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PRESENT CONCEPT OF MUSCLE

by

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Omaha, Nebraska

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INTRODUCTION

The muscle mass of the human body is greater than that of any other organ. Physiology, chemistry, histology and disease of this tissue are, in comparison, the least understood of any tissue. A review of these phases of the subject will be attempted. Neurological complications involving muscle will be avoided as much as possible as that is a field in itself and only an interpertation of the present concept of muscle in itself will be reviewed.

In this paper, therefore, a brief review of the development of the present concept of muscle histology, physiology, chemistry and pathology will be undertaken with an attempt to sum up the knowledge of this subject in the various fields mentioned.

HISTORICAL REVIEW

Physiology being the oldest of this group of sciences, work in this field dates back to the time of Aristotle. This worker (384-322 B.C.) discusses the action of muscle and gives us the first definitions of function. Claudius Galen (131-201 A.D.), can safely be said to be the father of experimental physiology (44). Galen was probably the first to observe that after excision from the body a muscle may still contract when appropriately stimulated (mechanically). Muscular rigidity and tetanic convulsions were well known to the ancients, Galen stimulated excised muscle and tried to explain what he saw as applied to the clinical problem of spasticity and contracture, and the suggestion made by him is singularly reminiscent of a modern controversy; "spastic contraction results from continuous stimulation." That Galen had in mind successive responses of muscle to successive stimuli as constituting a tetanus, is of course somewhat improbable.

When discussing the varieties of movement, Galen made four distinctions; (1) the movement of simple contraction; (2) lengthening, due to contraction of an antagonist; (3) passive movement, as when an arm drops under its own weight; (4) the "movement" by which, for example, an arm raised to the level of one's shoulder is maintained in that position. Galen draws attention to the fact that this latter involves no gross movement, but rather the essence of movement, that is a static contraction, and to this he applied the

"tonus". In so doing, Galen used the work in its strictly modern sense, as implying "active posture", which in recent years has been investigated so thoroughly from the histological standpoint. Galen showed moreover that this tonus of a muscle disappeared forever when the motor nerve had been cut. It is clear, also, from the quotation which has just been given, that Galen sensed the importance of reciprocal action of antagonistic muscles.

Following the works of Galen no schools of medicine enlarged upon his original observations until the sixteenth century. If any work was done the records have been lost. Andrea Vesalius (50) (1514-1545), who at the age of twenty-eight had dissected the whole of the human body and published his immortal work "De Humani Corporis Fabrica", reincarnated the spirit of experimental investigation once more. One thing must be mentioned here before considering the period of Vesalius. Prior to his advent on the horizon of contributions to medicine numerous painters had contributed much interesting work to gross anatomy but it was based in the main part upon unscientific basis. Perhaps the greatest of these artist-anatomists was Leonardo da Vinci (1452-1519) for in his notebooks are to be found accurate diagrams of the mechanical action of muscles which in many points compare favorable with the similar geometrical analysis made subsequently by Borelli.

In the last chapter of the "Fabrica" Vesalius describes
his physiological experiments on living animals. In this he
confirmed many of the results of Galen but amplified them in
many ways. Thus he found that by cutting or ligaturing one
nerve or another, it is possible to abolish the action of the
muscle which it innervated, and he observed that if the lig-
ature was not tight the muscle recovered its action on loosen-
ing. He observed also that the nerve sheath was not essent-
ial to its action, for the nerve continued to conduct after
the sheath had been removed. Vesalius recognized that the
fleshy parts of skeletal muscles were responsible for their
contractile power and not, as Galen supposed, the ligament-
ous elements which spread into the muscle from the tendon.

The first of "modern" authors (17) to publish a separ-
ate work on muscular activity was Fabricius of Aquapendente
(1537-1619), the teacher of William Harvey. He attempted
to analyze muscular mechanics along geometrical lines, but
as this was done before the conceptions of Galileo had be-
come established, we find in Fabricius little more than a
repetition in slightly new form of what Galen had already
taught. Outstanding developments in muscle physiology
took place, however, in the middle of the seventeenth cent-
tury. Steno in Denmark, Borelli in Italy, and Croone, Mayow,
Willis and Glisson in England, all contemporaries and all
more or less stimulated by the mechanical conceptions of Gal-
ileo, set out to solve the problems of muscular contraction.

Of this remarkable constellation of muscle physiologists the first to communicate his results to the world was the illustrious William Croone (1633-1684). He grasped the importance of the contractility of the fleshy portions of the muscle, and gave credence, though apparently with some misgivings, that the Galenical postulate of animal spirits, as the causation of contraction, was feasable. He appreciated the necessity of the circulation for the proper functioning of a muscle and constructed a most admirable diagram in which he represented his beliefs concerning the interaction of the substances derived from the blood with animal spirits conveyed by the nerves. He also attempted geometrical analyses of muscular action along the lines subsequently followed in greater detail by Steno and Borelli.

Steno (1638-1686) demonstrated that contractility must reside within the muscle substance and is not therefore dependent upon the intergrity of the entire muscle machine. Steno also had been gravely doubtful as to the Galenical hypothesis of animal spirits.

Important contributions to the physiology of muscular contraction were also made by Francis Glisson (1597-1677). A man of exceptionally wide philosophical outlook, it is interesting to note that he realized clearly that knowledge of muscle physiology was then in its inception (67). Through careful experimentation and logical reasoning Glisson was led to an unusual conception of the properties of muscular tissue which anticipated modern teaching by nearly a hundred

years. He argued that a given tissue is never provoked into activity unless it is irritated, and in order to have the power of being provoked into activity a tissue must have a special property which he designates irritability. Thus the conception of irritability may be traced not to Haller as is sometimes stated, but to Glisson. Glisson's most important contribution however, was of another sort. Willis, as we have seen, had reiterated the Galenical view that contraction is the result of flowing of spirits into the muscle through the channels of the nerves. If this were the case, Glisson contended, the muscle should increase in volume when in activity. On subjecting this possibility to experimental test he found that the volume of a muscle if anything diminished somewhat, when it contracts.

The beginning of the eighteenth century witnessed the publication of George Baglivi's (1668-1707) two important books, the De Fibra Motrice et Morbosa and the De Anatome Fibrarum, de Motu Musculoru, etc., both appearing first in 1700. Baglivi distinguished between what we now term " striated muscle" and "smooth muscle", describing the gross and minute appearance of the constituent fibers. He insisted that the former were designed for the execution of quick movements while the latter, being "membraneous", subserved functions requiring long-maintained activity. He does not mention tonus.

It was Leeuwenhoek, however, (36) who in 1715 gave the

first adequate description of the microscopical appearance
of skeletal muscle fibers. Though he had published several
previous observations on the subject, his contribution in
1715 summed up his beliefs on longitudinal striations, but
he believed that the transverse "striations" represented
the successive turns of a spiral threak twisted around the
fiber. Leeuwenhoek's work also demonstrated the existence
of the sarcolemma.

vonHaller (1708-1777), probably did the greatest amount
of work of any of the early workers. His experiments were
concerned with many phases of physiology, but his deepest
interest apparently lay in the problem of irritability, one
of his monographs on this subject alone occupying four vol-
umes. In discussing the more general aspects of irritability
Haller observed that the phenomenon was widely present both
in the animal and in the vegetable kingdom and indeed appear-
ed to be almost universal property of living tissue (23).
Haller insisted that the local circulation in a muscle is
not altered during contraction, though possible not strictly
true, is a point of interest.

Robert Whytt was the leading English physiologist of the
eighteenth century. He seemed to be aware of the existence
of the "stretch" reflex. He also appreciated that the ade-
quate stimulus for one nerve ending might not be adequate for
another (77). He states that "muscular fibers of animals are
so framed, as to contract whenever a cause proper to excite
their action is applied to them, or, in defect of this, al-

ways to remain at rest. This cause is either an effort of the will, or a stimulus of some kind or other: to the former are owing the voluntary motions; and to the latter all such as we call vital and spontaneous." Haller focussed his attention largely upon the isolated muscle and saw that clearly; Whytt concerned himself chiefly with the reflex control of movement, trying to visualize the organism as a whole.

The next development of a physical nature was "animal electricity", as the phenomenon was called when first observed, may be regarded as having been discovered through a chance observation of Galvani that frog's legs developed spasms on being suspended by copper hooks from an iron ballustrade, the spasms occurring when the muscles came into contact with any part of the iron structure (76).

This contribution did not in itself prove the existence of animal electricity; as we now know, it merely showed that a muscle can be stimulated into activity by the potential difference which results from the union of two unlike metals.

