THE PATHOGENESIS OF WAXY DEGENERATION OF
STRIATED MUSCLES (ZENKER'S DEGENERATION). 1

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Although there is a considerable literature on various features
of the waxy degeneration of striated muscles which Zenker
described in connection with typhoid fever, yet there has been nothing
definite ascertained concerning the cause of this very striking change
in the structure of voluntary fibers. Zenker believed that the cause
of the hyaline appearance is an infiltration of an albuminous material
from outside the cell, so that all the structures of the fiber are
packed and swollen with proteins, thus obliterating the usual struc-
tural elements. Later writers have taken the view that the essen-
tial process is a coagulation of the myosinogen, although, as
Beneke 2 pointed out, in rigor mortis of uninjured muscles there is
a coagulation of the myosinogen without the production of any-
thing resembling the characteristic hyaline appearance of waxy
degeneration. This author found that involuntary muscle fibers
placed in physiological salt solution show areas of hyaline trans-
formation resembling in appearance waxy degeneration, which he
attributes to the dissolving out of the muscle proteins that are
soluble in salt solution. The hyaline material produced in this
way swells up and dissolves quickly when placed in one per cent. of
hydrochloric acid or dilute acetic acid, and the change occurs more
rapidly if the muscle is immersed in a large volume of salt solu-
tion than when it is in a small amount of solution. Erb 3 found
that the presence of proteins in the salt solution decreased the rate
of development of this form of experimental degeneration, and it

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2 Virchow's Archiv, 1885, xcix, 71.

3 Virchow's Archiv, 1888, xliii, 108.
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goes very slowly in blood serum. Whether this sort of hyaline degeneration which occurs in non-striated muscles placed in salt solution is the same as that occurring in pathological striated muscles does not seem to have been determined, but it is difficult to correlate the conditions occurring in muscles in typhoid, acute myositis, etc., with those to which muscles soaked in salt solution are exposed.

Nesti claims that the waxy degeneration of pathological processes occurs after injury of the contractile substance of the muscle fibers when these fibers lie between living fibers, so that a partial absorption of the degenerating proteins is possible; this absorption of the contents of the sarcolemma he considers to account for the typical physical appearance of this condition. Waldeyer noted that the waxy muscle fibers reacted quite the same to various chemical reagents as did normal muscle fibers.

Cohnheim observed that the muscle fibers of the tongues of living frogs may undergo a form of waxy degeneration while being examined under the microscope, and this process has been studied further by Weihl and by Thoma. If a muscle of the tongue of a frog is injured with the point of a needle while being viewed under the microscope, within from three to five seconds two small waxy swellings will usually appear and in a few seconds or minutes spread across the fiber and draw away from one another; similar changes occur when the muscle is cut across. Thoma believes that the waxy appearance is due to the extreme contraction of the injured portions of the fibers, which cause the structural elements of the muscle fiber to be so closely packed together that the striated appearance is lost; the silver-grey appearance of the waxy muscle fibers is probably due to phenomena of refraction and interference caused by the compact striations. Although Thoma considers that this experimentally produced condition is in some respects similar to that occurring in the waxy degeneration of muscles of typhoid and other diseases, yet he points out that the degeneration of typhoid muscles extends for a considerable distance.

\(^1\) Lo Sperimentale, 1894, xlvi, 316; abstract in Cent. f. Path., 1895, vi, 215.
\(^2\) Virchow's Archiv, 1865, xxxiv, 473.
\(^3\) Virchow's Archiv, 1874, lxi, 253.
\(^4\) Virchow's Archiv, 1906, clxxxvi, 64.
while the degeneration in the frog's tongue is of very limited extent, and hence the processes may be different.

I have not been able to find any statements concerning the nature of the changes in the muscles in waxy degeneration that are more definite than those quoted above, which suggest several possible explanations of the hyaline appearance, namely: (1) Infiltration with protein until the muscle is made of a uniform homogeneous structure; (2) absorption of part of the muscle proteins, leaving others in a hyaline form; (3) coagulation of the muscle proteins in a homogeneous form; (4) optical phenomena, depending upon a close packing of the strie-forming elements until the structure appears to be uniform. There is, however, no definite proof that any or all of these processes play a part in producing the typical waxy degeneration of Zenker.

