# HYPERPLASIA AND REGENERATION OF THE MYOCARDIUM IN INFANTS AND IN CHILDREN *

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The purpose of this paper is twofold: first, to point out that in cardiac hypertrophy of infants there may be an active proliferation of myocardial elements in addition to growth by enlargement of the individual muscle fibers; and secondly, to prove that during childhood heart muscle fibers may regenerate following severe injury. Both of these observations are in contradiction to current opinion. In textbooks and journals it is stated that the increase in size of the heart in cases of cardiac hypertrophy is due to an increase in size of the individual muscle fibers, and is not the result of a multiplication of these. Furthermore, it is almost axiomatic that the one and only form of myocardial healing subsequent to necrosis of heart muscle fibers is by the proliferation of connective tissue with ultimate repair by fibrosis. The former hypothesis in all likelihood holds true for the enlarged hearts of adults irrespective of cause, and is based primarily on the following two reasonably well established facts. First, careful measurements of the muscle fibers of hypertrophied hearts of adults have shown that an increase in size and weight of the heart may be explained mathematically on the basis of an increase in size of the individual myocardial fibers. Secondly, patient search throughout the myocardium in such cases of cardiac hypertrophy has failed to reveal any positive evidence, in the form of mitoses, of true myocardial proliferation. This frequently recorded absence of mitoses is also the most important single fact on which the statement that heart muscle fibers can not regenerate is based.

## MYOCARDIAL HYPERPLASIA

It is rather difficult to determine at what age an infant's heart may be considered to have acquired its full complement of muscle fibers. It is generally believed that at the time of birth of a full-

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term child, the heart, though less than a tenth of its adult size, is completely formed. The rarity with which a single mitotic figure is found in average sized hearts, even at birth and during the first month of life, lends weight to this viewpoint and strongly suggests that an active proliferation of muscle elements under ordinary conditions ceases quite early. The increase in size of the infant's heart from this period to adult life, estimated by a progressive gain in weight, may be readily accounted for by an increase in size of the individual muscle fibers. The chance finding of an isolated mitosis in a heart muscle fiber of an average sized heart of a newborn infant is probably nothing more than a sign of a normal but somewhat delayed physiological process. In contrast to this the presence of many mitoses in heart muscle fibers of enlarged hearts in infants of 1 and 2 years of age, though probably nothing more than an acceleration of this normal growing process, may be justifiably regarded as a type of hyperplasia. This possibility of an increased proliferation of heart muscle fibers has been entirely overlooked as a factor in the histiogenesis of cardiac hypertrophy of infants.

A study of this problem of the normal and pathological growth of heart muscle elements was prompted by the finding of an unusually large number of mitoses in the myocardial fibers of an enlarged heart of a 6 months old child. This child died in uremia, the result of an anomalous development of the mucosa in both ureters, in which valve-like folds were formed causing complete intermittent urinary obstruction. The heart of this child was well formed. It weighed 60 gm., which is just twice the average weight for a child of this age and size. It showed particularly an enlarged left ventricle with an increase in thickness of the left ventricular wall. In a careful histological examination of two other enlarged hearts from infants of 12 and 20 months of age respectively — comprising a case of so-called primary idiopathic hypertrophy, as well as a case of cardiac hypertrophy secondary to coarctation of the aorta — it has also been possible to demonstrate the presence in heart muscle fibers of mitoses in all stages of nuclear division. The debatable interpretation of this finding as to whether it should be considered as true hyperplasia or merely a somewhat more active stage in the natural histiogenesis of the myocardium would seem to be of secondary importance. More important is

the indisputable fact that during this early age growth of the myocardium by an active proliferation of muscle elements may and does take place in cardiac hypertrophy of infancy.

The histological appearance of the myocardium in cases of cardiac hypertrophy in infancy varies. In the case of congenital idiopathic hypertrophy the increase in size of the individual fibers was scarcely perceptible. The fibers showed normal branching and well developed myofibrils. Mitoses were seen in the muscle fibers in the peripheral portion of the myocardium. In the 2 cases of secondary hypertrophy associated with coarctation of the aorta and diminished urinary elimination, the muscle fibers were distinctly larger than normal and the myofibrils were increased in number. This true hypertrophy was not found absolutely uniformly throughout the ventricular wall, for at times small delicate fibers and large thick fibers were seen lying side by side. In these 2 cases, in addition to an increase in size of the muscle fibers, mitoses were also found. They were most numerous toward the periphery and toward the tip of the left ventricle. Both cases showed normal myocardial branching. The fibers were regularly arranged and transverse striations throughout the myofibrils were everywhere seen. At this age, no transverse lines of segmentation, intercalated discs, have yet appeared.