When Galvan's contribution was first published it provoked a storm of criticism from his fellow countryman, Alessandro Volta, (1745-1827). Galvani had contended that contraction in his experiment resulted from "animal electricity" being conducted by the metal, while Volta objected quite rightly that the conclusion did not follow from Galvani's observations. Volta maintained, on the contrary, that the

stimulation resulted from the electricity which was generated by contact of dissimilar metals. There is no question but that Volta was justified in his criticism. Its adverse nature led Galvani to demonstrate conclusively the possibility of contraction without metals.

The early observations upon animal electricity proved only the existence of the "current of injury". Matteuci (1840-1841) had observed the "muscle current", as the injury current was then designated, becomes diminished during a tetanic response, but, as Bence-Jones points out (7) Matteucci later contradicted himself (1844) by saying that resting "muscle current" is increased during stimulation, finally he denied that activity had any effect upon the "muscle current", and attributed his former results to technical errors. Matteucci made the important discovery, however, of secondary contraction, which he first announced in 1842. When the nerve of one limb of a frog is placed upon the muscle of the second limb, the first limb will contract whenever the muscle of the second limb is caused to contract. Becqueral (17) attempted to explain this result by assuming that the contracting muscle must give rise to something akin to an electric discharge which stimulated the rheoscopic nerve, thus causing contraction. This was of course close to the truth, and while Matteucci was at first favorably inclined toward Becquerel's explanation, he subsequently abandoned it, and attempted to show that "induced" or secondary contractions are not electrical in origin but rather the result of "nervous

forces" in the primary muscle.

The more modern conceptions of the origin of bio-electrical currents introduced by Bernstein and Macdonald (41-42-43) lead us directly back to duBois-Reymond's conception of a surface of regularly oriented electromotive "particles". As Stewart points out, (69) if we but substitute electrically charged ions and the semipermeable membrane for duBois-REymond's surface of positive and negative "electromotive particles", we have the essence of the modern physico-chemical theory. There is now little doubt but that electrical manifestations of living tissues result from ionic concentrations at the "interfaces" within the cells. When the tissue is injured these electrically charged ions migrate freely from the normal to the injured area, thus setting up a new distribution of charges or a potential difference (injury currents). Bernstein, Brunings, and Beutner (6) have compared injury currents of muscle to the potential arising between solutions of the same electrolyte at different concentrations when separated by a "fatty" interface. When, owing to stimulation, the permeability of the internal interface is altered temporarily an electromotive disturbance is set up, and this constitutes the action current.

vonHelmholts's early contribution to knowledge of muscle was in the nature of its physical properties. He was able to demonstrate a rise of temperature during contraction. This he attributed to the chemical break-down which he had previously demonstrated in active muscles. It is interesting to note that his experiments on the production in nerves was

entirely negative (9). Fick made the important observation
that heat production increases with the initial length of
the muscle fibers. He also found that the quantity of heat
referable to each excitation of a tetanus varies almost in-
versely with the rate of stimulation. Fick's greatest cont-
ribution was his demonstration that chemical energy in the
case of muscle is transfered directly into work without pass-
inf, as in a thermodynamic machine, through an intermediate
stage of heat. He showed that muscle is to be regarded as
a mechanism in which chemical energy is, as has been stated,
transformed directly into work. Any heat which happens to be
evolved, is probably incidental to development of tension
and change in shape.

Gad was probably the first to suggest specifically that
lactic acid caused contraction and that it was subsequently
oxidized with the liberation of heat (16). This is now called
the heat of "oxidative recovery," The most significant cont-
ributions were those of Fletcher and Hopkins (15-29). They
showed that lactic acid owes its origin to glycogen, that
when lactic acid appears glycogen invariably disappears in
corresponding quantities, that carbon dioxide is evolved
from the neutralization by preformed carbonates of the lactic
acid set free, and finally that these processes of liberation
and neutralization occur in the complete absence of oxygen.

Early physiologists quite naturally attributed grad-
ation of muscular response to variations in the intensity of
stimulation. Many inferred, however, that a strong stimulus

sets up a large response because it gives rise to "larger" nerve impulses and to larger contractile responses than a weaker stimulus.

Gotch (19) made the important observation that nerve fibers appeared to give all-or-none responses, He observed that when one of the lumbar roots supplying the gastrocnemius muscle (frog) was stimulated, a certain proportion of the muscle fibers remained unstimulated and could be called into activity by stimulation of the other root. In view of this, and other evidence based upon the time relations of the action current, he suggested that gradation of muscular response was brought about through variation in the number of contractive units in activity at any one time rather than through variation in size of the nerve impulse.

Gotch's work was carried further by Keith Lucas (38). He found in such a muscle as the cutaneous dorsi of a frog, which is innervated by a small nerve containing only 7 to 9 fibers, that the degree of the contraction of the muscle increases in steps as the intensity of stimulation applied to the nerve is gradually increased and that the number of steps is never greater than the number of nerve fibers supplying the muscle. He found that after all the fibers had been called into activity by a stimulus of gradually increased intensity, further increase did not augment the extent of the contraction. The evidence from these experiments was extremely suggestive, and led many physiologists to readjust their views concerning the nature of the process underlying gradation of activity in muscle (4-46). It is true that the

experiments of Lucas and others did not provide direct evidence of the all-or-none character of the response of muscle fibers. This was demonstrated by Pratt (54-55) showing the all-or-none behavior of individual muscle fibers by direct observation under the microscope. Employing a pore electrode of somewhat smaller diameter than that of an individual muscle fiber, he was able to show that once a fiber had responded further increase in the stimulus did not make it contract further.

This brings up the question of innervation of the muscle. Innervation varies for the general types of muscle, namely, smooth, striated and cardiac. Striated muscles are supplied from the cerebrospinal nervous system and their contraction is customarily called voluntary. These are the muscles that receive practice when movement or posture is attempted. Cardiac muscle and smooth muscle are not under voluntary control but their action is intimately related to the action as sustained by the voluntary muscles. Skeletal muscle can be said to respond to stimuli either directly or indirectly, that is through its nerve. The response of skeletal muscle is only to that specific stimulus. Visceral muscle can enter a state of prolonged activity which is automatic or independent of the receipt of excitatory impulses from nerve centers.

In the active organism, muscle tissue frequently exhibits a condition of moderate sustained contraction which is commonly called tonus. As is well known, this disappears in skeletal muscle when the nervous elements are stripped

off, although the same is not true of the smooth variety.
J. Mueller (1838) and others of this early period believed
(48) that skeletal muscle tonus depended upon the action of
nerve centers, but they were in doubt whether this was
automatic or reflex. To answer this question, early exper-
imenters looked for a lengthening of the muscle after sev-
ering the motor nerve. This was not found by various invest-
igators, but (8) Brondgeest severed the afferent roots of
one hind limb of the frog; when the animal was held vertic-
ally the affected limb showed a loss of tonus, since it was
less flexed than the other. This proved that the greater
flexion of limb with normal innervation was due to muscular
tonus which was reflexly maintained through the afferent
nerves. His conclusions have been frequently confirmed, and
it is commonly agreed that an intact arc is required for the
maintenance of tone in skeletal muscle.

Sherrington (1915) (66) calls attention to the ambig-
uity of the term tonus. A "slight constant tension" is not
always presnet in healthy muscle. It is absent in the ex-
tensor muscles of the hind limbs of the squatting spinal
frog, as well as in those muscles of the decerebrate cat
which bend the spine downward, droop the neck and tail, flex
the head and depress the jaw. In the latter animal, tonus is
distributed to just those muscles which maintain erect post-
ure; if you bend the head down, the tone disappears from the
extensor muscles of the forelimb and the fore quarters sink,

while the hind limbs stiffen so that the attitude is that of looking for something under a shelf. Therefore it becomes evident that a slight steady contraction is not universally characteristic of healthy muscle; its presence or absence in a particular group of muscles is simply a part of the posture of that animal.

Present day views of tonus have been greatly influenced by the analysis of Sherrington(65). Reflex tonus, he declares, is postural contraction and has the following characteristics; (1)the low degree of tension it usually develops; (2) the long periods for which it is very commonly maintained without obvious fatigue; (3) the difficulty of obtaining by artificial stimulation reflex contraction at all closely simulating the postural contraction produced by the natural stimuli (what ever they may be); (4) ease of reflex inhibition; (5) lengthening and (6) shortening reactions.

