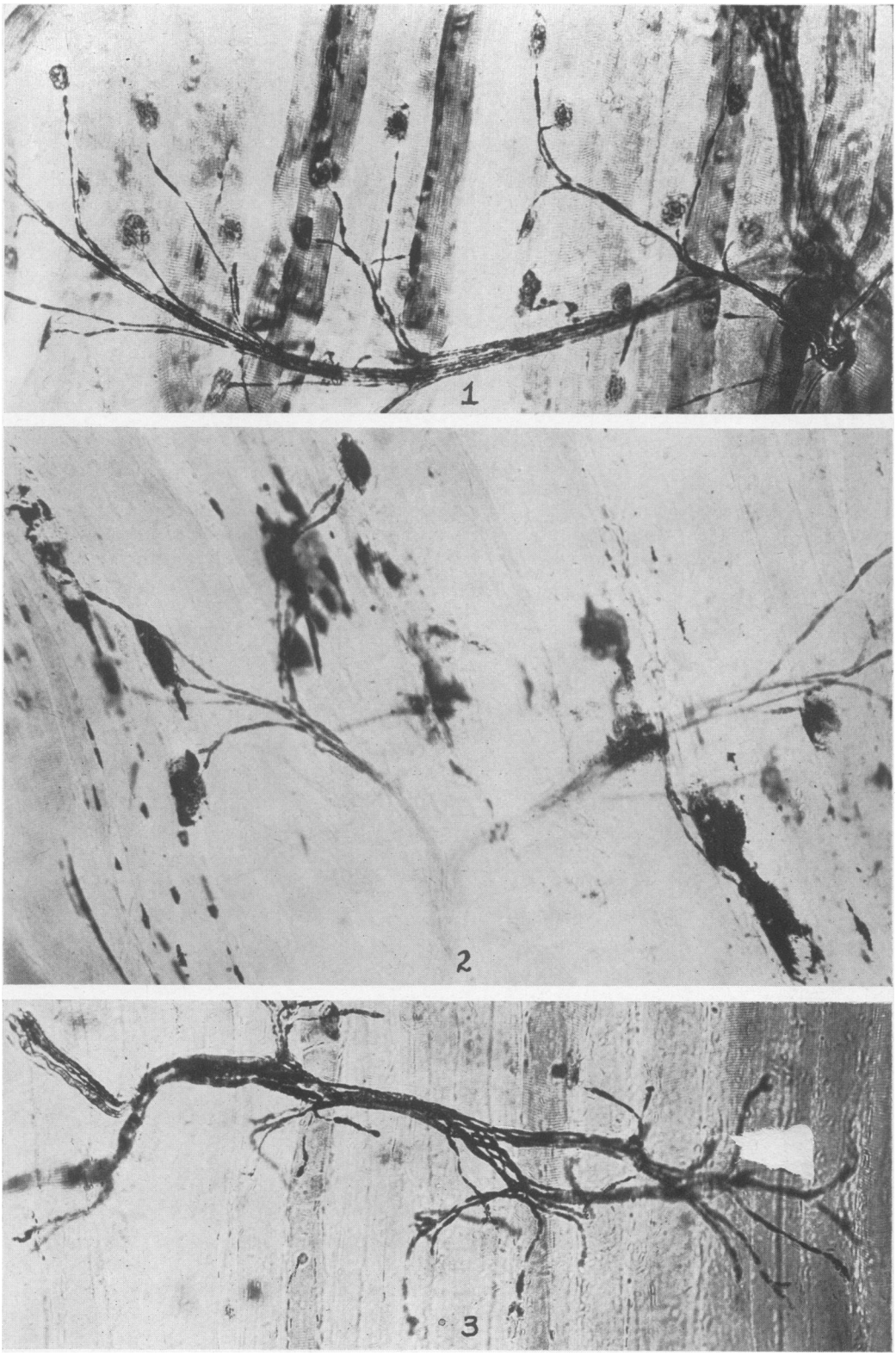
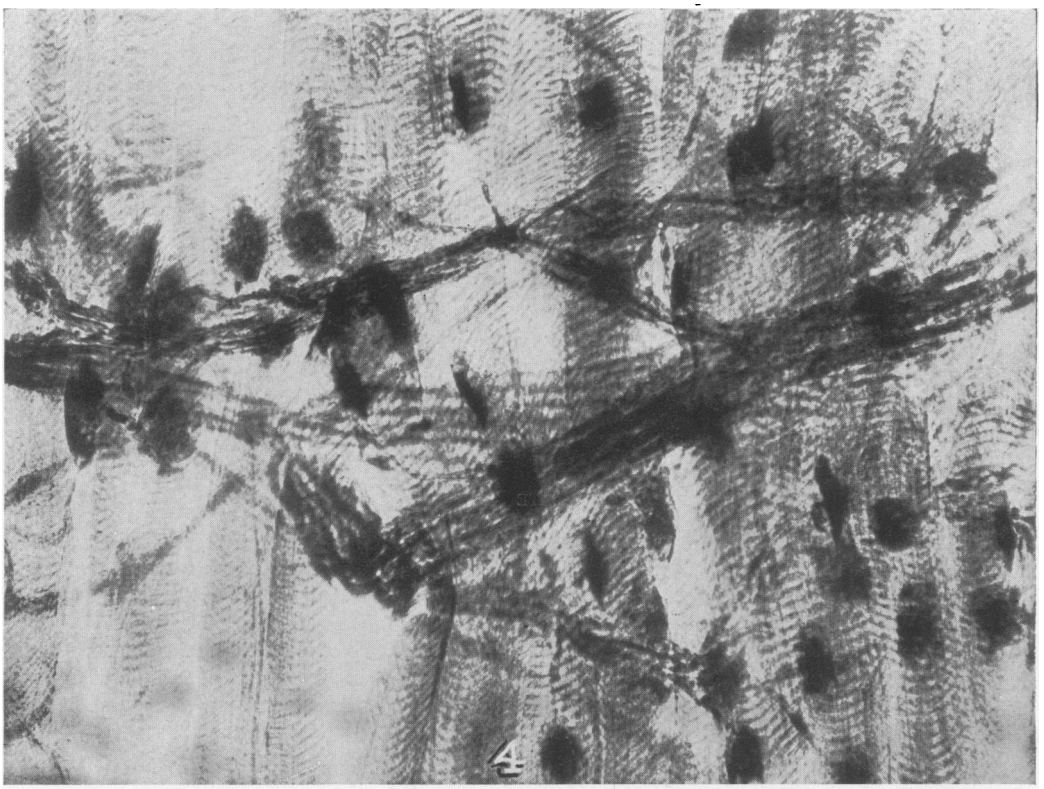
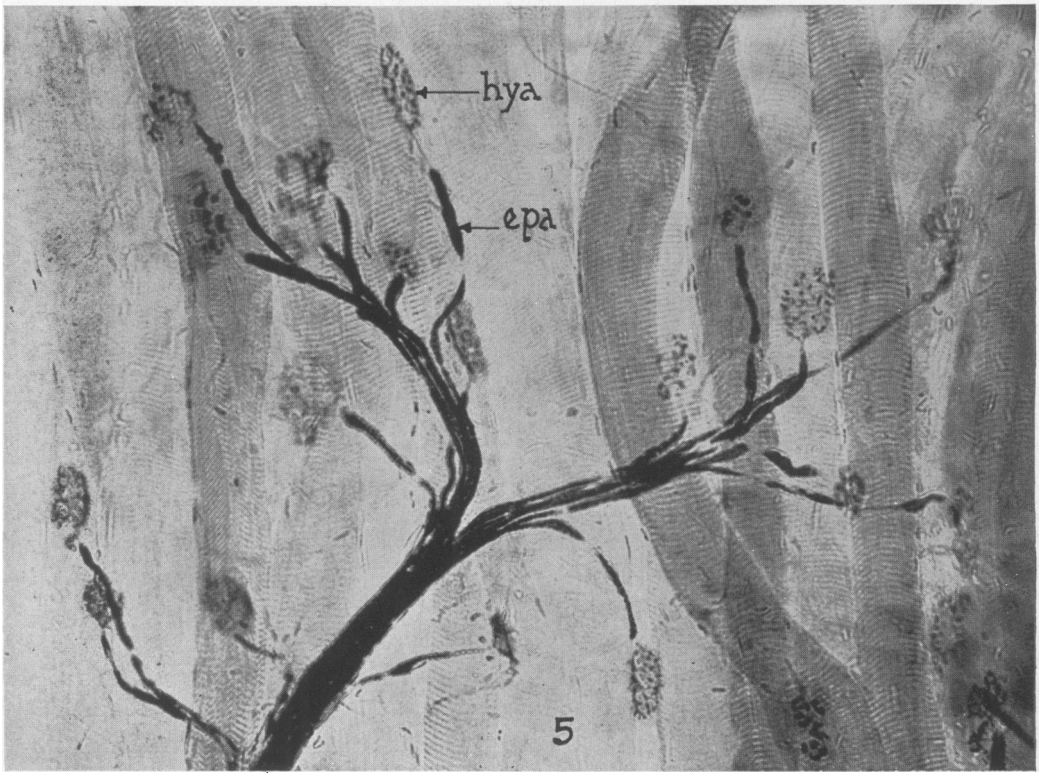

1
2
3

PLATE 37

FIGS. 4 and 5. Sprays of axons of medullated nerve fibers and motor end-plates of the gastrocnemius muscle of the white rat, 4 hours subsequent to the intraperitoneal injection of magnesium sulfate, 2 gm. per kg. (Fig. 4), and 10 minutes subsequent to the subcutaneous injection of strychnine sulfate (Fig. 5). There is a great retraction of about 35 per cent of the motor end-plates in the gastrocnemius muscle after the injection of magnesium sulfate. The epilemmal axons are faintly impregnated with gold. The muscle fibers are narrow and the cross striations form coarse bands. The muscle is in a state of flaccid paralysis. Some muscles, in flaccid paralysis due to magnesium sulfate, failed to respond to indirect stimulation of the sciatic nerve. By direct stimulation the muscles responded feebly to electric stimulation. The above changes (Fig. 4) are to be contrasted with those produced by strychnine sulfate (Fig. 5). Ninety-five per cent of the endings are expanded, and in some places the hypolemmal axon is fragmented (Fig. 5) into discrete granules, which give the stippled appearance. The epilemmal axons are wide in some places and very narrow in others and are intensely impregnated with gold. About 95 per cent of the muscle fibers have fine, closely spaced cross striations. These changes of retraction and expansion of the motor end-plates and the configuration of the cross striations produced by chemical action are to be used as a base line of departure in the interpretation of the changes produced by thermal shock. × 300.