The division of the nucleus occurs at the center of the fiber (Fig. 1). All stages of mitotic division are recognizable, including the single spireme, the monaster, diaster and double spireme (Figs. 2, 3 and 4). At the site of nuclear division one centrosome is seen at the end of each spindle (Fig. 5). The spindle is large and long search may be necessary to find one entirely intact (Fig. 6); serial sections are helpful in distinguishing questionable mitoses. The chromatin material appears as clumps of granules and short rods and stains intensely with hematoxylin. This chromatin material in a dividing nucleus may be scattered rather irregularly over the spindle (Figs. 2 and 3). The cytoplasm at the site of nuclear division is comparatively clear and is free of myofibrils (Fig. 6). Usually myofibrils showing transverse striations are seen at each side of the spindle, while just beyond each end of the dividing nucleus the cytoplasm becomes more intensely stained and delicate transverse striations, best demonstrated by Mallory's phosphotungstic acid hematoxylin stain, are visible in the myoplasm be-

fore longitudinal fibrils in this area are clearly recognizable. This differentiation of these transverse striations in the myoplasm appears to represent the early growth and development of the myofibril in the proximity of the dividing nucleus.

## MYOCARDIAL REGENERATION

During the preparation of this paper, which originally was planned to include only the problem of myocardial proliferation in cardiac hypertrophy in infancy, my attention was called by Dr. F. B. Mallory to an autopsy that was performed under his supervision in 1916. A boy, 6 years of age, had died several days after the onset of diphtheria. The most striking finding at the postmortem was the presence of a dilated heart showing a yellowish discoloration of the myocardium. A careful histological examination of the heart muscle showed severe degenerative changes with necrosis of the muscle fibers. This was associated with edema of the stroma and a moderate exudate of endothelial leukocytes and lymphocytes. There was an early proliferation of connective tissue of the myocardium. Most interesting, however, was the presence of isolated mitotic figures in heart muscle fibers bordering these zones of destruction (Fig. 7). This case appears to be the first to have been recognized as showing positive evidence, in the form of mitoses, of true myocardial regeneration. This is apparently a most unusual finding and yet its presence is absolute proof that regeneration may occur. Such observations as this point to the necessity of a more careful histological study of this condition in children. Moreover, it probably explains, in part at least, the frequent absence of myocardial scarring in hearts of children who, months or years earlier, had suffered severe myocardial injury. Finally, it supports from a histological standpoint the recognized need of prolonged rest during the period of recovery and repair following severe myocardial injury; and at the same time it offers the possibility and hope of a *restitutio ad integrum* subsequent to necrosis of myocardial fibers in children.

## REVIEW OF LITERATURE

To review the rather extensive literature dealing with the subject of the growth and regeneration of heart muscle fibers it is necessary to begin with a number of papers that appeared about

the middle of the last century. At that time the development and use of the microscope was limited and the methods used in the preparation of sections for histological study were comparatively poor. For these reasons it is difficult to evaluate the conclusions drawn in these early papers, for often these were based much more on theory than fact. Goldenberg in 1886 reviewed the literature on this subject since 1850, discussing the earlier papers of Kölliker,[1] Foerster,[2] Vogel,[3] von Rokitansky,[4] Friedreich,[5] Paget,[6] and Rindfleisch,[7] a group of investigators who considered the hyperplasia of muscle fibers in cardiac hypertrophy merely as an accepted fact. It is of interest that Lebert [8] as early as 1857 pointed out that there was no histological basis for this point of view. Goldenberg [9] believed primarily in the hypertrophy of the individual muscle fibers as the best explanation for myocardial hypertrophy. He said, however, that hyperplasia by longitudinal splitting could occur. Considerable importance was attached to a paper appearing in 1875 by Zielonko,[10] a student of Virchow. This investigator, working on the hearts of frogs and rabbits, came to the conclusion that the hypertrophy of the heart was not merely the result of an enlargement of individual muscle fibers, but probably the outcome of cellular hyperplasia as well. This hypothesis was transferred at once from animal to man to explain the myocardial hypertrophy of the human heart, but it lacked proof. No proliferation had been seen and the idea was based on a second and equally questionable hypothesis, "that hypertrophies are greatest in the young and middle ages, because during this period physiological development is still going on, and growing stimuli are at hand." Tangl,[11] after making careful measurements on heart muscle fibers, and after failing to find a single mitosis in a study of hearts showing cardiac hypertrophy, came to the conclusion that hypertrophy of the heart was to be explained entirely by a hypertrophy of the muscle elements. Ziegler [12] adopted a similar view but added that it is possible that the number of muscle cells are increased as well. Wideröe [13] also could find no mitoses and believed that in the absence of mitoses one could reasonably conclude that in cases of cardiac hypertrophy one was dealing simply with a hypertrophy of muscle fibers. Adami and Nicholls,[14] in speaking of hypertrophy of the myocardium, say, "Microscopically the muscle fibres are increased in