Sherrington concludes that the tonus of the striated muscles which he tested depends upon the afferent fibers of the tonic muscle itself, and that "in the decerebrate cat preparation no other afferent fibers than those of the tonic muscle itself are actually essential for the exhibition of the tonus."

Relaxation occurs after the cessation of impulses along motor nerve fibers extending to a muscle, but quite another phenomenon has been called "inhibitory relaxation." Sherrington (1893) (63) discovered that the knee-jerk in the "spinal" animal can be inhibited by repeated stimulation of a nerve on the same side. He noticed that the period of in-

hibition considerably outlasted the duration of the inhib-

itory stimulus and also that after recovery there followed

a period of enhanced excitability during which the knee-

jerks were of larger size than usual.

Then there is the question of the sympathetic innerv-

ation of the striated muscles. While the question is app-

arently a closed one at the present time it has caused no

little discussion in the past. It has been discussed fom

histological and physiological viewpoints for years.

In 1904 Mosso (47) suggested that tonus is the function

of nerve cells, expecially the sympathetics. He quoted

Bremer as the first to discover the sympathetic, in addit-

ion to the somatic innervation of muscle fibers and Grab-

ower as finding non-myelinated fibers in addition to the

myelinated in human muscle.

Much argument has centered about the innervation of

the small striated fibers of the muscle spindles discovered

by Kuhne in 1863 (11). Medulated nerve endings running

to these fibers were observed by Cajal in 1888, and by

Huber and DeWitt in 1897 (31). More recent work on this

subject will be discussed under another heading. Using

a cat and monkey in 1894, Sherrington cut certain ventral

nerve roots as well as the dorsal roots between the cord

and the dorsal ganglia. He observed medulated nerve fibers

in the spindles with normal appearance one-hundred and nin-

ety days after the operation. Cutting the sciatic nerve

likewise failed to produce atrophy of the muscle fibers of

the spindle. This proved that the spindle muscle fibers do

not depend upon somatic motor nerves as interperted by him.
This also will be discussed later in more detail. Kulchit-
sky's work in 1924 (33) altho recent falls into a historical
grouping since his work, although extensive, was not rightly
interperted by him. He concluded that the non-medulated
nerve fibers were of sympathetic origin; a conclusion in
harmony with the theory of Mosso and the early findings of
Sherrington. Kuntz also apparently confirmed this sympath-
etic innervation of muscle (34).

Various histologists have collected evidence that str-
iated muscle fibers may be innervated not only by medulated
nerve fibers but also by the non-medulated variety. Per-
roncito (53) working on the lizard, Kulchitsky working on
python and Hines on the frog all described unmyelinated
nerve fibers in muscle. Ranson in 1926 (56) states that
Hinsey has found that many or most of the non-myelinated
fibers are not of sympathetic origin, since they persist
in the terminal branches of the motor nerve after degener-
ation of all of the sympathetic fibers.

Leaving the question of the sympathetic innervation
of muscle at this point in its history, the next important
fact is the nerve impulse that activates the muscle. Spon-
taneous activity of nerve trunks has never been demonstrated,
it exists as such only after stimulation. It is generally
agreed that at least in peripheral nerves energy does not
flow in steady streams but in series of impulses. Helmholtz
using frogs was the first to measure the speed of such waves.
It was thought that nerve fibers carry stronger or weaker

impulses depending upon the strength of stimuli and causing a corresponding degree of muscular contraction. Now it is generally held that the nerve fibers like muscle fibers at any moment responds as fully as it then can or not at all. Adrian and Lucas have further proved this point (1).

Lucas points out that the nerve impulse is a disturbance which depends for its progression on the local energy supply in the nerve itself. He compares it in this respect with the firing of a train of gunpowder, and this has been practically proved by Adrian's early work (2). Lucas takes for granted that the nerve impulse depends for its transmission on the supply of energy by the nerve along its course as shown by the fact that the nerve uses oxygen and gives off carbon dioxide. As the nerve is stimulated at increasing rates per second, the heat per impulse falls off; in other words, the nerve apparently has insufficient time for a full return of energy, and, if the interval falls below certain limits, energy will be insufficient for a wave of propagation, which explains the absolute refractory period (24).

The effect of the central nervous system upon its peripheral affectors is the last portion of this long discussed question to be considered here. One thing that has been agreed upon for some time is that the tonus of skeletal muscles depends upon a more or less continuous activity of their motor nerves. This activity of the motor nerves is due to the flow of impulses along the afferent paths. The cerebellum is probably the terminal depot of most of these impulses. From the proprioceptive sense organs of muscles as

well as possibly from those of joints and tendons impulses

travel through the dorsal and ventral spinocerebellar tracts,

which enter the cerebellum respectively via the lower and

superior peduncles. This was brought out by Marburg in 1904

and Bing in 1906. From the cerebellar cortex impulses are

relayed to pontine nuclei, thence via the middle peduncle

to the median and lateral parts of the cerebellum. From

three cerebellar nuclei axons pass over the superior ped-

uncle to end in the red nucleus of the midbrain. This is

connected through the rubrospinal tract with motor cells of

the anterior horn of the cord, this together with other

connections to the thalamus and cerebral cortex. Import-

ant connections exist from the nucleus fastigii to the

nucleus of Deiters. Various descending pathways from these

pontobulbar centers finally lead to the spinal motor neur-

ones which maintain postural tone.

That the cerebellum has not only an excitatory but

also an inhibitory function in the regulation of postural

tone is demonstrated by the observations of Sherrington (64)

upon stimulating the superior vermis. Vestibular influence

must be mentioned and its function has been repeatedly

proven (72).

The pure histological aspects of muscle are very much

in question. The complexity of muscle was early recognized

and its minute detail is still much in question. The dif-

ficulty lies in the fact that much stress has been laid upon

the cross striations of skeletal muscle. Muscle does not

need the cross striations for function. They are more pro-

bably a special modification of the contractile mechanism for special functions. All theories based on the detailed microscopic appearance of the cross striations as functionally necessities and a basis for their action will be dismissed (57). It must be remembered too that the details of the cross striated structures are of a size near the limits of microscopic vision so that the visible appearances may be delusive. Haycraft (26) was able to obtain all the appearances of cross striated structure, except those depending on the birefringence of the muscle, by taking casts in collodion from the surface of muscles. He considered that the various structures described by histologists were the optical results of a very fine surface varicosity of the fibers. These observations have been ignored by most histologists. In general, cross striations are most conspicuous in the most rapidly moving muscles, such as insect's wing muscle. The most plausible suggestion yet made is therefore that of Hill (1926) (27) that cross striated muscle has an arrangement comparable (78) to "baffle plates" set across the length of the fiber to reduce the amount of flow of the semi-liquid contents. Loss of energy by internal friction in the muscle is the chief source of lowered mechanical efficiency when the rate of movement is increased. If the muscle fiber were like a hollow tube with the walls thickened at intervals, this would account for the cross striated appearance and be compatible with Haycraft's observations, supposing there was a swelling corresponding to the "baffle plates."

Chemistry of muscle has gone through many and varied steps. In its evolution each step reached apparently culminated all the work necessary on the subject. However, some workers are never satisfied and the work has gone on with the resulting revolutionary discoveries,particularly of late.

In 1920 Hartree and Hill (25) pointed out that in stimulated muscles from which oxygen had been carefully excluded a small delayed heat production occurs during the three minutes following contraction. Every attempt to get rid of the delayed anaerobic heat failed, until at last it is recognized as the sign of a reaction, recently discovered, by which phosphagen is restored anaerobically at the expense of energy liberated by delayed lactic acid formation.

In 1922 Embden had found that phosphate diffuses far more rapidly into Ringer's fluid from a fatigued than from a resting muscle. Unfortunately, for he might have discovered phosphagen, he did not attribute this to the new appearance of inorganic phosphate inside the muscle, but to a change of permeability of its surface. In 1924 Embden and his colleagues first reported experiments which claimed to prove that a considerable fraction of the lactic acid set free was the result of tetanic stimulation may appear after contraction is over. Unluckily, for there were various reasons, this claim was not accepted, although it proved ultimately to be correct. According to Ebden the

immediate energy for anaerobic muscular work was derived from phosphagen breakdown.

In 1925 Teigs (70) had found that creatine diffuses far more rapidly from a fatigued muscle than from a fresh one, and that this excess diffusion is stopped by oxygen. He, like Embden, had nearly discovered phosphagen, but unfortunately the clue was not followed up. Teigs moreover claimed to show that in muscular activity not only acid but alkali is produced, the latter being in the form of a more alkaline creatine.