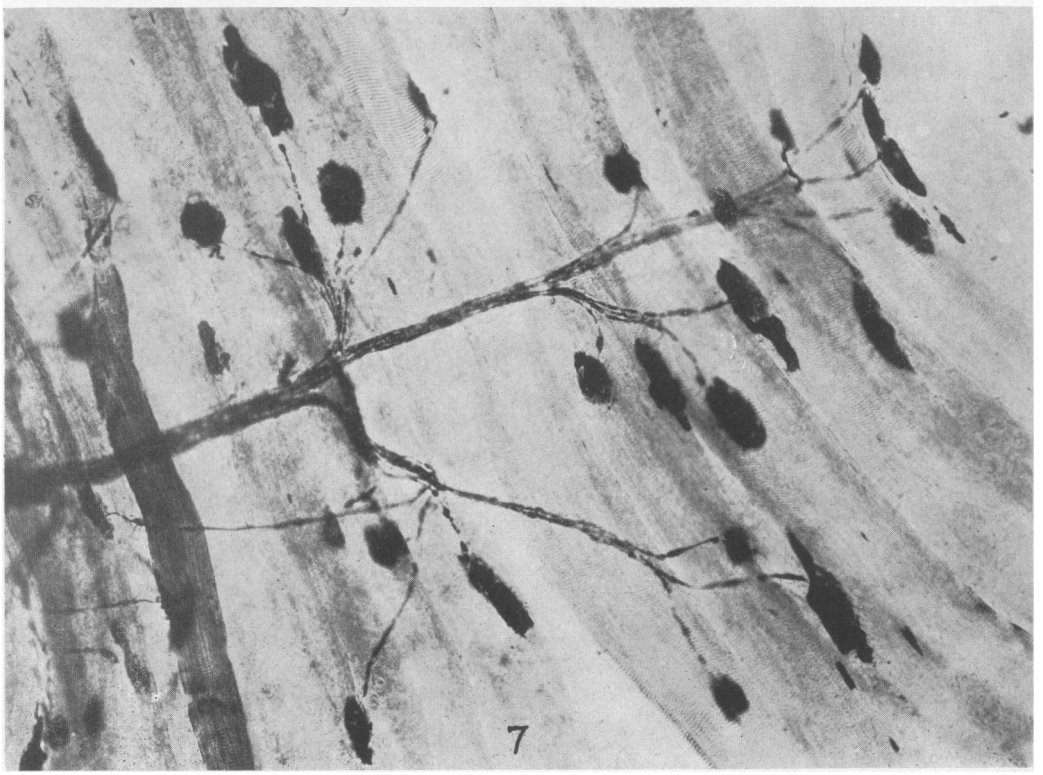




Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 38

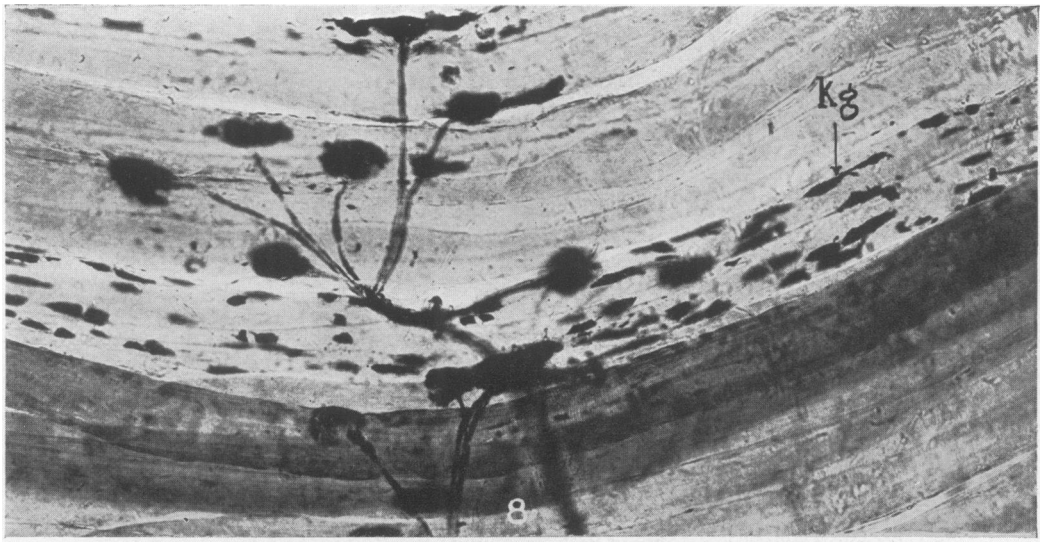
FIGS. 6 and 7. Sprays of axons of medullated nerve fibers and motor end-plates of the gastrocnemius muscle of the white rat, in the relatively normal animal (Fig. 6), obtained 15 minutes after the intraperitoneal injection of nembutal. There is variation in the type of muscle fibers and in the sizes of the motor end-plates. Some motor end-plates in the retracted condition are surrounded by a dense accumulation of Kühne's granules. The light, expanded end-plates have a diminution or complete absence of the surrounding granules of Kühne. It is evident that the first morphologic effect of the heat stimulus of a 10-second skin exposure in water at 90° C. is a hyperchrysophilia of the motor end-plates (Fig. 7). The muscle was excised 10 seconds after immersion. An augmented discharge of masses of Kühne's granules from the end-plates is made evident by the intense impregnation of this nervous material by gold. There is a beginning depletion and beading of the epilemmal axons. This phase of the secretion of the nervous material into the muscle fiber is a very early and ephemeral one. It soon gives way to explosive projection, diffusion, and subsequent dissolution of this nervous material in the myoplasm of the muscle fiber. × 150.

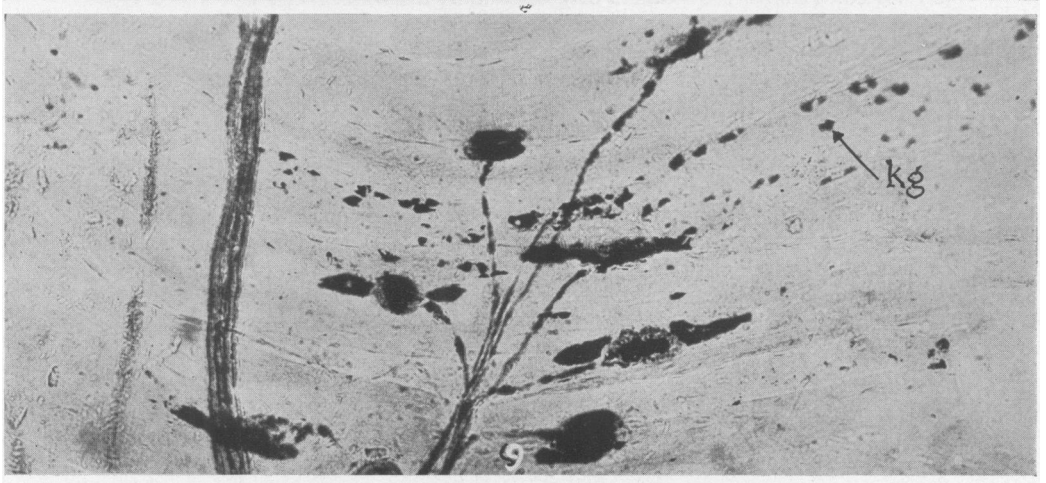


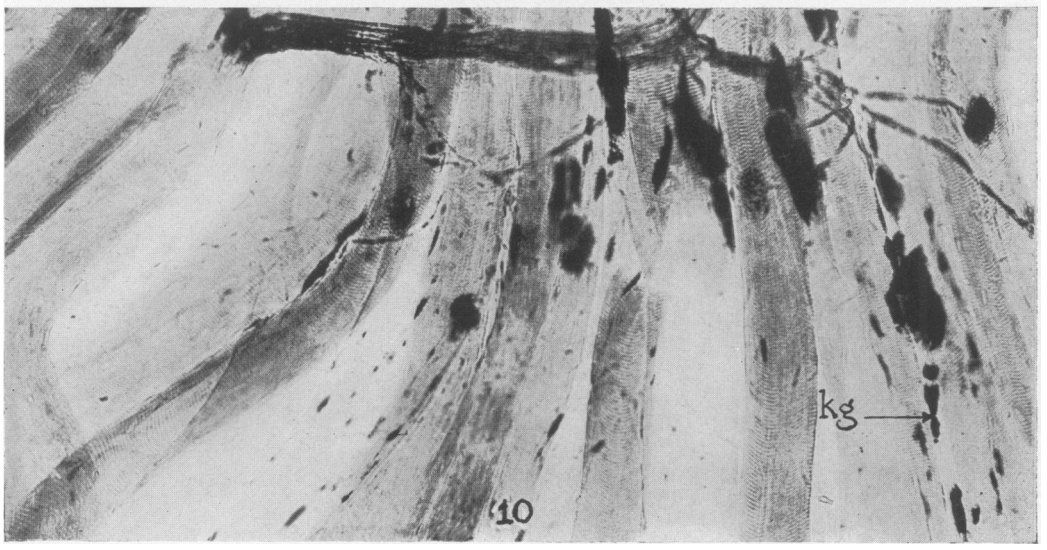
Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 39

FIGS. 8 to 10. Sprays of axons of medullated nerve fibers and motor end-plates of the gastrocnemius muscle of the white rat, 30 seconds subsequent to the heat stimulus of a 10-second skin exposure in water at 90° C. The first phase of the neuromuscular reaction of hyperchrysophilia and the second phase of axonorrhea, or discharge of the nervous material into the muscle fibers, are intermingled. The discharged nervous material may be either close to or at a considerable distance from the terminal axons of the motor end-plates. The arrangement of the secretion in close proximity to the end-plates is unipolar, bipolar, and multipolar. The structure of the secreted material is likewise variable, namely: (1) as discrete granules, (2) as vacuoles, (3) as short or elongated fusiform masses, and (4) as short or long arrow-like projections. The internal structure of the masses of Kühne's granules projected from the motor end-plates into the muscle fiber may be either densely opaque or cross-striated. The cross striations, when present, may or may not agree in periodicity with the related cross striations in the muscle fiber. These projected axonic masses of Kühne's granules are seen both within and without the muscle fiber. This is more clearly revealed in the studies of the cross sections of the muscle fibers. There is a torrential projection of axonic material that, for a short period, floods the contents of some muscle fibers. This excessive discharge of the nervous secretion from the motor end-plates is detected by the superabundance of gold-staining masses that vary in size and configurations. The ephemeral architecture and multiplicity of designs of the discharged nervous secretion in muscle are consistent with the various steps occurring in the dissolution of the secretion and its progressive incorporation into the substance of the myoplasm. There is, therefore, no constant and fixed line of demarcation between the motor nerve ending and cross-striated muscle. This variation in composition of the junction between the secretory nerve ending and muscle has made the search for an absolute line of separation between the two structures vain; there is no such constant partition between nerve and muscle. × 300.







Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 40

FIGS. 11 to 13. Sprays of axons of medullated nerve fibers and motor end-plates (Figs. 11 and 12) of the gastrocnemius muscle of the white rat, 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C. The second phase of the neuromuscular reaction, axonorrhea, is clearly manifested. Elongated streamers of gold-staining axonic material discharged from the motor end-plates into the muscle fibers are clearly evident. Some of these projected streamers of nervous material discharged into the muscle are over 1000 μ in length. At the other extreme of the variation in size, spheroidal granules, 0.5 to 1 μ in diameter, are to be found. There is, likewise, considerable variation in the distribution of this nervous secretion in the muscle fibers (Fig. 11). This is due to the irregularity of the nervous discharge as well as to the tenuous and ephemeral nature of the nervous secretion. The form of the nervous discharge (Kg.) is clearly evident: elongated fusiform masses, elongated arrowheads (shaped like an isosceles triangle, Fig. 12), or elongated Indian clubs (Fig. 13). There is, therefore, irregularity of the pattern of the discharged nervous material. The stimulus of heat applied to the skin likewise has a neoformative influence on the design of the motor end-plates in muscle. From some end-plates (Figs. 11 and 12) there is a vigorous outpouring of nervous secretion, impregnated black by gold, which forms elongated streamers in direct continuity with the end-plates. Figures 11 and 12, $\times$ 150; Figure 13, $\times$ 300.