thickness and probably in number," but found no absolute evidence of true proliferation.

The idea of myocardial proliferation gained some support from a group of investigators who studied the repair process following myocarditis. They believed they saw signs of active regeneration following severe injury. Saltykow [15] in 1908 made the statement that in both acute and chronic myocarditis the muscle elements play a very important rôle in regeneration, with the result that there is a formation of new myocardial fibers. No mitoses were found in any of these cases. This paper was supported by Heller,[16] who made many drawings of muscle fibers, showing variations in size and shape of the nuclei, but again no mention was made of the presence of mitoses. Warthin,[17] as recently as 1924, believed he saw signs of muscle regeneration in 3 of 15 cases of diphtheritic myocarditis and said, "Near the necrotic or degenerated portion of the heart muscle, the nuclei show great variety in size and form. They increase in length and show evidence of longitudinal splitting in every possible stage of division. The living muscle substance bordering the injured area also undergoes longitudinal splitting into muscle bands containing nuclei. These bands grow into the perimysial tubes filling these up, replacing cell detritus and connecting with the living muscle on the other side of the defect. Muscle bands without nuclei, but accompanied by myoplastic nuclei, also extend into the tubes occupied by the dead muscle substance. These bands lie at the periphery of the tube, and in some cases appear to form a hollow cylinder enclosing the remains of dead muscle substance." No mention is made here by Warthin of even a single mitotic figure.

The more recent papers of Collier [18] and Karsner, Saphir and Todd [19] conclusively pointed out that in myocardial hypertrophy there is an increase in width and length of the sarcomere, or in other words, a hypertrophy of the muscle fiber. These latter investigators repeating the work of Goldenberg and Tangl made careful measurements of the muscle fibers of both hypertrophied and atrophied hearts of adults. They considered that the number of nuclei per field in an atrophic heart is increased, but a most careful search failed to disclose a single mitotic figure. They added, however, "It is possible that since the hearts were obtained postmortem, any mitotic figures present might have been com-

pleted." Kaufmann,[20] Aschoff,[21] and Mönckeberg [22] also stated emphatically that in myocardial hypertrophy the fibers increase in volume with an increase in the number of myofibrils and a proportionate increase in the size of the nucleus. There is no proliferation with an increase in the number of fibers, and mitotic division of the nuclei is absent. MacCallum,[23] and Boyd [24] in their texts likewise subscribe to this view. Mention of the possible proliferation of myocardial fibers in infancy was made by Rössle [25] who said, "With age the fibers increase in thickness, the number of bundles increases, fibers increase in length and muscle elements increase after birth." The possibility of regeneration of muscle elements was supported by Mallory [26] who stated that in very young children there is a general hyperplasia of muscle elements following injury.

## Summary

Evidence is presented in the form of mitotic division of the nuclei of heart muscle fibers to indicate first, that in cardiac hypertrophy of infants a proliferation of heart muscle fibers can take place, and secondly, that in severe myocardial injury in children, regeneration of myocardial elements can occur.