In 1926 Hoet and Marks (28) discovered that muscles rendered glycogen free by previous administration of insulin and thyroid may pass into a peculiar form of rigor, without lactic acid formation or increase of hydrogen ion concentration. The inorganic phosphate of the blood was found to rise. Here was fore shadowed the behaviour of muscles poisoned with iodo-acitic acid, in which, as Lundsgaard showed later, contraction and contracture may occur without any lactic acid change.

Finally there had always been a gap, never satisfactorily bridged, between first, the heat set free when one gram of lactic acid is liberated in normal intact muscle, and second, the heat accompanying the formation of one gram of lactic acid in minced muscle to which glycogen and phosphate had been added. The difference was partly made up by the heat of reaction of lactic acid with the alkali-protein of the intact muscle, but Meyerhof had always maintained that something was still missing.

It had long been known that phosphorus compounds must
have some special part to play in muscular contraction.
Creatine, moreover, was known to be present in large amount,
but nobody had suggested a function for it, or the manner
if its combination. There still are substances, muscle hemo-
globin, carnosine, even potassium, present specifically in
muscle in relatively large quantities, but as yet no role
has been found for them. As regards the phosphorus compounds,
till phosphagen was discovered it seemed most likely that
these were intermediaries in the breakdown of other subst-
ances; one tended therefore to disregard them in calculations
of the energy exchange, and to concentrate on the initial
and final substances, glycogen and lactic acid. Had this
so called "inorganic" phosphate really been inorganic, had
the "organic" phosphate been chiefly a hexose phosphoric
ester and the source of lactic acid, then justification in
regarding the phosphorus compounds as intermediaries, as
not affecting the total energy exchange, is justified.
Grave errors were made however. The delayed anaerobic heat
could not be disregarded, and several important things occ-
urred, endothermic as well as exothermic, even in an oxygen
free muscle, long after contraction and relaxation were
complete. The "inorganic" phosphate was not mainly a hex-
ose ester, it was not the source of lactic acid, but was
largely adenyl-pyro-phosphoric acid.

The Eggletons (13) had shown, at the end of 1926, that when a muscle is excited phosphagen breaks down, and in the presence of oxygen is rather rapidly restored. The amount of phosphagen is greater in quick muscles than in slow, though recent work proves it to have the same role; the muscles being slower, there is more time for the phosphagen to be restored anaerobically, so the amount of it can be less. Its break-down is greater, relative to lactic acid formation, in the earlier than in the later stages of activity and fatigue. Shortly after, and independently of the Eggleton's publication, Fiske and Subbarow (14) reported the same discovery and showed, in addition, that phosphagen is a compound of creatine and phosphoric acid; they concluded also as Teig's work suggested and as Meyerhof has since confirmed, that its breakdown affects the buffering power of the tissue.

The breakdown of phosphagen (creatine-phosphoric acid) leads to a considerable evolution of heat; its resynthesis, therefore, must lead to a considerable absorption. Hartree and Hill (25) had examined the heat production of muscle, during and after activity, in oxygen and in nitrogen, with the greatest care. There was no evidence at any stage, of an absorption of heat.

They could not admit the possibility of heat absorption following activity; rather, they had again to point out the existence of a small positive delayed anaerobic heat, at any rate after a tetanus. If, therefore, the resynthesis of phosphagen really occured it must be accompanied by some strongly exothermic reaction. No such reaction had been suggested ex-

cept delayed lactic acid formation.

Phosphagen was discovered, together with its partial re-synthesis anaerobically after stimulation, and the heat production of its breakdown. Clearly a delayed lactic acid formation now became possible, since the absence of sufficient delayed anaerobic heat could be explained by the simultaneous occurrence of the endothermic restoration of phosphagen. In 1928, Lohmann proved that a considerable part of the supposed organic phosphate was really pyrophosphate, which later was shown to be linked with the adenylic acid group first discovered in muscle by Embden and Zimmermann. This compound has recently been found to be part of the co-ferment system in the hydrolysis of carbohydrate, and also to yield ammonia when it breaks down to inosinic acid and orthophosphate.

Lungsgaard in 1930, showed that muscles poisoned with iodo-acetic acid may contract, apparently perfectly well for a time, without any lactic acid formation only with the breakdown of phosphagen (39). After about one-hundred twitches, in place of the four-hundred which a normal muscle can give before exhaustion, a curious form of contracture sets in, and the muscle ceases to be excitable, or to be capable of recovery, even in oxygen. By this stage all, or nearly all, the phosphagen is broken down. Apparently phosphagen breakdown can supply all the energy for a perfectly normal contraction. Lungsgaard (39) immediately proposed the hypothesis

further found that in a poisoned muscle there is no anaer-
obic resynthesis of phosphagen after contraction; if lactic
acid cannot be produced phosphagen cannot be resynthesized.

Lundsgaard immediately proposed the hypothesis that
"phosphagen is the substance directly supplying the energy
for contraction, while lactic acid formation in the normal
muscle continually provides the energy for its resynthesis."
It became reasonable to believe in the delayed formation of
lactic acid, and it was found. By late autumn of 1930 it
was certain at last that a considerable part, if not all,
of the lactic acid set free as the result of stimulation,
appears after the contraction is over, during the period in
which the phosphagen is restored. One major question re-
mains unanswered--why can only a part of the phosphagen be
restored at the expense of lactic acid, why does a consider-
able fraction still wait for oxidative resynthesis?

The solution to the problem may have its foundation in
the more recents works(80) in which substances hitherto not
found are being brought to light and their role in general
physiology ascertained. The importance of such substances
as adenosine, adenylic acid, and adenosin triphosphate are
just being realized. These substances will undoubtedly form
the basis for the foundation of true muscle physioloby.

DISEASES OF MUSCLE

Localized disease of the muscular system of an acute or subacute nature, commonly designated muscular rheumatism, fibrositis, myositis, or myalgia, is probably one of the most widespread and frequently(52) occurring conditions to which human beings are subject, excepting mild infections of the upper respiratory tract. Quite in contrast to the above statement is the fact that inflammatory muscular diseases of a generalized nature, either, acute, subacute, or chronic, are exceedingly rare. The acute and subacute groups(62) are recognized; primary suppurative myositis which is only occasionally generalized; myositis; dermatomyositis; and polymyositis hemorrhagica. In the chronic group there are three types; the chronic form of dermatomyositis; myositis ossificans progressive; and primary myositis fibrosa. The latter condition, primary myositis fibrosa, is presumably the rarest of all types, there being only four typical cases reported in the literature, with, however, numerous doubtful or atypical cases reported. Myalgia, the most common, while not falling into any of these classes will be discussed first.

MYALGIA

Probably the most frequent involvment of muscle is simple myalgia. This term is used to describe a painful condition of muscle substance, the exact underlying pathological nature of which is unknown. It is the complaint which the laity refer to as "muscular rheumatism", and probably is a manifestation of the disturbance in physiology

which underlies arthritis at large expressing itself in this instance in the muscular tissues. In point of fact there are few cases of arthritis, subacute or chronic in nature, which are not at some time accompanied by more or less painful involvment of the muscular tissues. Histologically the picture is that of a low grade inflammation of the fibrous tissues, which has led Jones and others to regard this involvment of the fibrous elemtnts as one of the early and characteristic features of the arthritic or rheumatoid processes. The muscle tissue itself may be the seat of inflammation, although this does not seem to be quite so clear. It is the belief of some observers that the pain in this condition is due to involvement of the smaller sensory nerve filaments supplying the muscle concerned. Exposure, focal infections and other allied conditions linked up with arthritis in general are often mentioned as etiological factors(56). In a large series of cases studied by Pemberton over 33% of the cases showed inflammation of the muscle group that was accompanied by myalgia. No particular muscle group is immune from this affliction. Treatment of this condition is in general the removal of any infection, the application of heat to the part, rest or electrical current.

MYOSITIS

Myositis is the term used to describe a condition in which there is inflammation of muscle substance, apart from that of minor degree and unimportant nature following trauma. It is recognized as a specific entity, running an acute or chronic course, and existing in two chief forms. suppurative and non-suppurative.