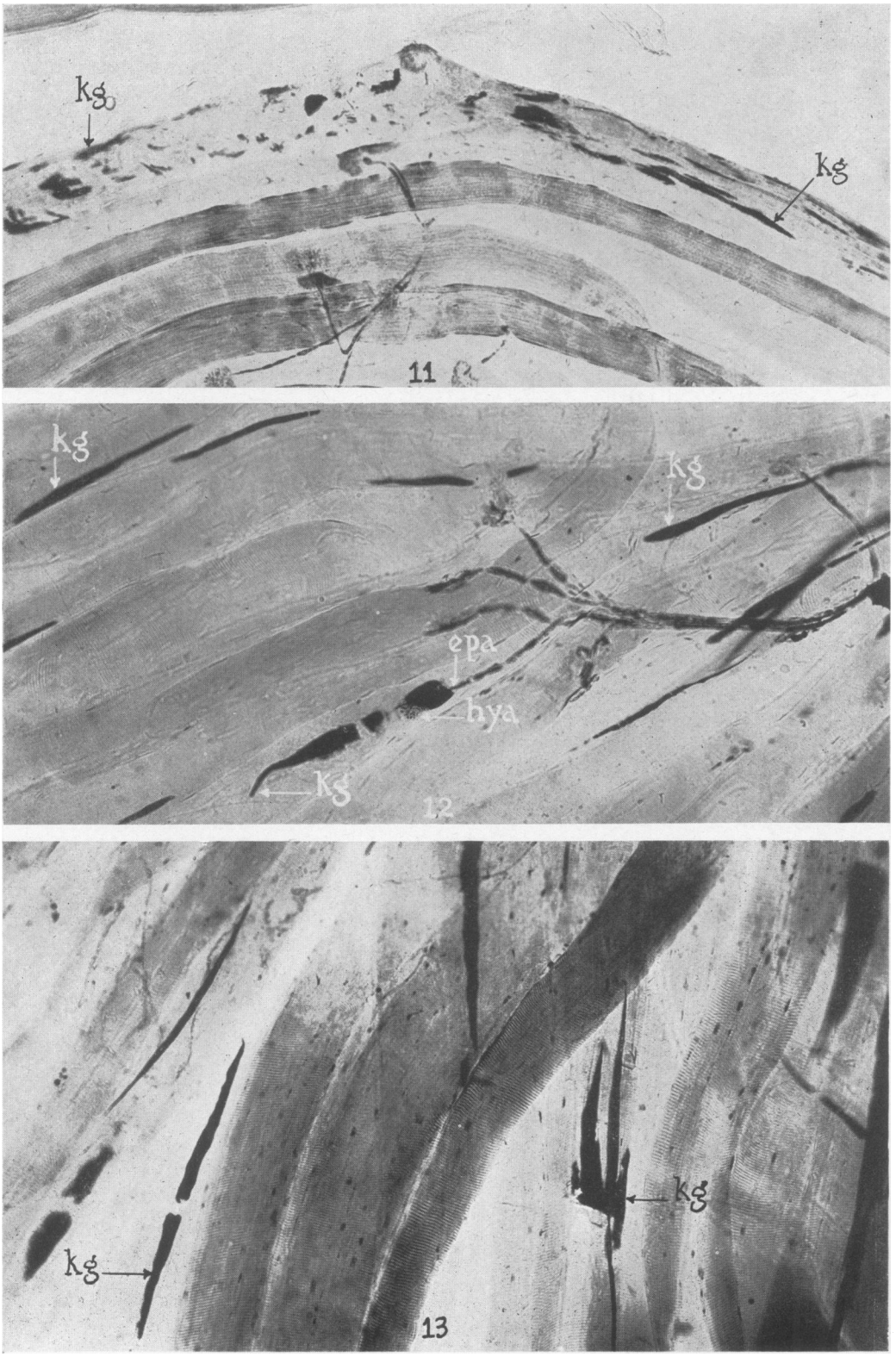
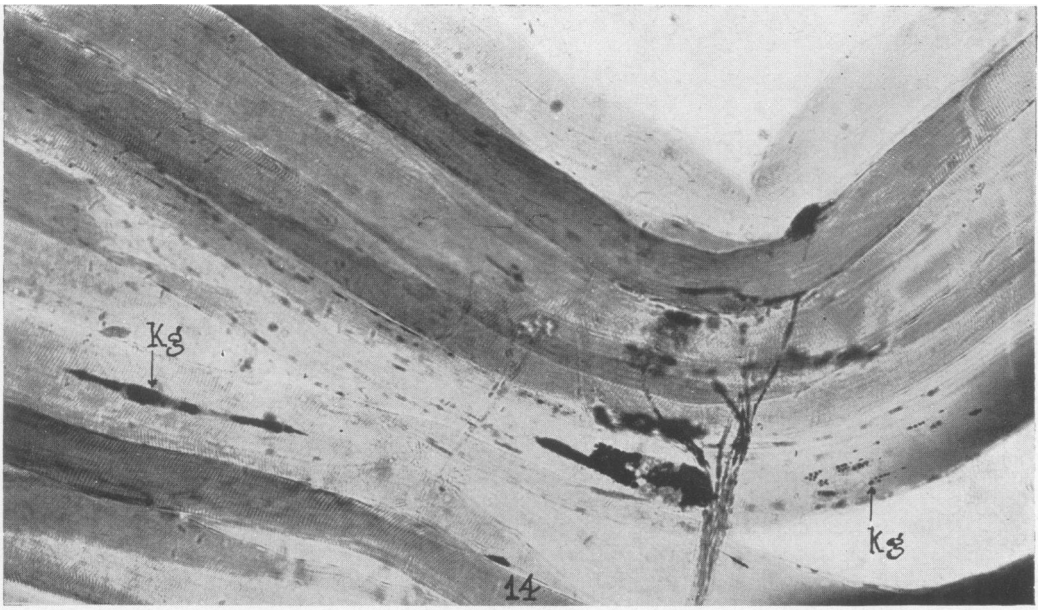
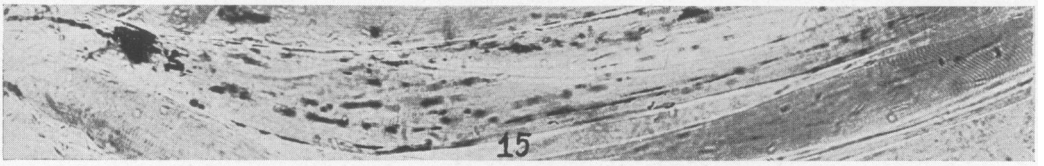
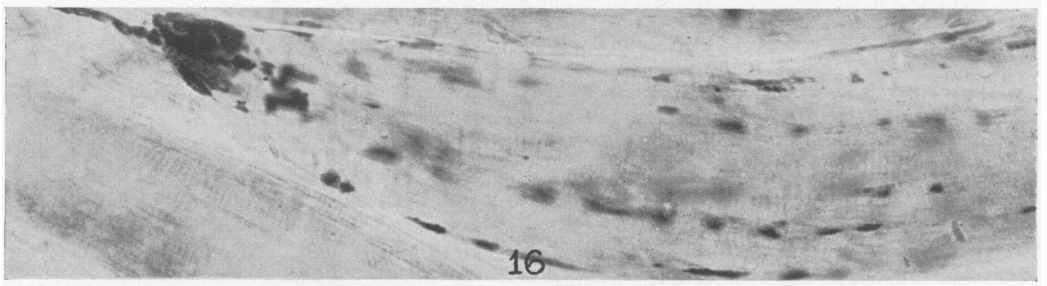

kg
kg
11
kg
kg
epa
bya
kg
12
kg
kg
13

PLATE 41

FIGS. 14 to 17. Sprays of axons of medullated nerve fibers and motor end-plates (Fig. 14) of the gastrocnemius muscle of the white rat, 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C. The second phase of the neuromuscular reaction to heat applied to the skin, axonorrhea, is clearly manifested. The nervous secretion discharged from the motor end-plates is distributed both close to and at a considerable distance from the end-plates. Some of the secreted material is in the form of fine granules to the right of the lower motor end-plate (Kg., Fig. 14). The elongated streamer of nervous secretion to the left of the lower motor end-plate (Kg., Fig. 14) is 450 μ in length. In some places it is cross-striated and in others densely opaque. Some motor end-plates are fortuitously caught in the phase of pouring out a shower of nervous material into the muscle fiber. This is manifested (Figs. 15 to 17) in the various magnifications of the same motor end-plate and muscle fiber. Extending to the right of the discharging motor end-plate there is a flood of secreted nervous material, evident as dark, projected masses, into the myoplasm of the muscle fiber. There is morphologic evidence of a great flow of nervous material into the muscle by the streamlining of the very fine muscle striations. Figures 14 and 15, $\times$ 150; Figure 16, $\times$ 300; Figure 17, $\times$ 750.


Kg
Kg
14


15


16

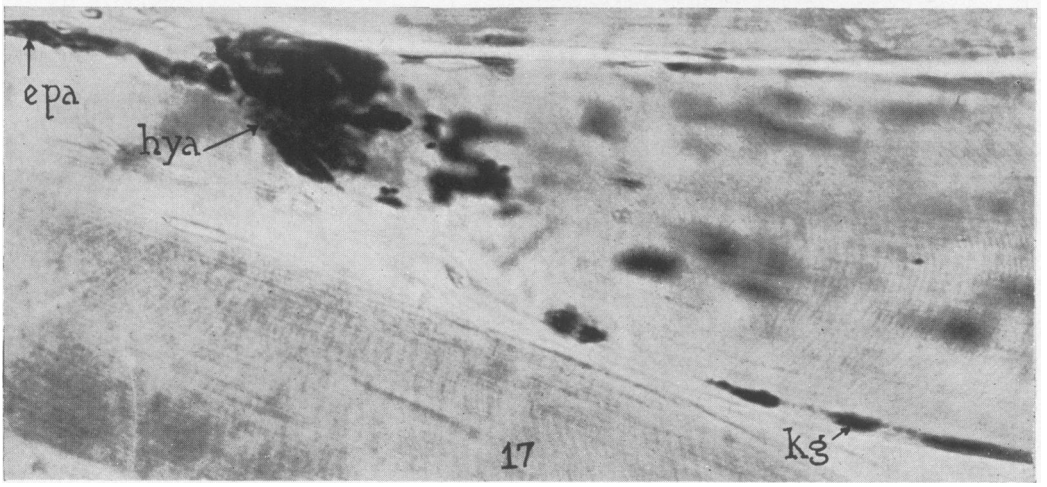

epa
hya
17
kg

PLATE 42

FIGS. 18 to 22. Ultraterminal projections of axonic masses from the motor end-plates (Figs. 18 to 22) of the gastrocnemius muscle of the white rat, 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C. The second phase (axonorrhea) of the neuromuscular reaction to heat applied to the skin is manifested by many variations in structure. The term "ultraterminal" is applied to an unmyelinated projection which arises from the axonic material of the motor end-plate and which terminates in the same or in a neighboring fiber. Terminations of both types may be observed. The termination may be globular, fusiform (Figs. 18 and 19), or penniform (Figs. 20 to 22). There is an elongated axonic strand that connects the hypolemmal axons of the motor end-plate with the projected terminal mass. There is a definite streamlining of the labile cross striations of the muscle fiber in immediate relation to the terminal swellings (Figs. 20 to 22) of the ultraterminal projections of axonic material into the muscle fiber. These ultraterminal projections are intermediate phases in the discharge of the secretion of nervous material from the motor end-plates into the muscle fiber. At a slightly later stage the attenuated strand connecting the motor end-plate and the discharged mass undergoes solution. The continuity, therefore, of the discharged masses of Kühne's granules with the motor end-plate is an early stage in the manifestation of the secretion of nervous material into the cross-striated muscle fiber. This overflow of projected nervous substance into the muscle fiber is the result of overstimulation and augmented permeability of the terminal axons of motor nerves in muscle. The delay in the dissolution of the excessive nervous discharge may be due to the local increase of lactic acid and other metabolites in the overstimulated muscle. The continuation of this vigorous outpouring of the nervous fluid into muscle results in structural exhaustion and complete disappearance of the motor end-plates. This produces early denervation of muscle at the myoneural junction. Figure 18, × 300; Figure 19, × 750; Figure 20, × 200; Figure 21, × 400; Figure 22, × 750.