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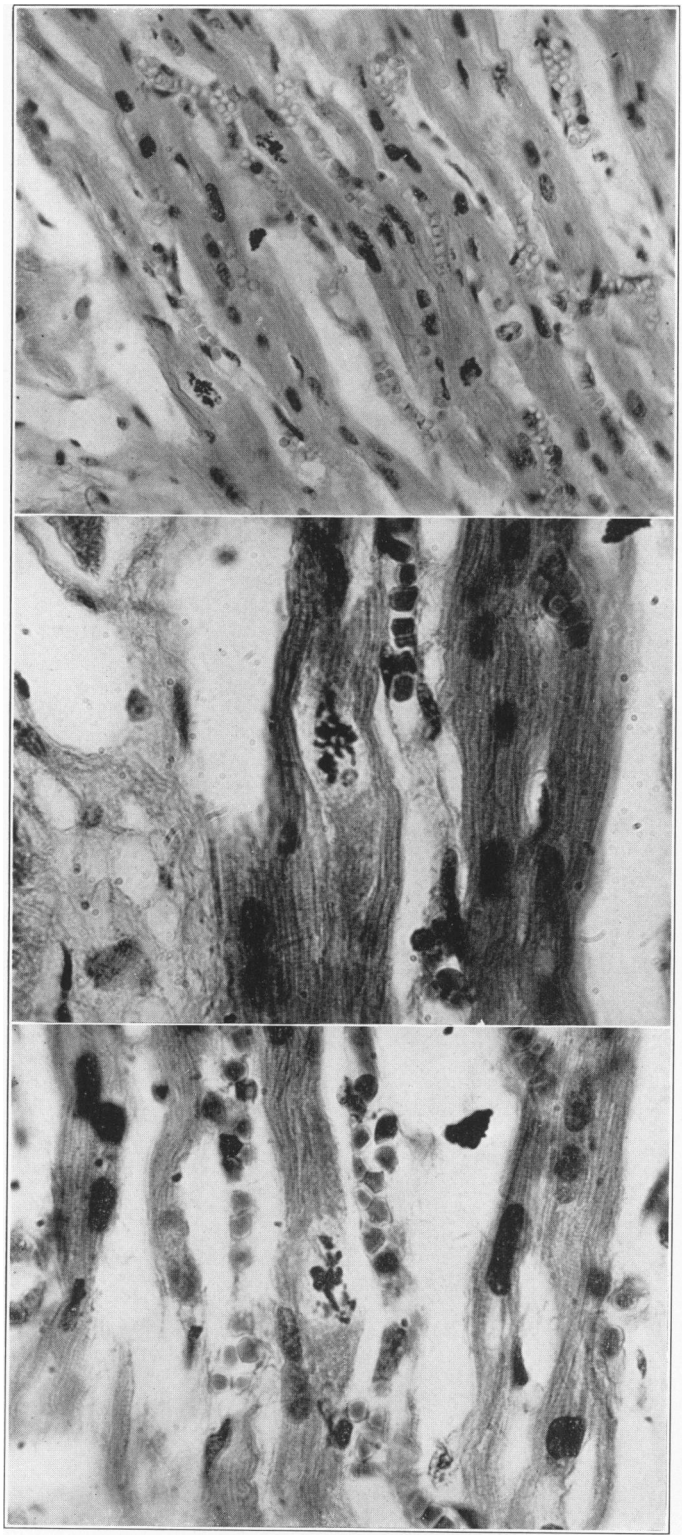
## DESCRIPTION OF PLATES

### PLATE 117

FIG. 1. Section of myocardium showing three mitotic figures in heart muscle fibers. The fibers vary in width and show branching. Capillaries are dilated. There is an increase in fluid in the intercellular spaces. Myocardial hyperplasia, congestion and edema. × 330.

FIG. 2. One of the three mitotic figures from Fig. 1 at greater magnification. This nucleus is cut slightly on the bias; the small circle is just below one pole of the spindle, and the chromatin material appearing as rods and granules is clustered about the spindle. No definite arrangement of the chromatin can be distinguished. The cytoplasm immediately adjacent to the spindle is comparatively clear, rather finely granular and free of both transverse and longitudinal striation. Myofibrils showing transverse striation are visible at both sides of the dividing nucleus. × 740.

FIG. 3. One of the three mitoses seen in Fig. 1 at higher magnification. A spindle is not visible. The chromatin appears as rods and granules unevenly distributed, forming in the center a rather coarse clump. The cytoplasm at the site of nuclear division is comparatively clear. At each side myofibrils showing cross striations are visible. × 740.