Rosenow and Ashby (58) in an attempt to solve the problem of the etiology of myositis, studied twenty eight cases carefully. In this group of patients the clinical symptoms varied from mild acute attacks, transient but recurrent attacks of localized myositis to marked chronic generalized myositis which had incapacitated the patients for work for several years. Among the twenty five patients from whom suspected foci of infection were removed, improvement resulted in twenty two, in two the results were unknown and in one no improvement followed. In the more acute cases the improvement was immediate; the chronic cases did not respond nearly as rapidly. Complete recovery has lasted in many cases for several years. Culturally there were twenty seven positive cases of the streptococcus which showed an elective affinity for the muscles in twenty four cases. Streptococcus and staphylococcus were isolated in two, and staphylococcus aureus occurred alone in one case.

In comparing the clinical histories of the patients with experimental results, it was found that the cases could be

classified into three groups; acute and chronic myositis
with or without other demonstrable lesions; symptoms of myo-
sitis predominating, but periarthritis and arthritis are
also present; symptoms of myositis predominating, but neur-
itis or perineuritis also present. It was also found that
bacteria from generalized myositis tended to produce numer-
ous small muscle lesions in the animals injected, while those
from localized myositis tended to produce a few localized
lesions.

The lesions found in the animals were or two main typ-
·es; small linear or oblong hemorrhages, and equally numerous
linear grayish white necrotic streaks. The former was us-
ually the early stage of the latter, though with some strains
of bacteria only the hemorrhagic lesions developed, and with
others only the necrotic areas. In the cases where the staph-
ylococci localized in the muscles, suppuration frequently
occurred with edema and hyper-emia. Deposits of calcium
salts occurred relatively early in the necrotic lesions.
A study of the microscopic changes in the blood-vessels of
the muscles in the experimental animals, howed that with
bacteria from cases of acute myositis, there was a leucocytic
reaction, with aggregation of leucocytes within the lumen
and less commonly in the perivascular lymph spaces. With
bacteria from chronic generalized myositis, however, there
were few or no leucocytes, and the reaction was chiefly endo-
thelial, the endothelial cells lining the vessels being swo-
llenand proliferating.

Injection of animals with formaldehyde killed strepto-
cocci from cases in which the living organisms produced mar-
ked lesions in muscles, produced similarly localized lesions.
This indicates that the property upon which localization de-
pends resides not in the muscle but in the bacterial cell.
From these findings the authors draw the conclusion that myo-
sitis, including even the milder transient affections, is
caused by the localization in the muscles of bacteria, us-
ually streptococci, that have an "elective affinity" for mus-
cular tissue.

Primary Suppurative Myositis

The suppurative form of myositis is caused in the maj-
ority of instances by staphylococcus pyogenes, although sta-
phylococcus albus and the streptococci are sometimes the act-
ive agents. Occasionally no organism can be identified with
the condition, but it seems in general to be of bacteriolo-
gic origin. Experimentally Miyake has shown that overuse of
a muscle could cause separation of its fibers, with the occ-
urrence of punctiform hemorrhages which offer a favorable
site for the development of infection.

The onset of primary suppurative myositis is like that
of an acute infectious fever. It is ushered in by a chill,
with rise of temperature, headache, and generalized pain(40).
The affection may be limited to a single muscle, or many
muscles may be involved. Those affected are swollen, indur-
ated, spontaneously painful, tender upon manipulation, and
non-adherent to the surrounding tissues. The muscles are in

a state of contraction, causing limitation of both active
and passive movements. The overlying skin may be erythematous,
but, as a rule, it is normal in appearance. Edema of the sub-
cutaneous tissue may be present. In a few days, in the
great majority of cases, the indurated masses soften and signs
of suppuration become evident. In a small percentage of
cases resolution occurs without abscess formation but maybe
with calcification(22). The muscles most frequently involved
are those of the upper and lower extremities, chest and lum-
bar region, or with extensions from ay of these primayy
sites(61).

The muscles affected vary in appearance according to the
stage and intensity of the inflammatory process. Early they
are dark red, later becoming grayish red from the infiltrat-
ion and breaking down of the tissue. The muscles may show
diffuse purulent infiltration, multiple small abscesses, or
a larger solitary abscess. The abscess wall is composed of
grayish-yellow necrotic muscle tissue and the cavity filled
with a thick, yellow or greenish-yellow pus containing nec-
rotic tissue and sometimes blood. The abscess may be so
large as practically to include the entire muscle.

Microscopically, both interstitial and parenchymatous
changes are seen. In the early stages the intersititial
tissue may not show much change, but it is considerably in-
creased in long-standing cases and may almost entirely re-
place the muscle tissue. The changes in the muscle fiber
may be slight with only swelling, or there may be the dis-

appearance of cross striations. There is always a prolifer-
ation of muscle nuclei and the actual change in the fibril
may be anywhere from hyaline changes to complete disappear-
ance of the fibril(45).

This comdition has a favorable outlook if the diagnosis
is prompt and treatment by incision and drainage is carried
out. These cases with multiple sites and metastasis are the
unfavorable ones for treatment and death often intervenes
after an endocarditis or pneumonia has developed.

DERMATOMYOSITIS

Dermatomyositis is a disease characterized by inflamm-
ation of the skin and muscle, non-suppurative, and running
an acute, subacute, or chronic course, associated with edema,
dermatitis, and a multiple muscle inflammation.

The first description of this disease as a clinical en-
tity was made in 1886 by Wagner (75). In 1903 Steiner (68)
collected twenty eight cases that were typical. The disease
generally attacks persons in the prime of life, although it
may occur in children. The onset of the disease is almost
always gradual. It may, however, be sudden with the pro-
dromal symptoms of malaise, waakness, pains in the extremit-
ies, headache, anorexia, and especially in children, gastric
disturbances. Fever may be noted but it is usually mild.
The patient is soon confined to bed because of weakness and
stiffness. The pains are described as drawing, tearing, and
boring. They rapidly take on a more definite character and
become circumscribed or localized, different muscular groups

being successively attacked. Eventually the whole body is more
or less affected. The pains occur not only spontaneously, but
also upon active and passive movements. In most cases the
patient finally lies in bed utterly helpless as if he were
completely paralyzed. The muscles are very painful to press-
ure. At times they are swollen and hard and at other times
soft. At times contractures have been observed. Frequently
the edema of the skin conceals the condition of the under-
lying muscles. As the disease progresses, the muscles may
become atrophic(49). The muscles of the proximal parts of
the extremities are more frequently involved. The hands and
feet are often unattacked. The muscles of the neck, back
and abdomen may be implicated as well as the muscles of re-
spiration, the intercostals, and the diaphragm, as the re-
sult of which asphyxia may ensue. The process may extend
to the muscles of deglutition, so that aspiration pneumonia
may result. The muscles of the face and the eyes may like-
wise be included in the disease. The heart muscle is unaf-
fected.

The second characteristic symptom is the dermititis and
edema, the latter appearing with the fever and at times in-
volving the whole body. Generally it is first seen on the
face, expecially above the eyelids.

The edema is more frequently present in the proximal
parts of the extremities, the shoulder, arm elbow and thigh.
It is asymmetrical. At times it may pit on pressure, but
usually a dense, hard infiltration of the subcutaneous tis-
sues is observed, the duration of which is usually limited

to the acute stage of the disease.

The acute cases run their course in one to eight weeks. When death occurs it is usually the result of an aspiration pneumonia. The subacute cases occupy a period of from two to six months, and the chronic form one to two years. Frequently in the chronic forms muscular atrophy ensues.

On pathological examination the skin covering the involved muscles it firm and hard. The subcutaneous tissue presents a firm and tense edema and is infiltrated with a yellowish serous fluid. The muscles are swollen; they are pale red or yellow in color and may occasionally reveal a yellowish-gray streak. They are suffused with serum and quite moist. At times they are hard and firm while again they are soft and boggy and even friable. Microscopically, the changes are those of parenchymatous and interstitial inflammation. The fibers are found in all stages of degeneration. They may be normal in size, edematous, or atrophied(45) varying in degree from granular, hyaline, waxy or fatty degeneration. Typical interstitial foci of small round cells are found in the perivascular connective tissue and to a lesser extent in the muscles. In the subacute and chronic cases there is increased amounts of connective tissue, which may be marked in both the perimysium, either externally or internally. In patients dying soon after the development of the disease, no degenerative changes were seen in the muscles, so that it would seem that the interstitial changes are the primary ones and the muscle degeneration secondary.

The etiology of this disease is unknown. Kell (32) attributed the disease to intoxication since he reports three cases occurring after partaking of fish. The infectious origin of the disease can not be overlooked however, since there is a rise in temperature accompanying the skin and muscle symptoms and as a rule there is a finding of an enlarged spleen.

Treatment consists of relief of the pain usually the salicylates being used. Morphine is used as a last resort. The only other methods of greatment are maintainance of nutrition and in the later stages of the disease passive movements, massage, and electricity.