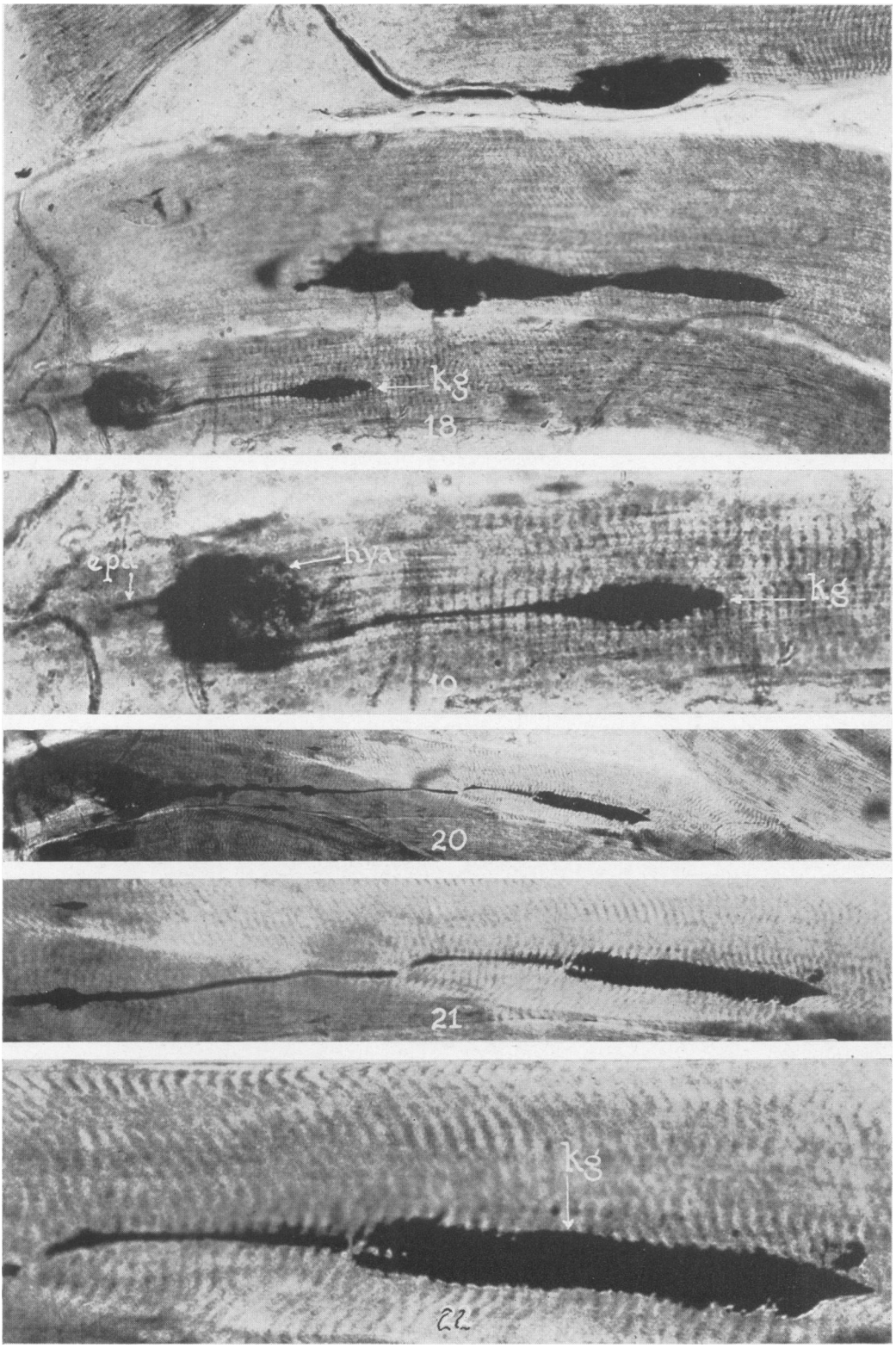
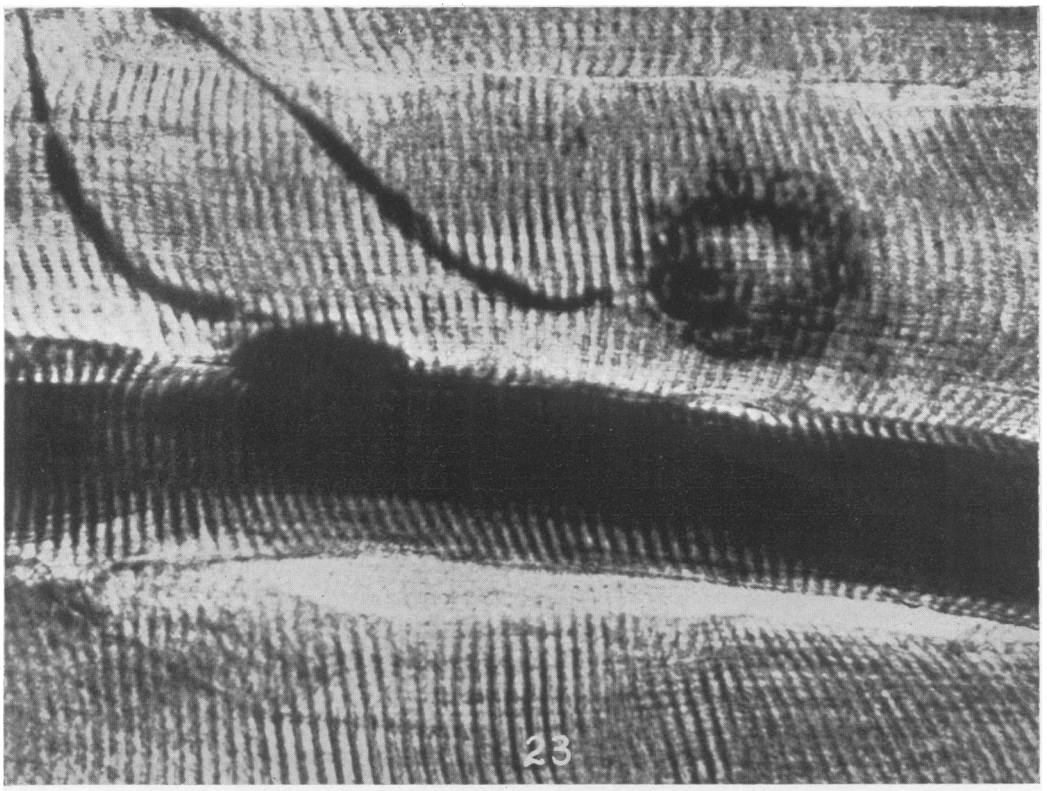

kg
18
epa
hya
kg
19
20
21
kg
22

PLATE 43

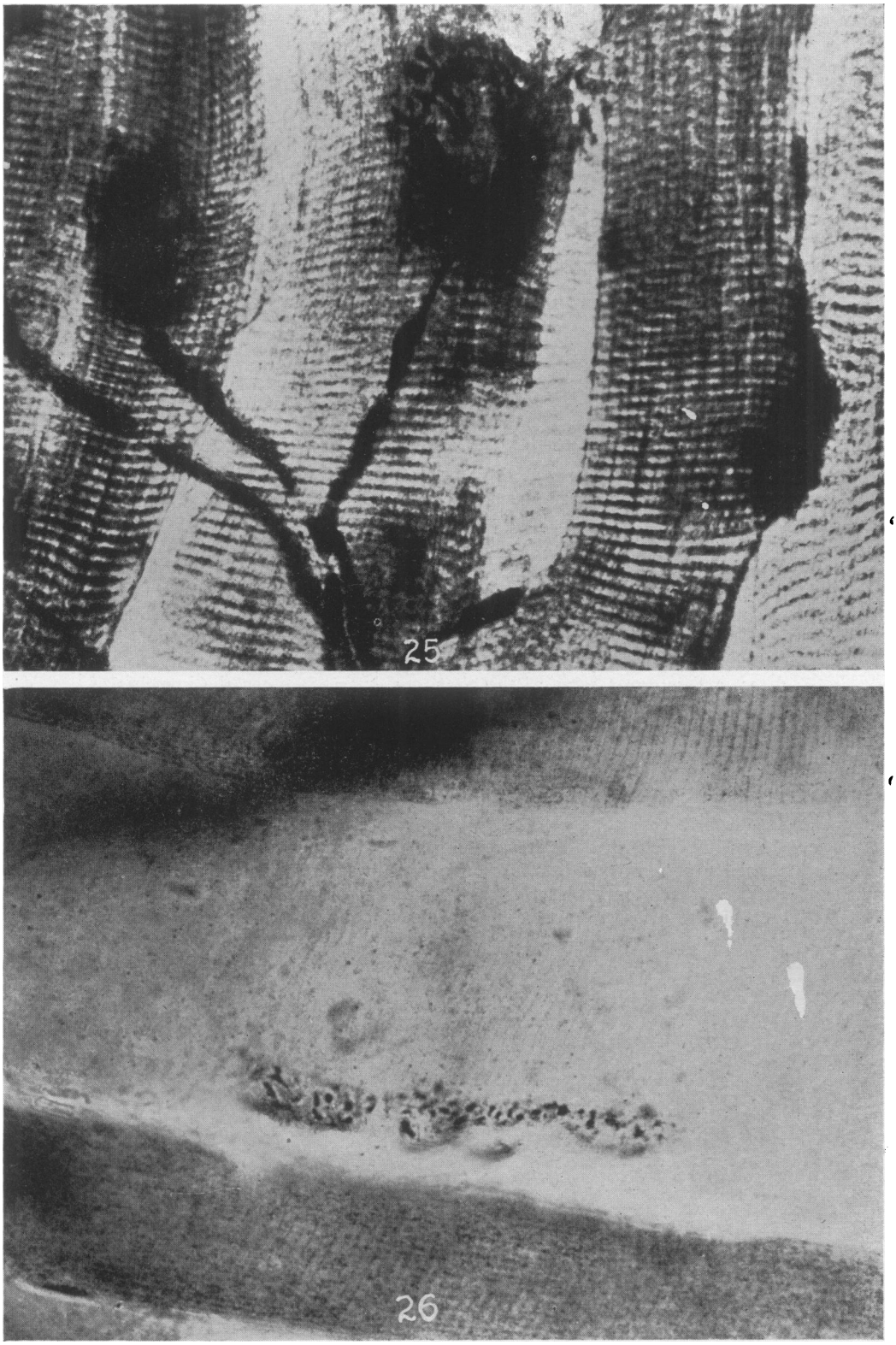
FIGS. 23 and 24. Sprays of axons of medullated nerve fibers in the relatively normal gastrocnemius muscle of the white rat, excised 15 minutes after the intraperitoneal injection of nembutal. There are variations in the width and types of muscle fibers in the relatively normal muscle. Some of the muscle fibers are narrow (Fig. 23) and densely impregnated with gold. Others are wide and less densely impregnated, giving a light appearance. There are many intermediate gradations in the width of the muscle fibers between the two extremes. The dark cross striations in the narrow muscle fibers are frequently broad, and the light banding narrow. The light, wide muscle fibers (Fig. 24) usually have fine, narrow cross striations. There are variations, however, in the internal structure of the muscle fiber depending on whether the muscle is fixed in the condition of isometric or isotonic contraction. The narrow muscle fibers may show a variation of fine striations, and the wide muscle fibers may show striations of the broad type. These labile cross striations, therefore, are not fixed, static membranes that form permanent partitions in the muscle. They are as variable as the functional activity and the chemical concentration and composition that underlie the activities of the muscle. The motor end-plates in the narrow muscle fibers are retracted and take a dense stain with gold. There are variations in the degree of expansion of the axonic terminals of the motor end-plates. There is a decrease in the quantity of the granules of Kühne around the expanded end-plates. There is a concomitant attenuation of the axonic branches in the expanded motor end-plates. Retracted motor end-plates have been associated with relaxation and expanded end-plates with contraction of the muscle fiber. The motor end-plates in this relatively normal control muscle are of the type designated as "*terminaison en plaque.*" × 750.


23


hya
kg
epa
24

PLATE 44

FIGS. 25 and 26. Sprays of axons of medullated nerve fibers in the relatively normal gastrocnemius muscle (Fig. 25) of the white rat, excised 15 minutes after the intraperitoneal injection of nembutal. The motor end-plates in this relatively normal muscle are of the type designated as *"terminaison en plaque."* Some of the end-plates (Fig. 26) in the gastrocnemius muscle, excised 10 seconds subsequent to the heat stimulus at 90° C. of a 10-second immersion of a rat, have the grape-like terminals designated as *"terminaison en grappe."* These grape-like terminals are an exhaustion phase of the ordinary motor end-plates due to overactivity and oversecretion in response to the heat stimulus. They are frequently associated with a muscle fiber that has fine, closely spaced, dark cross striations and with an unmedullated epilemmal axon. The demyelination of the epilemmal axon is, likewise, associated with exhaustion due to overstimulation. The reversible structure of the motor end-plates is due to variations of functional activity. The grape-like motor nerve ending has attenuated and, in many places, discrete swellings of the fine axons, which terminate in little ball-like masses. There is a depletion or complete absence of the surrounding granules of Kühne. The unmyelinated epilemmal axon of this grape-like nerve ending is out of focus when the ending is clearly in focus. × 750.



Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 45

FIGS. 27 to 38. The pleomorphism of the normal motor end-plates is evident from these photographs made from the gastrocnemius muscle of the white rat in the relatively normal state, excised 15 minutes after the intraperitoneal injection of nembutal. Many of the retracted nerve endings (Figs. 27 and 28) are surrounded by a dense rim of Kühne's granules and are related to narrow muscle fibers that contain coarse, widely spaced cross striations. There is a great variety of configurations of the expanded motor end-plates. Some have coarse hypolemmal axons (Figs. 29, 30, 33 and 36) related either to fine cross striations or to a complete replacement of the striations by diffuse granulation. Other expanded nerve endings have very narrow hypolemmal axons and a great diminution or complete depletion of the granules of Kühne. The granules of Kühne constitute a fine spray of secretion discharged from the axons in the expanded nerve endings in some locations (Figs. 29, 31, 32, 36). These minute granules of Kühne become quickly incorporated by diffusion and dissolution into the myoplasm. Under normal conditions the neuronic secretion into muscle is exceedingly tenuous and ephemeral. Therefore, it has been hard to detect and interpret some of the clear, oval spaces between the branches of the axons. In the external granular rim they are occupied by nuclei of the granular sole. These nuclei are rendered more clearly visible by counterstaining with hemalum or hematoxylin. This counterstaining, however, frequently smudges the definition of the other parts of the neuromuscular apparatus. In some places there is a clear, halo-like space between the axon and the granules. In others there is a direct continuity between the granules and the axons. It is clearly evident that the architecture of the neuromuscular apparatus under relatively normal conditions is characterized by great variation and irregular patterns. The pleomorphism of these motor end-plates is due to variations of ameboid motion of retraction and expansion, and material exhaustion due to secretion. The epilemmal axon is irregularly beaded. × 750.

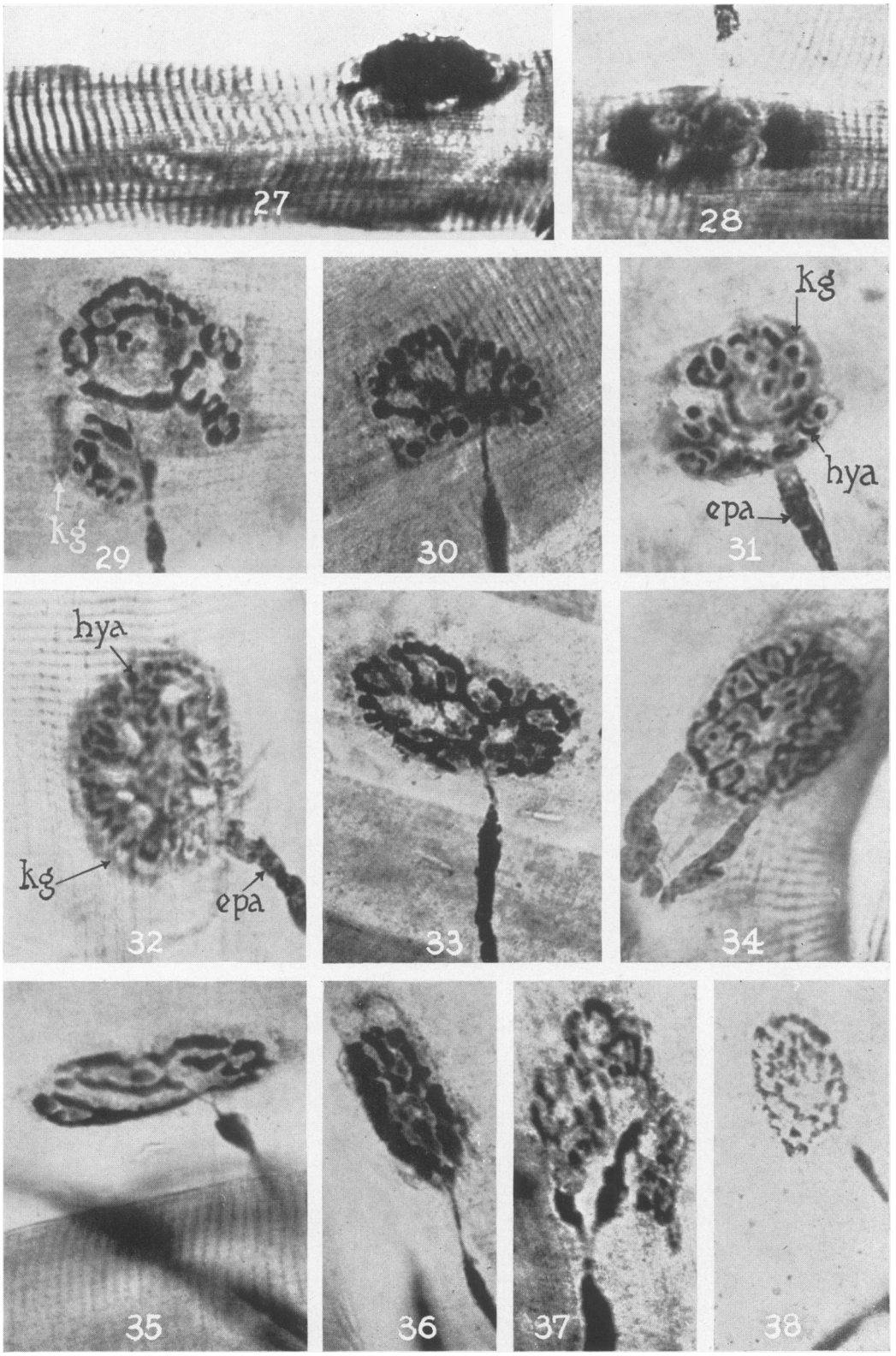

27
28
kg
29
30
kg
hya
epa
31
hya
kg
epa
32
33
34
35
36
37
38

PLATE 46

FIGS. 39 to 49. The pleomorphism of the motor end-plates is clearly evident, also, in the gastrocnemius muscle of the white rat, excised 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C., applied to the skin. The hypolemmal axons may form a complete ring open in the center (Fig. 39), or may contain dense, rounded masses of Kühne's granules that form either a small (Fig. 40) or a large hub (Fig. 41). This central mass of Kühne's granules may form a ring with a thick rim (Fig. 42). There may be irregular distribution of the rounded islands of Kühne's granules (Fig. 43). There may be large rings (Fig. 44) or irregular rings (Fig. 45) formed by the expanded axons of the motor end-plates. The hypolemmal axons of the motor end-plates become gradually more and more attenuated as they become transformed into the granules of Kühne (Figs. 44 to 48). There is fragmentation (Fig. 47) and complete transformation of the hypolemmal axons of the motor end-plates into granules (Figs. 48 and 49). In this explosive transformation (Fig. 49), there is, likewise, a replacement of the periodic cross striations into an irregular mass of granules in close proximity to the end-plate which is undergoing rapid liquefaction. The epilemmal axons have irregular configurations in relation to the descent of the axonic material into the hypolemmal axons. The structural loss of innervation at the myoneural junction is due to the transformation of the terminal axons into granules. The rapid diffusion and incorporation of the granules into the myoplasm results in peripheral nervous exhaustion by depletion of the nervous axonic fluid discharged into muscle. × 750.

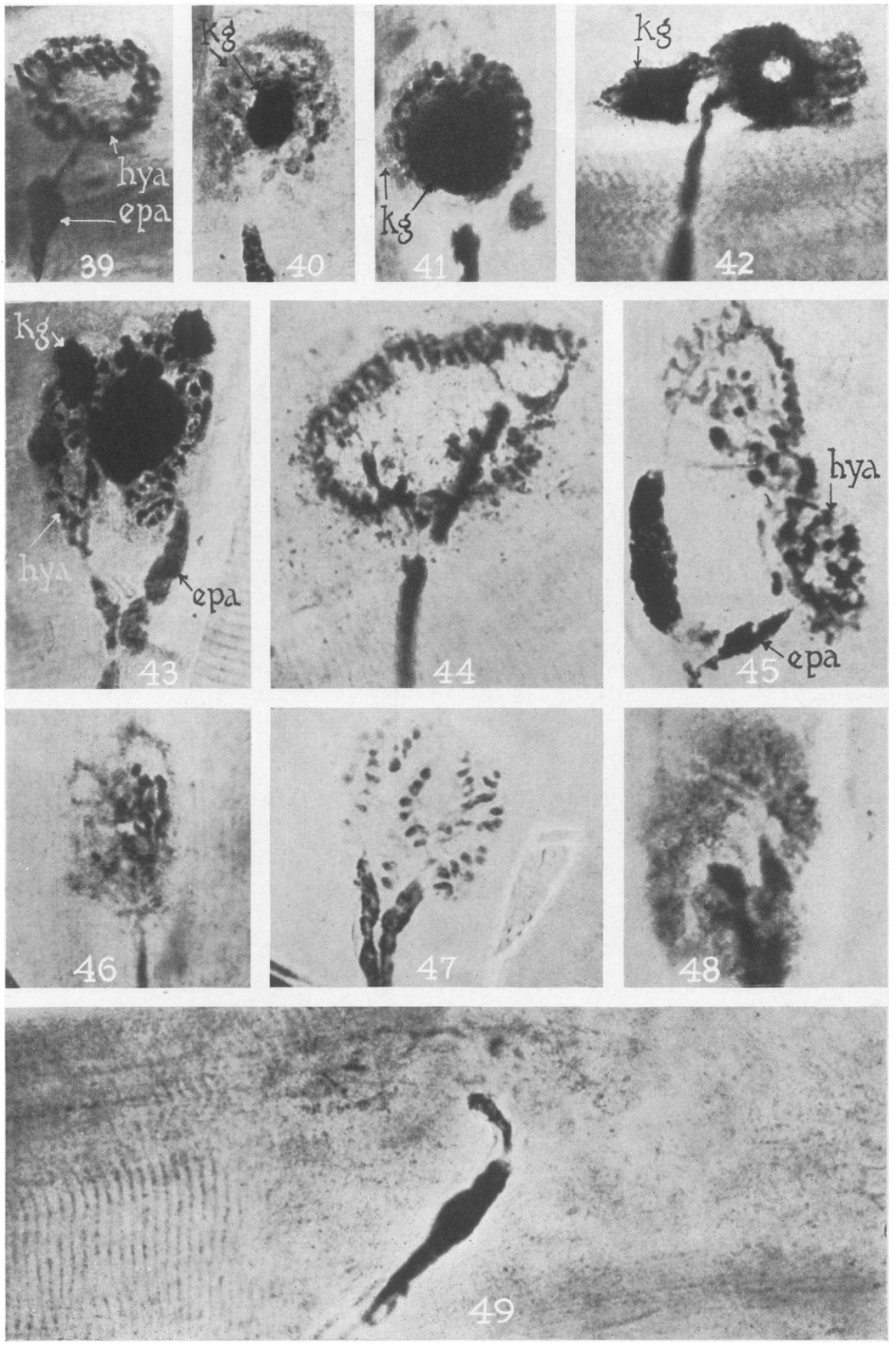

hya
epa
39
kg
40
kg
41
kg
42
kg
hya
epa
43
44
hya
epa
45
46
47
48
49

PLATE 47

FIGS. 50 to 55. The pleomorphism of the motor end-plates is illustrated further from the gastrocnemius muscle of the white rat, excised 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C., applied to the skin. The hypolemmal axon is in a condition of hyperchrysophilia due to the augmented accumulation of axonic material that has a specific affinity for the impregnating gold. This condition is not due to overstaining. The intense impregnation with gold is due to the fact that there is an increased quantitative accumulation of the axonic material in the end-plate, which material has an affinity for gold. There are various phases in the discharge of this nervous material into the muscle fiber by direct continuity from the motor end-plate. The elongated extensions of Kühne's granules may occur as short projections (Figs. 50, 51, 52), or as unipolar fusiform projections (Figs. 53 and 54), or as a duplex series of fusiform projections (Fig. 55), related to a depleted motor end-plate (Fig. 55). The fine cross striations are granular and closely spaced (Figs. 53 and 54) or they have undergone a complete replacement by a diffuse arrangement of granules (Figs. 50, 51, 52, and 55). × 750.