One rather striking fact about this waxy degeneration as we observe it in pathological processes is that it is produced under much the same conditions that give rise to cloudy swelling or coagulation necrosis in other types of cells, e. g., bacterial toxins, ischemia and trauma. Why the muscle cytoplasm should become hyaline from the same causes that make the cytoplasm of other cells granular became to me a question of interest, and in discussing the matter with Prof. A. P. Mathews he suggested as another hyaline transformation of proteins the homogeneous swelling which occurs in fibrin that is placed in dilute acids. In view of the fact that muscles are known to produce considerable quantities of sarcolactic acid under certain conditions, and that muscle contains a coagulable protein quite similar to fibrinogen, the analogy seemed very suggestive and I have performed a number of experiments to ascertain whether the lactic acid of the muscle cell might not play a part in producing the condition of waxy degeneration which is so peculiar to muscle cells.

The results of these experiments seem to indicate that this hypothesis is well founded: namely, that the homogeneous transformation of muscle fibers typical of Zenker's waxy degeneration is analogous to the swelling of fibrin in acids, and may be due to the action of the sarcolactic acid formed by the muscle fibers themselves. It hardly seems necessary to give in detail all the protocols of the
experiments, both positive and negative, largely on account of their simplicity. The results may be given briefly as follows: If small pieces of voluntary muscle, freshly obtained, are placed in physiological salt solution and kept either at room temperature or at 37° C., with toluol to render the materials aseptic, the muscle cells undergo autolysis, and histological examination of fixed and stained specimens removed at different intervals shows a gradual decrease of the staining power of the cytoplasm, the longitudinal striations becoming coarser and more distinct, and eventually the cytoplasm falls into a granular debris. The nuclei persist for a few days, becoming pyknotic and gradually disappearing, while more or less of the striated appearance can be discerned even after the autolysis has continued for a month at room temperature. If heated serum is used instead of salt solution the changes are very much the same, except that the solution of the muscle components is somewhat slower, while when fresh serum is used autolysis takes place much less rapidly, although the structural changes in the muscle are quite the same in character. Evidently, therefore, simple antiseptic autolysis of muscles in vitro does not cause changes at all comparable to those of waxy degeneration, but produces rather the ordinary granular disintegration common to all autolyzing cells. In aseptic autolysis accomplished by sterilizing the external surface of large pieces of muscle by scalding, and keeping in sterile dishes while the central parts of the muscle digest themselves, similar negative results have been obtained.

If, on the other hand, the muscle is placed in varying strengths of lactic acid in physiological salt solution, the results are quite different. Even as dilute a solution as 1/4 N. lactic acid causes within an hour or two at 37° C. a distinct swelling of the ends of the fibers, and of the entire length of the most superficial part of the muscle where the lactic acid comes into most intimate contact with the fibers; the swelling is associated with a loss of the transverse and an obscuration of the longitudinal striations. Solutions of 1/2 N. strength cause in from one to three hours a very striking homogeniety of the structure of the swollen fibers, perfectly comparable to the appearances typical of the waxy degeneration seen in pathological muscles. In such homogeneous muscles
the nuclei still stain, although they are smaller and stain more intensely than normal muscle nuclei. If solutions stronger than $\frac{1}{8}$ N. lactic acid are used the swelling and loss of striation are less evident, apparently because of a tendency of the strong acid to fix the protoplasm through coagulation. These experiments, repeated with various modifications, and using muscles from dogs, rabbits and man, seem to show that lactic acid possesses the power of causing changes in striated muscle fibers that are microscopically quite similar to those observed in typical Zenker's degeneration. This effect seems to be due to the hydrogen ion, for sodium lactate does not have any such effect, whereas hydrochloric acid causes much the same changes in more dilute solutions, e. g., $\frac{1}{128}$ N. hydrochloric acid is about as effective as $\frac{1}{64}$ N. to $\frac{1}{32}$ N. lactic acid, agreeing with the much greater degree of ionization of hydrochloric acid in solutions of these strengths.