POLYMYOSITIS HEMORRHAGICA

Polynyositis hemorrhagica is a form of myositis characterized by the presence of intra-muscular hemorrhage, usually having an acute onset, and running an acute, subacute, or chronic course. Vernon (74) gave the first description of this disease on record. In 1902 Thayer reported only nine cases to that date that were typical. There is an acute (71) onset, usually without prodromal symptoms, but attended with fever, pain in the extremities and swelling of the muscles. The muscles of the lower extremities are generally affected first and in common with those involved later are hard and very tender upon manipulation. Starting in a single muscle or group of muscles, the condition spreads and ultimately involv almost the entire voluntary muscle system. Owing to

Owing to the severity of the pain and tenderness, voluntary
movements of the extremities are greatly restricted. Edema
of the subcutaneous tissues may be present and the skin be-
comes hyperemic, often purpuric, or even hemorrhagic.

The myocardium is invariably affected, this leading to
a wide range of circulatory symptoms varying from cardiac
palpitation to dilatation, and not infrequently death re-
sults from cardiac failure. Bleeding from mucous membranes
is not infrequent. Unlike dermatomyositis, the condition
is generally not associated with enlargement of the spleen.
However, nephritis is frequent and albumin and casts are
found in the urine.

There is an acute onset with fever, a hemorrhagic or
purpuric skin erruption, and marked circulatory symptoms
from the myocarditis. Macroscopically the muscles, includ-
ing the myocardium, are reddish brown in color, and contain
numerous hemorrhagic foci. Microscopically, intramuscular
hemorrhages are found between the muscle fibers, the latter
in many instances having lost their nuclei and undergone
vacuolization and degeneration. In the chronic cases there
is a marked increase of connective tissue and more or less
atrophy of the muscle fibers, and the presence of blood-
pigment is noted.

The cause of this disease is still undetermined but
it is thought to be some form of infection. The disease
has been known to follow some throat and cervical cellulitis.
This is a very grave disease with a majority of the cases
terminating fatally. Palliative treatment is indicated.

PRIMARY MYOSITIS FIBROSA

Primary myositis fibrosa is a rare disease characterized by inflammation of one or more muscles, which later become replaced more or less completely by fibrous tissue. The disease is of unknown origin and runs a chronic or subacute course. Recognition of the disease dates from the report of a case by Gies in 1878 (18). Despite the length of time elapsing since the disease was first reported until the present, only a few cases have been reported.

Kreiss in 1886 reported the second case that is on record, and Janicke in 1895 reported the third case but the first authentic case which in accepted as such. Gowers in 1899 (20) in a lecture on polymyositis described an unusual case which has been designated as a case of myositis fibrosa in a recent review of the literature (9). In citing this case the intense pain at the onset of the illness, the early appearance of foot drop, and the loss of deep reflexes leads other authors to believe that the condition was perhaps a peripheral neuritis or widesptread distribution with secondary atrophic changes in the muscles. More-over, histological evidence to support the diagnosis of myositis fibrosa is lacking. The case of Batten in 1904 (5) was the first to be accompanied by a detailed pathological study. Rosenstirn (59) gives two cases that had been previously reported as myositis ossificans progressiva and states that he thinks that they were erroneously diagnosed and that the extensive fibrous changes in the muscle were predominate.

Little if anything is known concerning the etiology of
this rare disease. It seems rather likely that it is related
pathogenetically to the localized myositides in that the
histological picture of the muscle tissue in generalized
myositis fibrosa does not differ greatly from that in the
later stages of fibrosis. If so, the disease may be added
to that in the later stages of fibrosis. If so, the dis-
ease may be added to that already very large group design-
ated as the rheumatoid or arthritic syndrome. Batten sug-
gested the possibility of this condition being allied to
myositis ossificans progressiva largely because his case ex-
hibited microdactylia of the large toes. Several facts con-
cerning the two diseases renders this relationship not im-
possible. Ossification of muscle tissue in nearly all cases
is preceded by a myositis. According to Rosenstirn, the
primary pathological change in myositis ossificans is capillary
hemorrhage, and Llewellyn and Jones have shown that the early
change in fibrositis is a dilation of the small blood vessels
and capillaries, with not infrequently minute hemorrhages.

Macroscopic examination of the muscle shows the muscles
distinctly lighter in color and even a greyish tint. On
palpation they are firmer than normal and on section cut
with increased resistance.

Microscopically the muscles show degeneration, inflam-
mation and fibrous changes. The three types of changes are
noted usually in all muscles involved to different degrees.
In both longitudinal and cross sections the individual fib-
ers exhibit great variation in size, some of them appear

larger than normal, wheras others appear reduced to as much
as a fifth of their normal size. In many fibers all striat-
ions are gone while others show the longitudinal striations
with loss of the transverse ones, and vice versa. Hyaline
degeneration and hydropic infiltration is common. Scattered
throughout the muscle tissue varying numbers of inflammatory
cells and in certain areas collections of inflammatory cells
are present. In certain areas the muscle has undergone com-
plete degeneration. By far the larger number of infiltrated
cells were those of the gymphocytic group. A small number of
plasma cells may be present along with large endothelial
cells and fibroblasts. Variable amounts of connective tissue
are present and it is found to constitute varying amounts of
the muscle volume. In general it can be said that the peri-
pheral nerves reveal no departure from the normal.

The clinical findings in the reported cases show that
age and sex apparently play no part as predisposing factors
in the causation of this disease. The onset of the disease
is usually insidious but once begun seems to progress fairly
rapidly, the process requiring only a few months to cause
definite impairment of the muscle function. Batten's case
required five years to reach an advanced stage, wheras
Hoover's (30) case was rendered an invalid in two years.
Previous diseases or infections were in some instances in-
criminated as factors in the causation of the muscular con-
dition.

As before stated, pain is conspicious by its absence
in this condition even with considerable involvment.

In the absolute diagnosis of this disease microscopic examination of the muscles is impairative. The characteristic feeling on palpation, being boggy or doughy, is of importance. The absence of pain is important together with the lack of constitutional symptoms. The absence of skin lesions readily differentiates myositis fibrosa from the chronic form of dermatomyositis. The primary progressive myopathies or muscular dystrophies offer little difficulty in the differential diagnosis. The familial manifestations, the tendency to a symmetrical involvement of muscle groups, and th marked atrophic, or in some instances the pseudohypertrophic, changes in the muscles are the outstanding points to be remembered. In the myopathies, weakness of the involved muscles is the outstanding symptom, wheras in the true generalized myositis fibrosa stiffness of the muscles is the predominant functional derangement.

A consideration of the small number of reported cases justifies th conclusion that the outlook is not hopeful. The disease is always progressive in nature. Its duration is variable. In the later stages of the disease the patient's general health undergoes marked deterioration and death from some intercurrent infection is probable.

Little has been said as regards therapy. Drugs are of no value. Massage (I) is used but to little avail. Careful search for foci of infection should be made and if it exists should be eradicated if possible.

CASE REPORT

O.E., a negro boy, 14 years of age, a student, entered

the hospital complaining of stiffness of the entire body with some pain in the chest. Family history essentially negative. Past history essentially negative. Present illness; about one year prior to entry into the hospital the patient noticed a dull aching pain in the upper part of the chest. This symptom was present more or less continuously and was not intensified by respiration. At about this time he started to "lag" in his work. A few weeks later stiffness started in his hands. About five weeks later he noticed that he was unable to play with other children. His back became stiff about this time. To the time of entrance he lost no weight, no constipation, nocturia, or polyuria. Physical examination was negative except for a peculiar shineyness of the skin over the wrists and the stiffness of the muscles. Laboratory examination was also negative.

After entering the hospital the patient made no change in progress for several weeks at which time he became febrile showing a slight afternoon temperature. He began to have precordial pain and to loose weight at the rate of two to three pounds per week. The patient gradually became weaker and died three months after admission apparently of tuberculosis. Autopsy was negative except for the lungs which showed an acute tuberculous process and the typical findings in the muscle. The microscopic examination showed the typical fibrous changes characteristic of this disease.

MYOSITIS OSSIFICANS PROGRESSIVA

Myositis ossificans progressiva is a chronic, progressive, inflammatory ondition, of unknown origin, characterized by the formation of osseous tissue in the muscles, tendons, fascia, and ligaments, with outgrowths from the bony skeleton. This disease is probably the most common of the true myopathies and as a consequence is probably the best understood from certain viewpoints.