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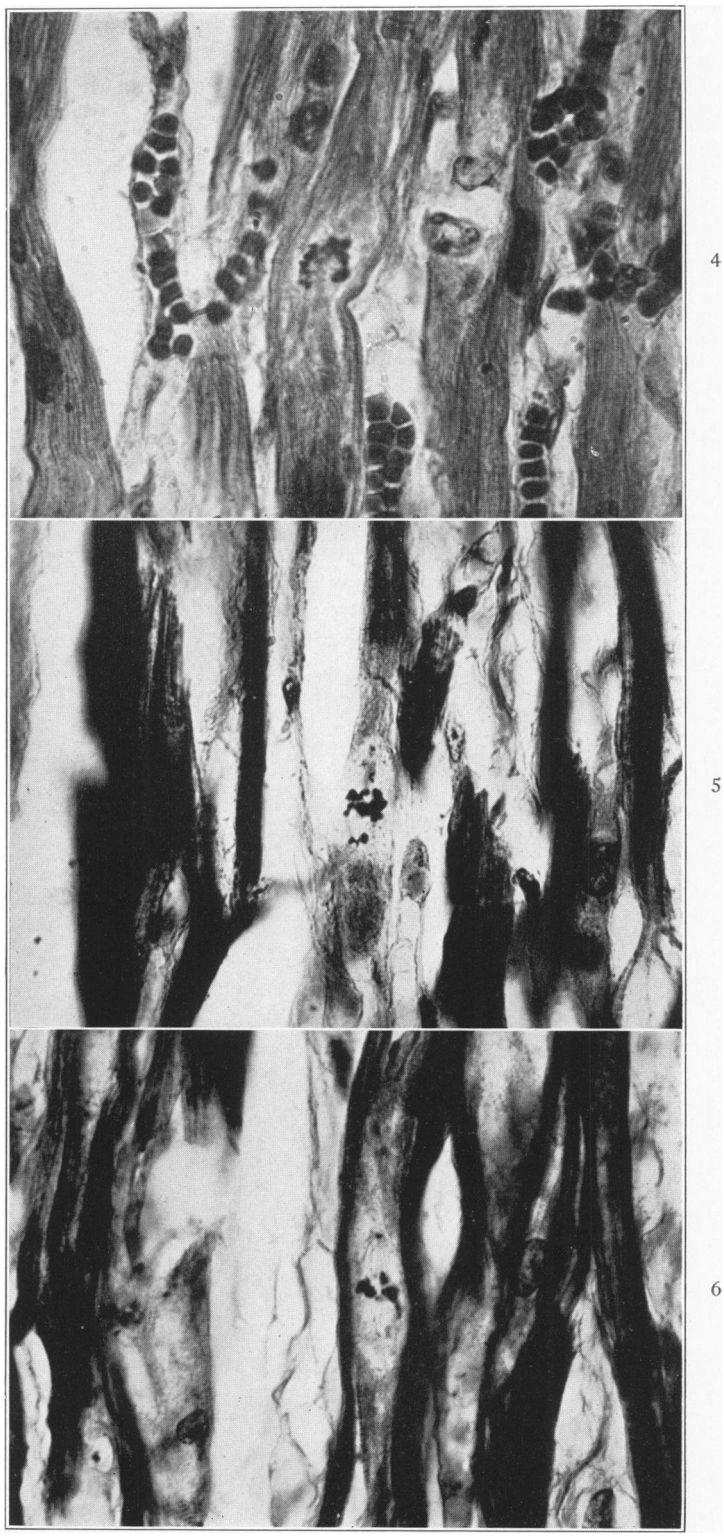
## PLATE 118

FIG. 4. One of the three mitoses seen in Fig. 1, more highly magnified. The mitotic figure is incomplete. No spindle can be distinguished. The chromatin is forming an incomplete circle, appearing as short rods and granules. A comparatively clear zone completely surrounds the dividing nucleus. Myofibrils showing transverse striations are distinguishable laterally and above and below. × 740.

FIG. 5. Section of myocardium, showing a mitotic division of a nucleus of a heart muscle fiber. A complete spindle with centrosomes is visible. The chromatin is arranged at the center, forming two rather even rows of coarse granules and rods (monaster). The cytoplasm at the site of nuclear division is clear and very finely granular. Laterally a delicate, nonstriated membrane bounds the muscle fiber. Above and below the nucleus the cytoplasm is denser, stains more deeply, and transverse striations appear before individual myofibrils are recognizable. × 740.