Similar results may be obtained by injecting solutions of lactic acid in physiological salt solution into the muscles of living animals; there follows the appearance of typical waxy changes at the point where the lactic acid has been forced into the muscle and along the needle tract. The only respect in which this form of waxy degeneration differs from that observed in typhoid is in that the fibers do not tend to break up into short segments so much, but even this effect sometimes appears, and it seems to result oftenest if the injected muscle is not removed for several days, as if the segmentation were the result of postnecrotic changes. In support of the last suggestion is the observation that similar fragmentation of the muscle fibers is observed in muscles undergoing aseptic autolysis for several days, even although no hyaline change has taken place.

It is perfectly possible for the degree of acidity of living muscles to reach an amount equal to that found necessary to produce a homogeneous transformation of the fibers. The most careful study of the development of lactic acid in the muscles has been made by Fletcher and Hopkins, who, however, worked with frog muscle. They found that frog muscles would after heat rigor yield as much as 0.5 per cent. by weight of zinc lactate, or about 0.35 per cent. of lactic acid, which corresponds to about a $\frac{1}{25}$ N. solution; nearly

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*Jour. of Physiol., 1907, xxxv, 247.*
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as large amounts are obtained if the muscle is merely kept in an atmosphere poor in oxygen. As the metabolism of mammalian muscle is much more active than that of amphibian muscle, it is probable that if anything even greater amounts of lactic acid can be produced in mammalian muscles, especially when the oxygen supply is cut off by thrombi, at the same time that the fibers are stimulated to activity by bacterial toxins.

Although there is no difficulty in producing typical waxy degeneration by injecting bacteria into the muscles of living animals, yet the same variety of bacteria acting upon the dead or excised muscle in vitro do not produce waxy changes. Several experiments of this kind have been tried in which staphylococci, colon bacilli and typhoid bacilli, both living and killed by toluol, have been allowed to act upon small pieces of muscle for varying periods in the incubator. Such muscles upon sectioning and staining may be found invaded throughout with bacteria, and yet the fibers show their striations well preserved. Evidently, therefore, it is not alone the action of bacteria upon the muscle that causes the hyaline transformation, but apparently the living muscle itself has something to do with the process.

Simply ligating a muscle, so that it is entirely deprived of its blood supply, does not produce waxy degeneration. There develops a high degree of edema, particularly in the interstitial tissue, so that although the muscle as a whole is much enlarged the individual fibers are not noticeably swollen and their striations persist until the muscle cells disintegrate. If such ligated and necrotic muscles are chopped fine and extracted thoroughly with hot water, the amount of alkali needed to neutralize the extract to phenol-phtalein is always much less than with similar extracts made from the corresponding muscle of the other limb of the same animal. This negative result is not of much significance, however, for in the first place most of the acidity found in the normal control muscle is probably produced as a result of the stimulation of the muscle during its removal and the process of chopping it up for extraction, as Fletcher and Hopkins have shown, while of course the dead ligated muscle would not produce acid during these manipulations. Secondly, the infiltration of plasma into the ligated muscle would largely suppress
any acidity that might have resulted from the anemia produced directly after the ligation. Indeed, it is the influence of such unavoidable factors as these that have made it impossible to actually determine that there is or is not a development of lactic acid in muscle fibers during the production of the waxy changes. For example, if typhoid bacilli are injected into sound muscles of one limb and there produce typical waxy degeneration, titration of extracts of these muscles shows the same amount of acidity to phenolphthalein as the corresponding muscles of the opposite limb if the titration is performed at once or within three or four hours; but if the muscles are not removed until after twelve, twenty-four or forty-eight hours, when an inflammatory cedema has developed, then the extract from the infected muscle requires less alkali to neutralize it to phenolphthalein than does the control. It is perfectly possible, and indeed probable, that an infected muscle fiber may at some particular stage of its infection be stimulated violently to production of lactic acid, which causes hyaline changes in the fiber in which it was formed; this acid then diffusing outward would be neutralized by the blood plasma and thus be rendered incapable of detection by chemical means. Therefore, the fact that negative results were obtained in all attempts to demonstrate an increased acidity by titration of muscle in which waxy degeneration had been produced by injection of typhoid bacilli, does not speak against the hypothesis that lactic acid causes the waxy transformation of the muscles in the so-called Zenker's degeneration.