John Freke was probably the first to describe myositis ossificans progressiva. In the Philosophical Transactions of the Royal Society of London for 1736 he wrote;"Yesterday there came a boy of healthy look and about fourteen years old, to ask of us at the hospital, what should be done to cure him of many large swellings on his back, which began about three years since, and have continued to grow as large on many parts as a peny loaf, particularly on the left side. They arise from all the vertebrae of the neck and reach down to the os sacrum; they likewise arise from every rib of his body, and joining together in all parts of his back, as the ramifications of coral do, they make, as it were, a fixed bony pair of bodice. There were no symptoms of rickets observed on any joint or limb."

The disease is probably best discussed by following the classification of Gruca (21).

      1. Myositis Ossificans Traumatica.

          a. Bone formation following a severe single injury by blunt force.

  b. Bone formation following dislocations.

  c. Along site of puncture wounds without injury

   to bone.

  d. Bone formation following clean cut wounds.

 2. Myositis Ossificans Chronica.

  a. Bone formation occuring after slight repeated .

   injuries.

  b. Bone formation due to occupational overstrain.

  c. Bone formation without apparent trauma.

 3. Myositis Ossificans of Infectious Origin.

 4. Myositis Ossificans Para-arthritica.

 5. Myositis Ossificans Neurotica.

 1. a. Bone formation following a severe single injury
by blunt force is probably the most frequent form of myo-
sitis ossificans that is encountered. Schultze found it
232 times out of 296 collected cases. It is common in some
occupations, as horse servants, workmen, sportsmen, etc. As
the most frequent trauma was noted falling or being struck
by a heavy object. This form develops most frequently in the
anterior and lateral aspect of the thigh and upper arm.
Very rare are such localizations as the os pectineus muscle,
masseter, or as the temporal, gluteal or thumb muscles noted.
To this group belongs also ossification of joint capsule and
ligament, ossification of shoulder-joint capsule after a single
blunt injury, etc.

  b. Myositis ossificans subsequent to dislocations dev-
elops most frequently after backward dislocation of the elbow.
It has been observed also as a rare complication of a supra-

acromial dislocation of the clavicle, after luxation of the
hip, of the knee, and of the shoulder.

c. Development of bone alont the track of perforating
gunshot wounds, when the projectile either did not injure
the bone or only touched it.

d. Myositis ossificans after clean incised wounds.
Its appearance after clean incised abdominal wall wounds
at the "white line" following operations on the stomach is
the commonest one and was described several times, by many
authors. This form, otherwise very rare, has been seen also
after a suppa-pubic prostatectomy by Lewis, after a hernio-
tomy by Jones, after puncture wounds by Bender, Werner,
after incised wounds of the thigh by Cranwell, at the glutei
by Schwartz, etc.

2. a. Myositis ossificans chronica is the name applied
to the formation of bone after repeated slight injuries. To
this group belongs the "rider's bone" in abduction muscles,
following steady irritation at horseback, the cavalryman bone
at the outer side of the thigh from sabre hits, etc.

b. Bone formation owing to occupational overstrain-
ing of some group of muscles, occurring among joiners, shoe-
makers, etc. This group or type does not give a history of
any single severe injury.

c. Myositis ossificans circumscribed, occurs spont-
aneous when even a single or repeated slight injury can be
excluded. This is a very rare condition.

3. Myositis ossificans of infectious origin may occur.

This may follow after metastatic abscesses, after a pyaemic abscess or a phlegmon of the forearm as reported by Roskowski.

4. Myositis ossificans para-arthritica, a term applied to bone formation in muscles and tendons occuring near joints, following a chronic inflammatory process, as arthritis deformans or tuberculosis. There need be no injury in relation to this type. The cuase can be said to be either the chronic inflammation in the neighborhood or the factor exciting the the main disease.

5. Myositis ossificans neurotica; development of ossification of muscles and tendons subsequent to tabes, syringomyelia, traumatic paraplegia and myelitis. This is probably due to increased opportunity to injuries or to trophic changes.

The course of myositis ossificans traumatica is a typical one and can be divided into three stages. In the first typical traumatic symptoms are predominant. They subside within a few days, only limitation of movement, improved somewhat with the ceasing of traumatic symptoms, does not disappear entirely. In the second stage at the end of the second week, or later, according to the care and rest given to the damaged region, the pain, spontaneous and on movement, reappears, the impairment of motion increases and the circumscribed, somewhat not elastic, swelling becomes slowly larger. There are either no, or very little, symptoms of inflammation in this stage. Three or four weeks after the in-

jury the X-ray examination reveals a faint shadow, irregularly and indistinctly limited, not homogenious, with darker and lighter areas, situated parallel to the shadow of the bone of the skeleton, but separated from it by a light zone, present also in cases in which an attachment to bone is certain. There is a marked incongruence between the size of the palpable mass and its size in the X-ray.

In the third stage the growth of the mass stops or the lump increases slowly by periosteal apposition. The pain disappears or remains unchanged. In X-ray pictures the shadow is more homogeneous, intense, sharply limited and at times smaller than before. The duration of the growths time of the mass is variable from ten weeks to six months.

As a rule there is no fever in the course of myositis ossificans. There are but few cases known in which were marked inflammatory symptoms. There were also very rare cases in which the ossification developed some years after injury.

In other forms of myositis as myositis ossificans chronica ossification after laparotomy wounds, neither the patient not the physician could determine precisely when the mass began to develop. In laparotomy scars the bone was found earliest at the end of the third week after the operation. Rider bone and similar forms appeared mostly after three to four months.

The parosteal bone may be different in form and size.

There have been irregular masses of some centimeters to plates occupying a part or even the whole of a muscle, surrounded usually by a strong connective tissue capsule, periosteum like, many centimeters thick, grown together with the muscles, degenerated within the mass to some degree.

The mass was lying either separated from the shaft without any bony or connective tissue attachment to it, or grown to the bone by a connective tissue band, therefore but little movable, or by a bony pedicle attached to skeleton bone. The pedicle can be large or narrow, joining the mass to a bone of the skeleton at one end, or in the middle. It is not seen in the recent cases in the X-ray picture because it is still porous and without calcium deposits. It does appear when the callus is quite mature.

In some percentage of cases, according to Strauss, up to ten percent, the new bone contained a cyst filled with a light yellowish, sometimes reddened, synovia resembling fluid. The scysts were always placed at the lower extremity of the thigh, but in the case of Nimier the cyst was found in the brachialis internus muscle. Such cysts were reported by many others also.

The microscopical picture of myositis ossificans is very characteristic; there is an irregular mixture of bone, cartilage, muscles and connective tissue. The usually spongy bone forms variably shaped trabeculae, surrounded by connective tissue layers of differing amounts of inter-cellular substance and sometimes by mostly discontinuous rows of osteo-

blasts. The bone plates seemed to arise from the connective tissue either directly; the fibrous connective tissue beginning in some place to lose its structure becoming homogeneous and changing by deposition of calcium salts and converting the fibroblasts into bone cells without any distinct limit into osteoid or bone tissue; or indirectly, the bone trabeculae arising from connective tissue by cartilage stage. The muscle, according to most writers, plays no active role in the whole process; it becomes compressed by newly formed connective tissue and undergoes degeneration. In later stages there are no signs of rapid growth, but contemporary to the resopption by giant cells the bone increases by periosteal or osteoblasts apposition at margins. In most instances no, or but small, signs of inflammatory nature were found. But according to some it is due to the late period of the process. In the early stage marked inflammatory reaction could be confirmed microscopically. It would be of interest to remember that the same pictures and stages were seen, also by the study of the progressive form of myositis ossificans, and, similarly and in the same period of time by callus formation after the fractures of long bones, as stated by Bancroft in his experimental work (3).

Diagnosis of this condition is made easy in the later stages by the use of the X-ray. In the earlier stages, however, the X-ray may be of no assistance. Many conditions of a similar nature must be excluded such as; hematoma, muscle callus, muscle tumor, osteomyelitis, interstitial syphilitic process, periostitis,(traumatic and infectious) fractures

and neoplasms.

To the development of a parosteal bone some regions are particularly disposed. Specially where the bone is covered with a thick layer of muscle, where the muscle inserts broadly into the periosteum and near the joints, as on the thigh anteriorly and sideward, as the quadriceps and adductor muscles, and on the arm, the brachialis internus and triceps muscles.