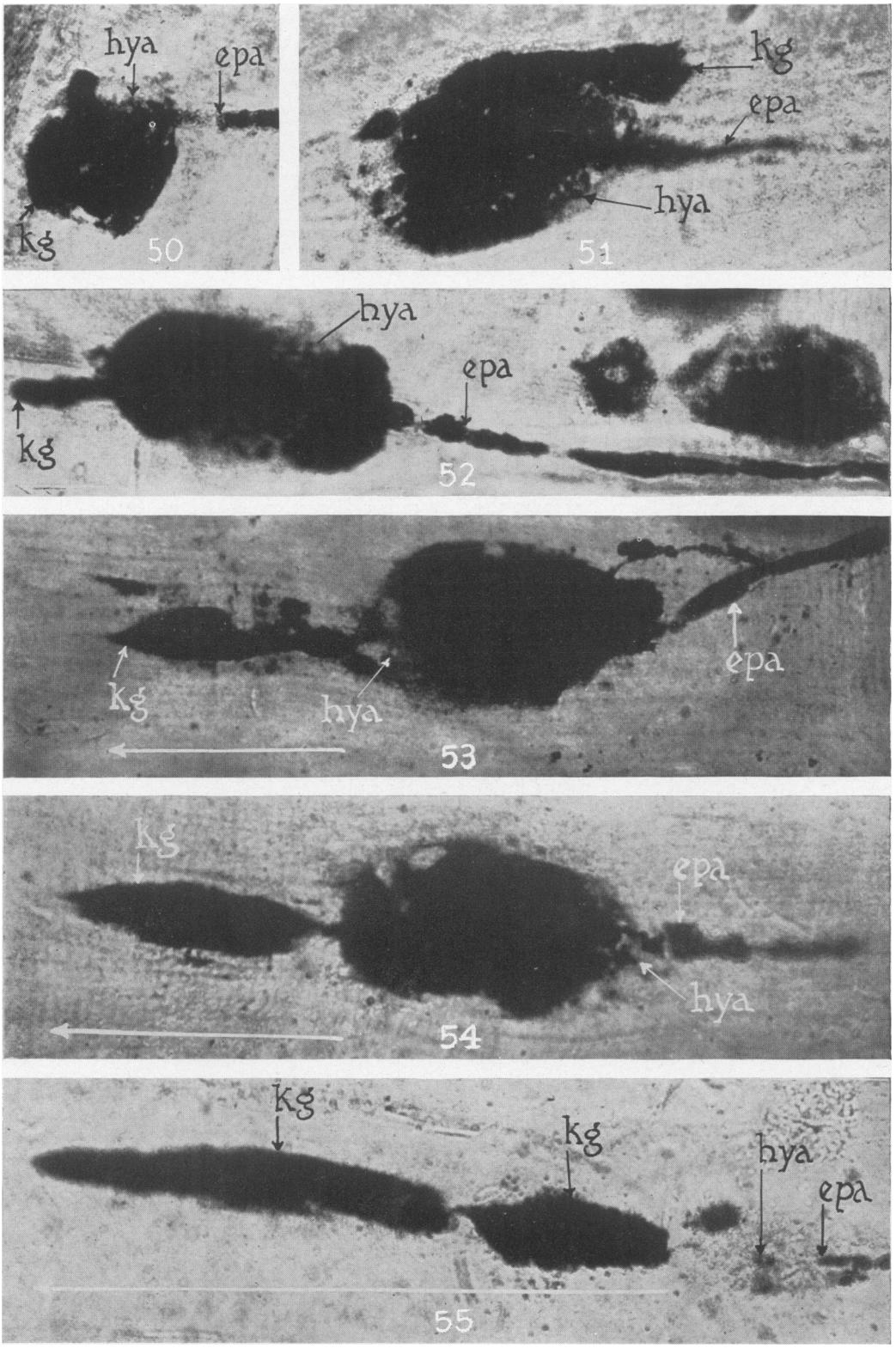
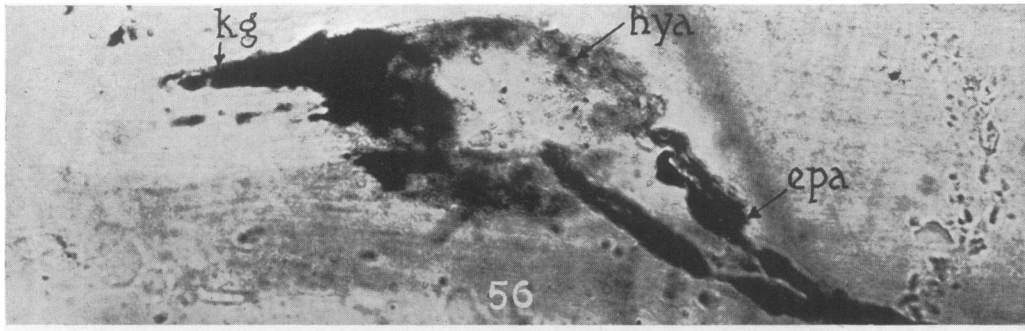
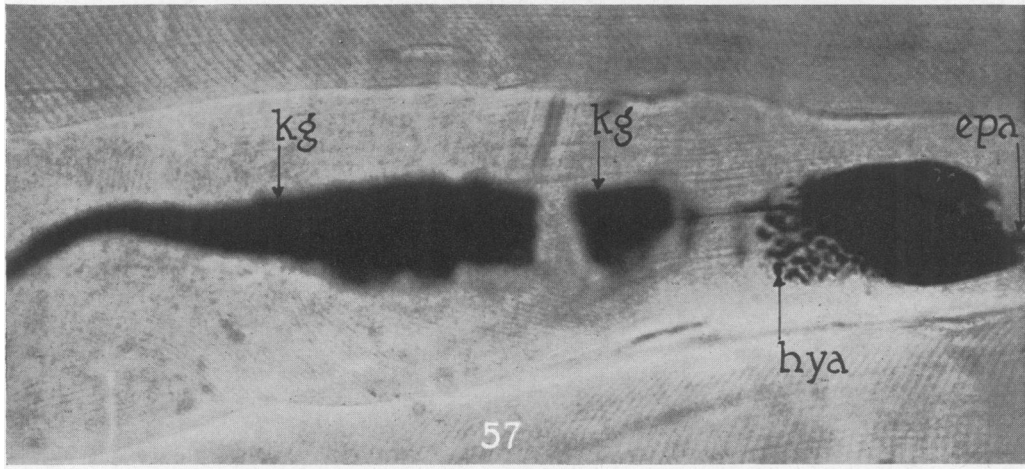
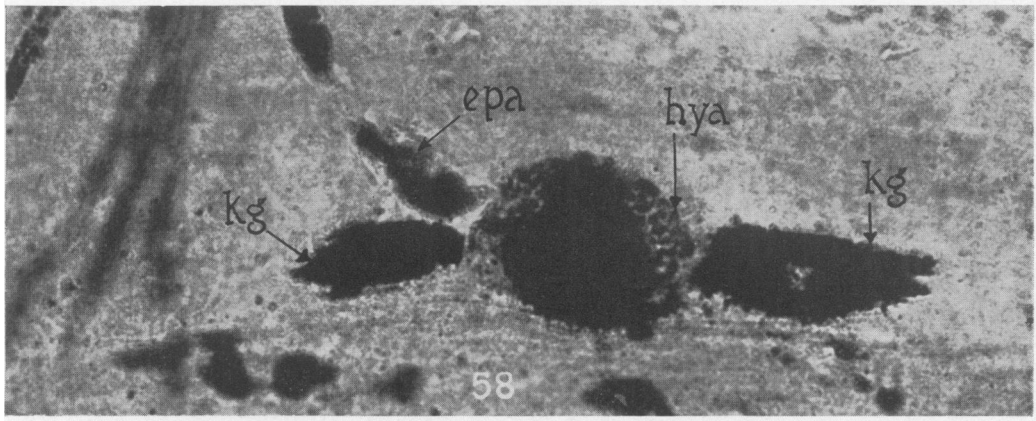

hya
epa
kg
50
kg
epa
hya
51
hya
epa
kg
52
kg
hya
epa
53
kg
epa
hya
54
kg
kg
hya
epa
55

PLATE 48

FIGS. 56 to 59. The pleomorphism of the motor end-plates is illustrated from the gastrocnemius muscle of the white rat, excised 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C., applied to the skin. The hypolemmal axon is in a condition of hyperchrysophilia due to the augmented accumulation of axonic material that has a specific affinity for the impregnating gold. This condition is not due to overstaining. There is a unipolar disposition (Figs. 56 and 57) of the discharged masses of Kühne's granules to the left of the motor end-plates. There is a bipolar disposition of the discharged granules of Kühne (Figs. 58 and 59) to the left and to the right of the motor end-plates. The motor end-plate forms an open ring (Fig. 56) in some places, and in others the axonic ring of the end-plate encloses a dense island of discharged granules of Kühne (Figs. 57 to 59). In some places the cross striations are exceedingly fine and closely spaced (Fig. 57). In such places there is a streamlining effect produced on the pattern of the cross striations. This is evidence that these striations are easily displaced by the material from the nerve ending that becomes incorporated into the myoplasm of the muscle fiber. In other locations (Figs. 56, 58, and 59), the fine cross striations are undergoing replacement by a diffuse arrangement of granules. The alteration of the irregular configurations of both the motor end-plate and the cross-striated muscle occurs instantaneously and with explosive violence. By overstimulation of the neuromuscular apparatus, reflexly produced by heat applied to the skin, a flood of liquid nervous material with a variety of patterns is discharged into the muscle. × 750.


kg
hya
epa
56


kg
kg
epa
hya
57


epa
hya
kg
kg
58

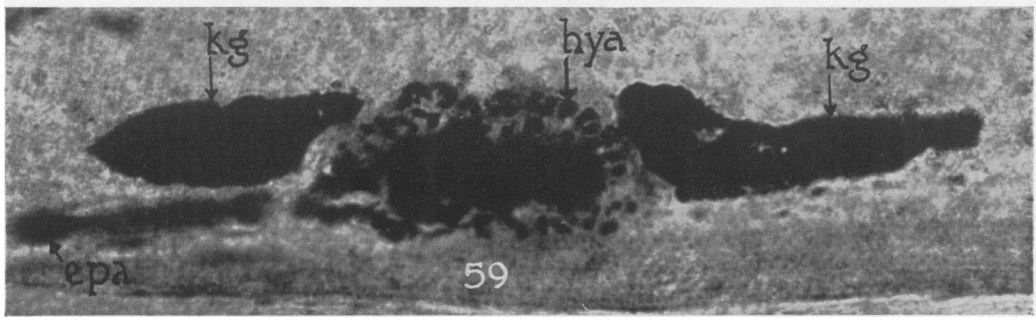

kg
hya
kg
epa
59

PLATE 49

FIGS. 60 to 62. The pleomorphism of the motor end-plates is clearly evident in the gastrocnemius muscle of the white rat, excised 30 seconds subsequent to the heat stimulus of a 10-second exposure in water at 90° C., applied to the skin. There is great variation in the width of the epilemmal axons (Fig. 60) in relation to the motor end-plates. This variation is consistent with the periodic descent of axonic material into the motor end-plates. The discharge of great masses of this material from the nerve ending into the muscle may be multipolar in arrangement (Figs. 61 and 62). The hypolemmal axons of the motor end-plates decrease in size in direct proportion to the transformation and discharge of the granules of Kühne. It is clearly evident that the heat stimulus applied to the skin has an immediate neoformative influence on the structure of the motor end-plate. The variations of design of the neuromuscular apparatus are related directly to variations of physiologic and pathologic activities. The relative disposition of the parts of the motor end-plates is not static and fixed, but is dynamic and highly variable in its architecture. × 750.