As further evidence that waxy degeneration may be the result of the presence of excessive amounts of lactic acid in the muscles, we have experimental evidence that under conditions in which lactic acid is produced in large amounts by muscles made to contract rapidly and violently until fatigued, a very typical waxy degeneration may appear in the otherwise uninjured muscle fibers. This was demonstrated by the following experiments. The sciatic nerve was isolated in rabbits and submitted to repeated stimulation with induced current, so regulated that the force and frequency of shocks was just short of throwing the muscle into tetanus. This was continued for about an hour, until no more satisfactory contractions

*For assistance in these experiments I am indebted to Mr. J. R. Greer.*
could be secured on account of exhaustion of the muscle or the nerve; the muscles were then quickly removed and small pieces dropped into Zenker's fluid (without acetic acid). The stimulated muscle appeared paler than the normal muscles, and in places seemed to be almost waxy. Histologically, such muscle, which had been stimulated to the maximum for about one hour, showed very strikingly and typically the appearance of waxy degeneration. Frequently an entire section would show practically no fibers that were not more or less affected, but usually the changes were somewhat focal, and resembled perfectly the changes seen in degenerating muscle. Most of the fibers in such areas appear swollen, perfectly homogeneous, and entirely devoid of either transverse or longitudinal striations; and some show transverse clefts increasing the resemblance to Zenker's degeneration. In such fibers the nuclei appear somewhat smaller and more deeply stained than normal. Not a few fibers show a peripheral zone which stains deeply and in a diffuse manner with hematoxylin; as hematoxylin is a basic stain with a chemical affinity for acid tissue elements, it would seem possible that these deeply staining areas in the fibers represent places where an excessive amount of acid protein or syntonin-like substances have been formed by the action of lactic acid upon the muscle proteins.

In order to decrease the oxidation and if possible to increase by this means the formation of more lactic acid in the muscles, the same experiment was repeated after isolating the muscles from their blood supply by ligatures which did not include the nerves. Such muscles, however, could be made to keep up their contraction for a comparatively short time, about fifteen minutes, and so the final result was if anything less degeneration than was obtained with the muscles with intact blood supply, which had contracted for an hour before exhaustion. While there is no positive evidence that the hyaline transformation observed in these exhausted muscles is due to the lactic acid formed in their active metabolism, rather than to some other unrecognized cause, yet taken with the facts previously brought out and the fact that muscles thus stimulated are known to produce a large amount of lactic acid, the evidence seems to be strongly in favor of associating the lactic acid and the hyaline transformation as cause and effect.
SUMMARY.

In view of theoretical deductions and the positive results obtained in the above experiments, it would seem probable that the production of waxy degeneration depends upon the action of lactic acid which is formed by the living muscle under the stimulation of infecting bacteria or their toxins, the formation of large amounts of lactic acid and its accumulation being perhaps favored by defective circulation through the injured muscle. The hyaline transformation of muscle acted upon by lactic acid is analogous to the swelling of fibrin placed in dilute acids. This view is supported by both negative and positive experimental evidence—the negative evidence being that simple anemic necrosis, aseptic or antiseptic autolysis whether in vivo or in vitro, or the action of bacteria of various sorts on muscle in vitro, are all incapable of causing changes in muscle cells resembling those characteristic of waxy or hyaline degeneration of striated muscle. The positive evidence consists in the demonstration that lactic acid, even in dilutions comparable to the amounts that can be formed in living muscle, can produce a similar or identical waxy transformation of the striated muscle fibers, both in vitro and in vivo; and also the observation that muscles stimulated to exhaustion, under which condition lactic acid is known to accumulate in the muscle, show microscopically changes identical with those of Zenker’s waxy degeneration.