FIG. 6. Section of myocardium, showing a mitotic figure in nucleus of heart muscle fiber. The entire spindle is recognizable, including one centrosome. The chromatin appearing as clumps of granules and short rods is gathered about the center of the spindle to form an equatorial plate. There is a clear zone about the nucleus. Myofibrils showing transverse striations are seen at each side of the nucleus. Above and below the nucleus the cytoplasm is more intensely stained and transverse striations are visible in the myoplasm before longitudinal fibrils are clearly seen. × 740.



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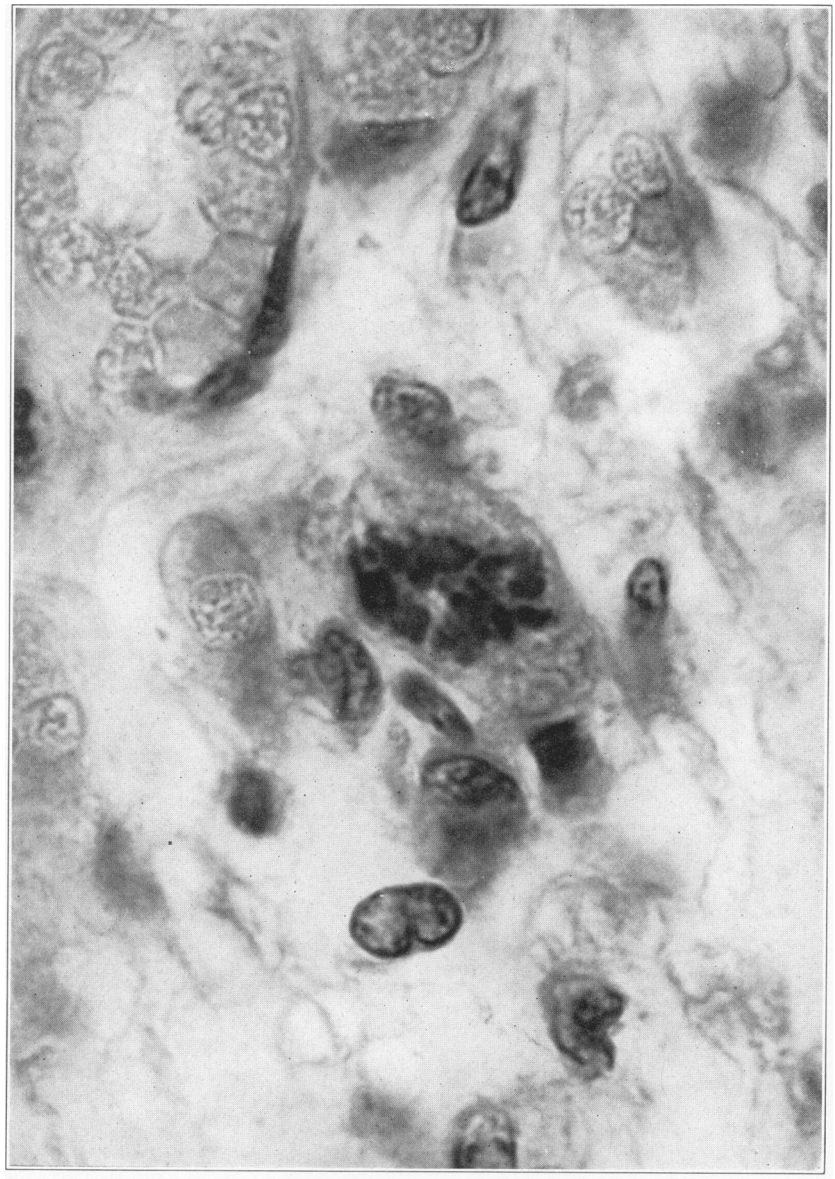
## PLATE 119

FIG. 7. Section of myocardium from a 6 year old boy who died from diphtheria. In the center of the field is a segment of muscle fiber showing a nucleus in an early stage of mitotic division. The chromatin appears as coarse clumps and short rods and is gathered to form an irregular spireme. At this stage no spindle is recognizable. Capillaries are dilated and the tissue shows both a fluid and cellular inflammatory exudate. (BCH–A–16–66, Dr. Mallory.) × 2000.



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