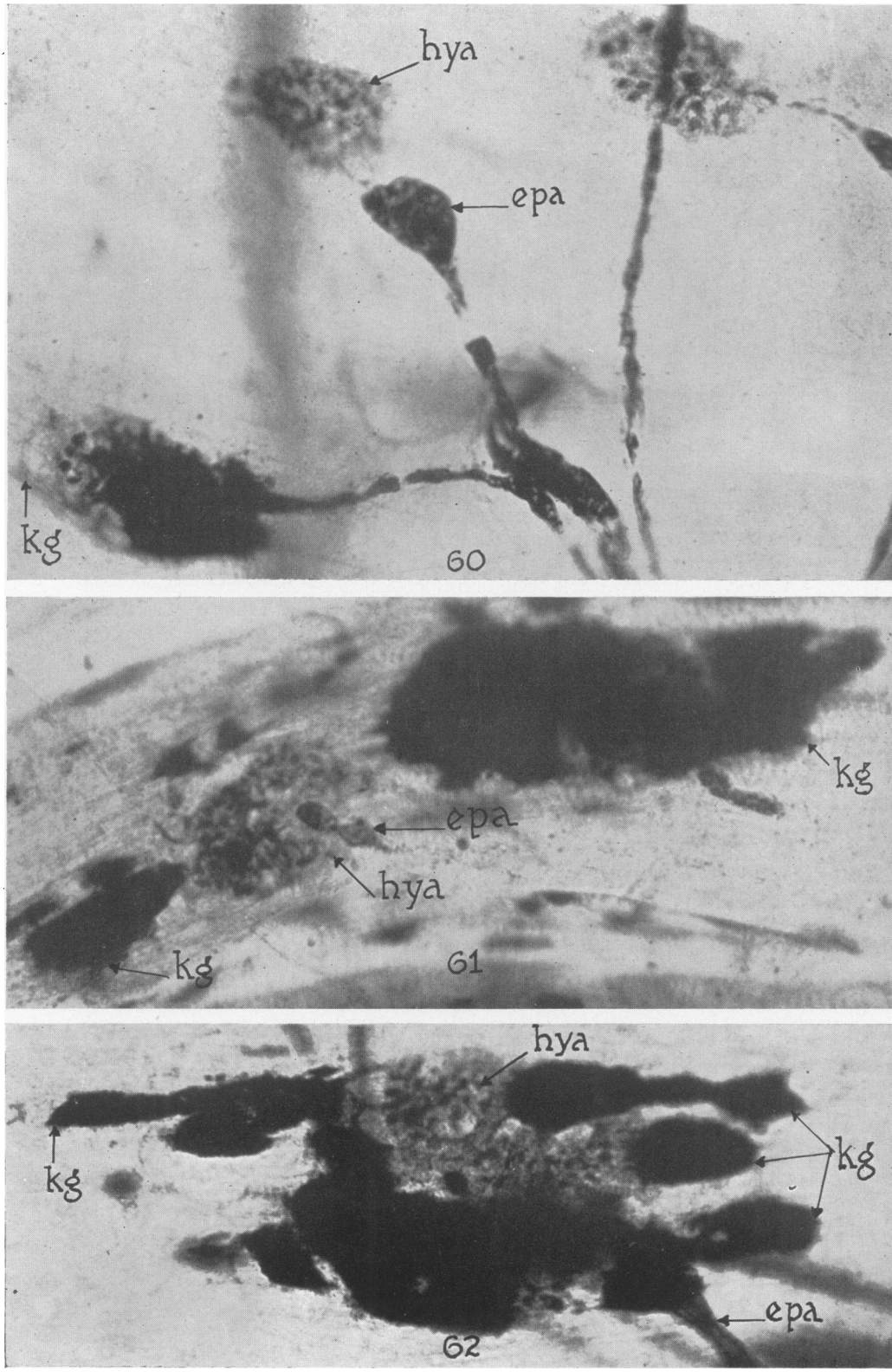
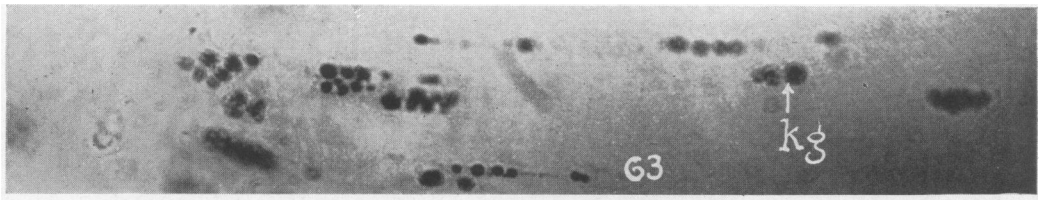
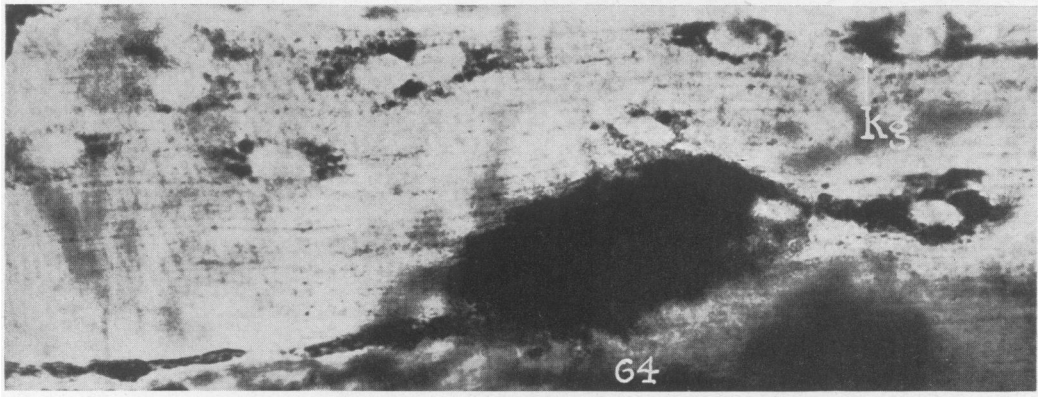
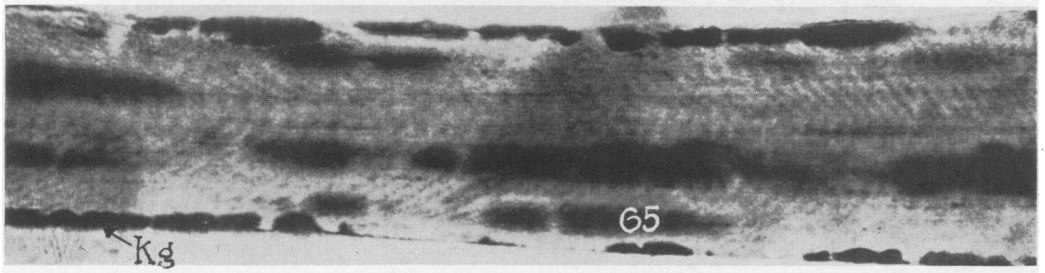

hya
epa
kg
60
kg
epa
hya
kg
61
hya
kg
kg
epa
62

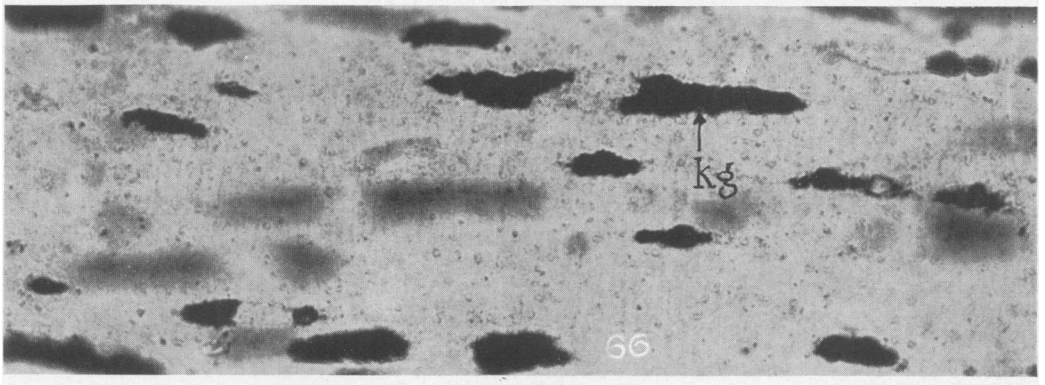
PLATE 50

FIGS. 63 to 67. The pleomorphism of the discharged granules of Kühne into the muscle fiber is clearly evident. These discharged granules are arranged in a variety of patterns, namely: discrete granules arranged in clumps or in series (Fig. 63); discrete or duplex vacuoles (Fig. 64); and elongated streamers or irregular masses (Figs. 65 to 67). It is clear that some of these masses lie within the muscle fiber and underneath the sarcolemma (Fig. 65). In other places they are found between the muscle fibers. In many locations the discharged secretion of the motor end-plates is dense and opaquely impregnated with gold. In other places these masses of Kühne's granules are cross-striated and their pattern of striation may or may not agree with that of the muscle fiber. These masses of nervous secretion discharged into the muscle undergo progressive dissolution and incorporation into the colloidal substance of the myoplasm of the muscle fiber. It is clearly evident, therefore, that there is no fixed boundary or line of demarcation at the junction of nerve and muscle. The substantial secretion from the motor nerve-ending becomes incorporated into the explosive mixture that forms muscle. The neuronic secretion into muscle may be compared roughly to the mercury fulminate that causes the explosion of black powder. × 750.


kg
63


kg
64


65
kg


kg
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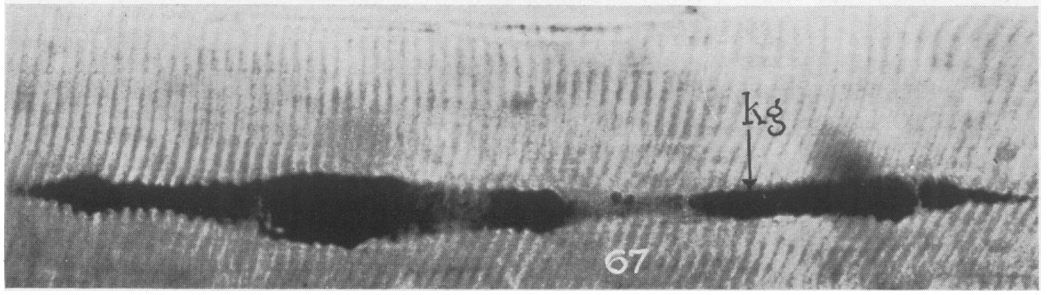
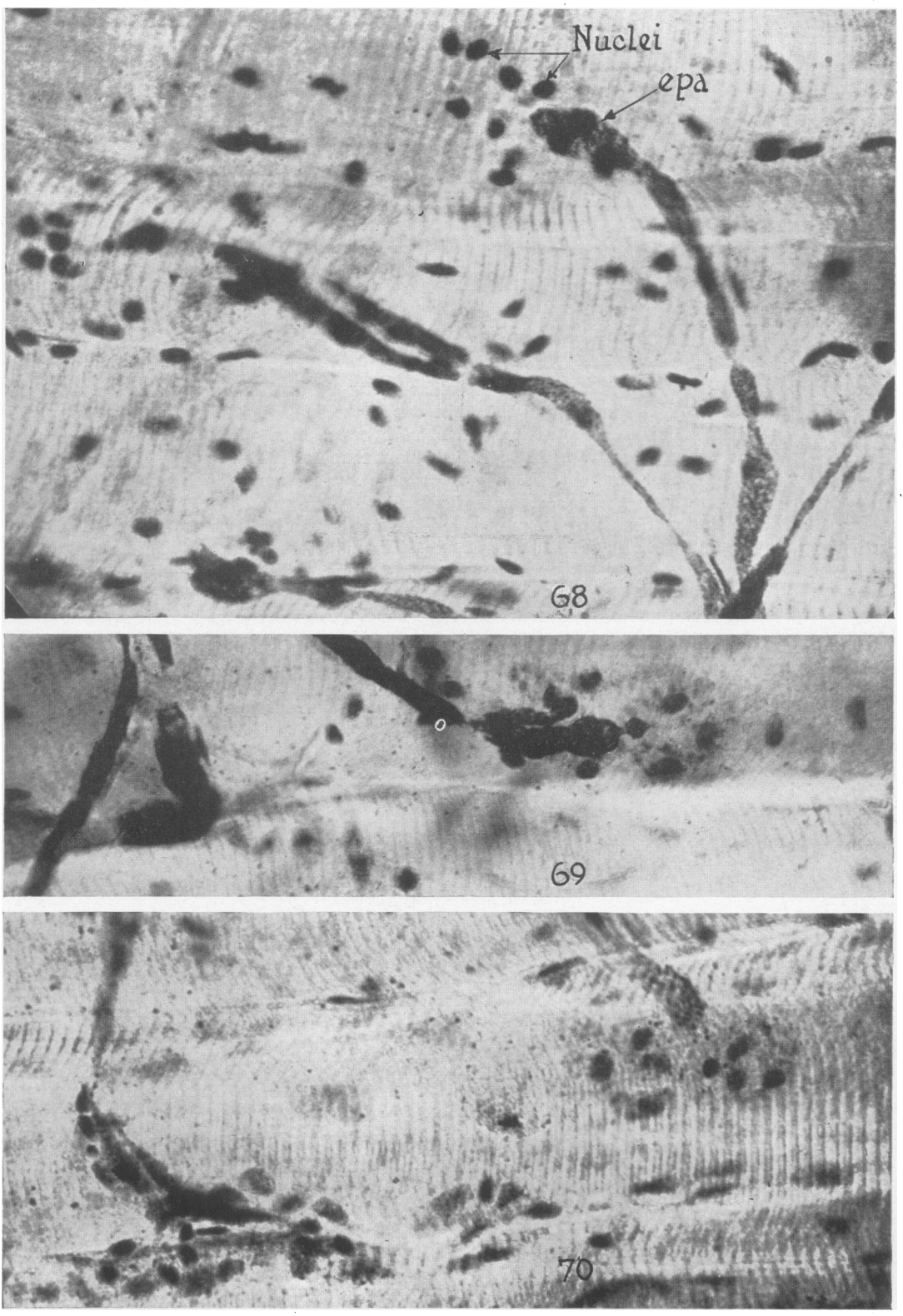

kg
67

PLATE 51

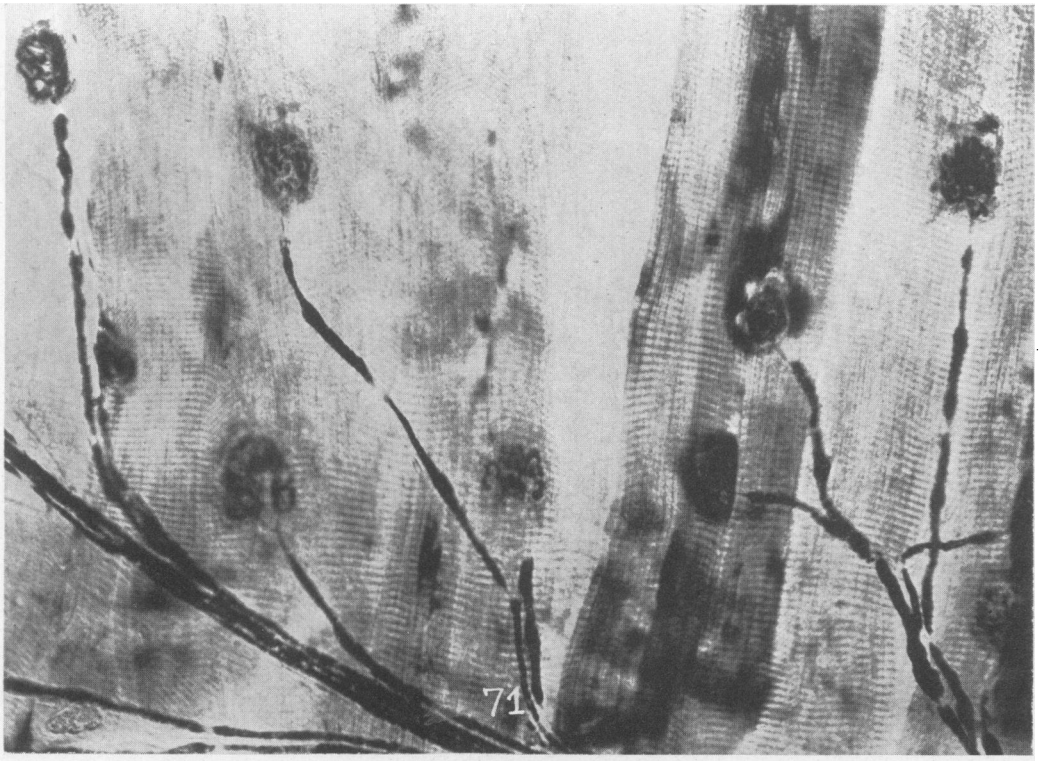
FIGS. 68 to 70. Sprays of epilemmal axons depleted of motor end-plates, 3 hours after scalding the skin of the rat in water at 75° C. for 5 seconds. There is both a hypochrysophilia and an achrysophilia corresponding to the progressive dissolution of the motor end-plates. The terminals of the epilemmal axons form enlarged ends. The hypolemmal axons have disappeared. In the previous location of the epilemmal axons are clusters of dark, pyknotic, rounded nuclei, 6 to 15 in number. These nuclei of the original granular sole of Kühne appear to be modified nuclei of the muscle fiber. Within the cluster of nuclei of the depleted motor end-plates there is granulation of some of the cross striations of the muscle fiber. These morphologic changes are comparable to those produced by the injection of lactic acid locally into the zone of innervation of the muscle. Gold chloride and hemalum stain. × 750.



Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 52

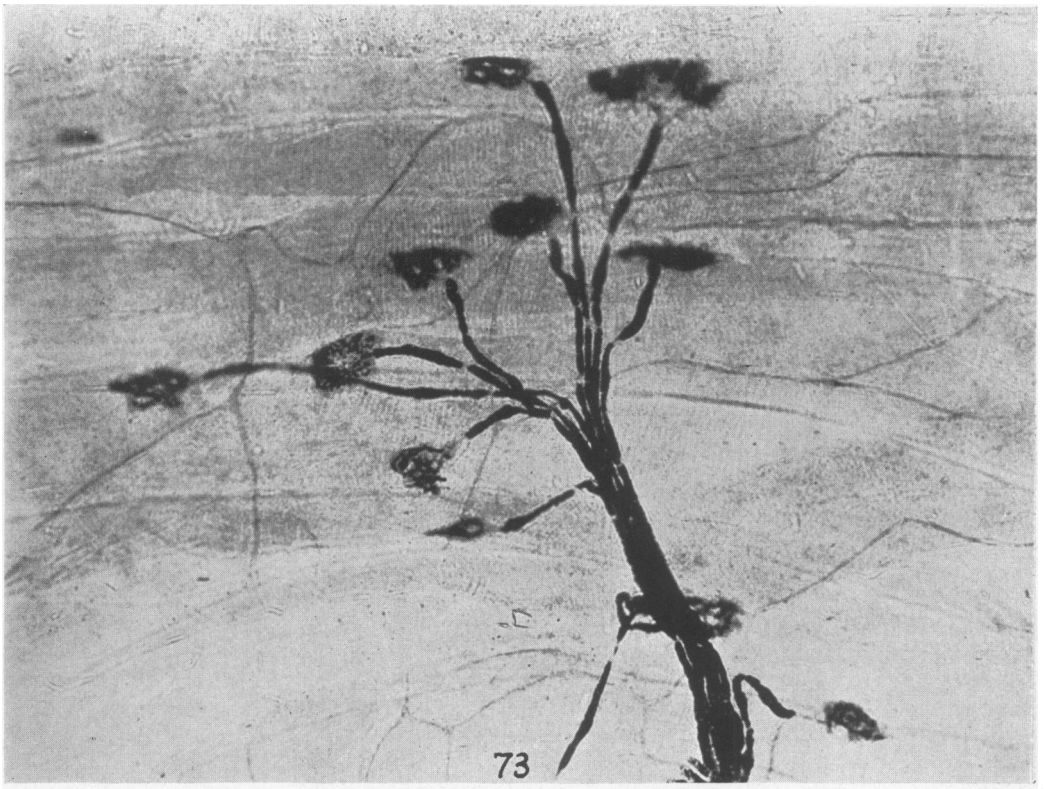
FIGS. 71 and 72. Sprays of axons of medullated nerve fibers of motor end-plates of the gastrocnemius muscle of the white rat, in the relatively normal state, excised 15 minutes after the intraperitoneal injection of nembutal. The variations in the structure of the relatively normal motor end-plates and muscle fibers (Fig. 71) are obvious. The retracted nerve endings are surrounded by a dense rim of Kühne's granules, blackened by impregnation with gold. In one location there is an irregular, halo-like space between the axons of the end-plate and the rim of Kühne's granules. The majority of the end-plates are expanded and have diminution or complete absence of Kühne's granules. The epilemmal axon, although irregularly beaded, is intensely impregnated with gold. The progressive dissolution of the motor end-plates (Fig. 72) is found 2 hours after scalding the skin for 10 seconds in water at 75° C. There is a progressive hypochrysophilia that terminates in complete achrysophilia of the motor end-plates during their progressive dissolution. The internal structure of the muscle fiber is composed of fine cross striations undergoing various stages of granulation. × 300.



Carey, Massopust, Zeit, and Haushalter Motor End-Plates in Thermal Shock

PLATE 53

FIGS. 73 and 74. Sprays of axons of medullated nerve fibers of motor end-plates of the gastrocnemius muscle of the white rat, in the relatively normal state, excised 15 minutes after the intraperitoneal injection of nembutal. There is a variation in the structure of the relatively normal motor end-plates (Fig. 73). The majority, however, are in a state of expansion, and the related muscle fibers are composed of exceedingly fine, closely spaced cross striations. The clearly defined epilemmal axons have an intense affinity for the impregnating gold. This normal morphologic state (Fig. 73) is in striking contrast to the motor end-plates and epilemmal axons from the gastrocnemius muscle (Fig. 74) excised 2 hours after the entire body of the rat (except the head and neck) had been immersed for 10 seconds in water at 75° C. There is a complete disappearance of the motor end-plates, the previous location of which is characterized by achrysophilia or absence of impregnation with gold. There is an irregular cluster of granules that occupies the location of the liquefied motor end-plates. There is a hypochrysophilia of the epilemmal axons. The depletion of these epilemmal axons of their gold-staining material extends in a centripetal direction away from the granular sites of the previous location of the motor end-plates. Exposure of the skin surface to water at a scalding temperature results in a thermal shock, part of the lesions of which are reflected in the neuromuscular apparatus. There is a denervation of the muscle fibers due to the structural disappearance of the motor end-plates and epilemmal axons. The study of the sequence of changes from the normal state to the stage of complete structural exhaustion reveals the secretory mechanism of the neuromuscular apparatus. × 300.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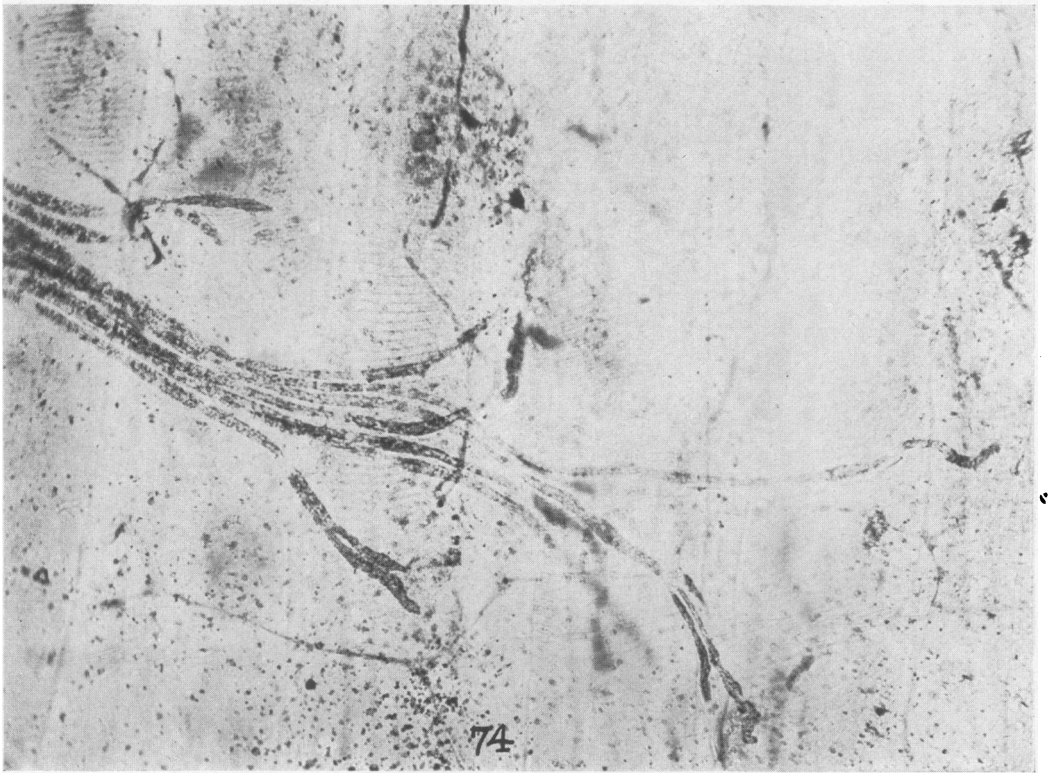
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