In early times when myositis ossificans was insufficiently known and especially when it was often mistaken for a neoplasm, it was treated by radical operative measures, regardless of the stage of its development. Most of the present day surgeons recommend conservative treatment, in the early stage of the process especially, and even in later periods, only palliative treatment is employed. Myositis has the tendency to shrink or even disappear completely without any interference. The early operations were often followed by recurrences, mostly, however, in cases of broad attachment to the bone of the skeleton. At the early stage of the disease it is very difficult to deal with tissues changed in outlook and anatomical position, inhibited with blood, therefore with a tendency to become infected. One must also consider that inflicting another injury to parts inclined in that period to ossification, one may renew the activity of t the morbid process.

Early operation may be indicated in cases where loss of function may result from the bone forming process. In most

cases a simple excision of a mass, being stationary, as advocated by many authors, is sufficient to bring recovery. In some cases it seems advisable to curette away the periosteum of the underlying bone. Rest seems to be a safe proceedure in all cases. When, however, the mass becomes stationary or begins to decrease, energetic osteopathic treatment is to be employed.

Etiology at present revolves around two theories. The one assumes parosteal bones are arising from the periosteum of the neighboring bone, the other advances a metaplasia of local connective tissue.

The theory of periosteal origin of parosteal bone, is based upon clinical observation; there are many cases of myositis where the attachment of the bony mass to a skeleton bone was proved both clinically and at the operation. The parosteal bone formation may be accomplished by many ways. A severe blow crushes the muscles into a pulp and injures the periosteum opposite to it. The osteoblastic layers of the periosteum proliferates then, the osteoblasts escape into the crushed area of muscle and there form a bone. A muscle is in action, receives a blow, some of its fibers tear themselves from their bony origin and retracting into the mass of the muscle still connected with the bone, carry therefore particles of periosteum. These particles grow in their new environment, are true bone grafts, and can form intramuscular osteomata, unconnected with, though originating from the peri-

osteum.

Another explaination is; a severe blunt injury at once subcutaneously strips off and destroys the periosteum and crushes the muscles in contact with the bone. Bleeding occurs from the surface of the denuded bone and with the blood osteoplasts, in a free and possibly ameboid condition, escape into the pulped muscle tissue and blood and there produce a growth of bone. Healthy muscles left in contact with denuded bone form protective fibrous adhesions from their interstitial connective tissue and take on the limiting function of the periosteum. But severely contused muscle tissue mixed with blood provides a favorable medium for the osteoblast.

The importance of a hematoma has been advocated by some. Pochhammer tried to confirm its importance experimentally. He formed a pocket from pedunculated periosteum flaps on rabbits, filling it with coagulated blood, and was able to state that bone developed only in spaces filled with blood clots. When the growing new bone comes in contact with healthy tissues it stops.

Detached flaps of periosteum at the muscular insertion and subsequent stimulation by electricity has been shown to develop bone in as soon as four months experimentally in rabbits. Grohe has shown that in free transplants of periosteal grafts traces of bone proliferation, but they are limited in size and disappear after a time.

Dawis and Hunnicut, on the basis of their experimental study, came to the following conclusions: "Periosteal transplants in the majority of cases do not produce bone; pedunculated flaps of periosteum produce no bone, except for the pedicle connecting them with the bone, free periosteal flaps and pedunculated flaps with bone shavings attached produce bone in every instance."

Lexer and his school made extensive experimental studies on this subject and state that free transplanted periosteal flaps in normal conditions produce no bone, for free transplanted periosteal grafts produce bone only when detached with the osteoblast layer, which is only possible if irritated and showing a proliferation of osteoblasts. To produce a proliferation experimentally is a very difficult matter. Bone production succeeds when periosteum of grown-up animals can produce bone if there are osteoblasts on it and when blood vessels are not cut. The new formed bone disappears soon, when there is no function for it.

Some differences between the results obtained by several authors are due to different methods employed and the fact that several sorts of animals were used. As is well known, rabbits incline very much to excessive callus formation, while cats occupy the diamethrally opposite position. Dogs show a tendency equal to that of man, roughly.

Summing up the above evidence, one must come to the conclusion that periosteal grafts, free or even connected with muscles, produce bone inconstantly and only in young

individuals in the period of growth. In adults if it was torn off in the stage of proliferation of osteoblasts, if inflammed or if taken off with a piece of cortex. In the last instance the new bone grows very slowly and disappears after a time. Sucn conditions are undoubtedly very uncommon in myositis, for it occurs almost exclusively in individuals of middle age. This suggests that the periosteal theory in its present form is not sufficient to explain the development of parosteal bone after a single injury. If it arises from periosteum, other conditions accompanying are necessary, not repeated at present experimentally.

The other theory assumes that parosteal bone to result from a metaplasia of connective tissue. This theory is based upon clinical observation. In most cases of myositis ossificans no connection was found with a skeleton bone even of fibrous tissue. The microscopical finding seems also in many cases to indicate that the connective tissue cells are converting into bone and cartilage cells. The X-ray examination reveals almost constantly bone formation in large spaces with many points of ossification, a form uncommon to the periosteal ossification.

The existence of metaplasia is well known to pathologists. Metaplastic bone formation has been seen in almost every part of the human body, as in the heart valves, lung, skin, brain, liver, in arteries, various glands, etc. The connective tissue cells convert into bone either directly; calcium salts depositing in intercellular substance and connective tissue cells becoming bone cells, or indirectly by progressive metaplasia, connective tissue cells transforming into cartilage,

respectively, bone cells at first and produce then a bone.

There is also no obstacle to assume the ability of connective tissue to convert into bone. The connective tissue, cartilage and bone genetically arise from the same embryonic layer and transform later into each other. According to Wolter the only difference between all kinds of tissues developing from mesoderm lies in the difference between their intercellular substance and is not sharp. They all react to an injury with formation of a new tissue accommodated to new conditions. The connective tissue incline above all other tissues to a hyperproduction than to a specific regeneration. It refers especially to the intramuscular tissue and tendons.

Osteoblasts may arise from periosteum as well as from connective tissue. There may be also an incomplete differentiation between the tissues descending from mesoblasts. Among many other factors suggested to cause a metaplasia is to mention the synovia. Eden, stating that the most privilgged regions to development of myositis ossificans are those near joints and the joint capsule was often grown together with the mass, attributed a very significant role to the synovia. Some authors have found within the ossified mass a cyst filled with a synovia like fluid.

Berndt is of the opinion that to slight hematogenous infection is due to the development of parosteal bone formation because in some cases, operated upon, there was slight rise in temperature. In the initial course in some instances there were marked inflammatory symptoms, or oss-

ification followed upon metastatic abscesses (37). Lewis .
believes some cases of myositis to be undoubtedly secondary
to some infectious process in the muscle.

Neurotrophic changes are held by some as predominant
factors causing a metaplasia. It may be that the want of
checking influence of nerves plays an important role; the
tissues lose their normal interrelationship.

Zanoli (79) states that the main factors are intoxic-
ations and infections. The toxins act as irritants upon
tissues, being in a state of less resistance. The decal-
cifications common in paraplegics, accompanied by dircul-
atory disturbances, help to calcium salt deposits.

The etiology of bone formation occurring in clean in-
cised wounds of the abdominal wall is also an open question.
Some believe that there also a periosteal stripping is pos-
sible. Others assume a sort of predisposition. The lineae
transversae are the remains of a rib and the white line a
prolongation of the sternum. For this reason they contain
sometimes osteogenic elements developing when injured, with
bone formation.

Others assume a pure metaplasia on the basis of
microscopical pictures, showing a marked transition of the
connective tissue to bone with signs of inflammation, under
the influence of a hematoma, or effect of acid gastric
secretion, or acid urine, for in most instances a myositis
ossificans in the abdominal wall developed after operations
on the stomach. Concerningly it must be stated that during
the performance of a stomach resection or a gastro-entero-

stomy, gastric juice should have no opportunity to come in contact with the abdominal wall, just for precaution.

Rohde made extensive experimental studies upon metaplasia and favors the assumption that the cells are undifferentiated cells, having a tendency to transform. A well-developed connective tissue is not able to convert into bone, even under the influence of calcium salts, either bioled or dead ungoiled bone. He says, one never meets with a parosteal bone formation in the neighborhood of pathologic destruction of a living bone.

Bancroft, studying bone repair, advances the theory that "the so-called osteoblasts have very little to do with bone production. Calcium salts are deposited in the extracellular elements of connective tissue. The fibroblasts then become fone cells. Undoubtedly the periosteum with its areolar tissue and numerous small blood vessels is the best structure for bone formation, but is not the only one."

Aschoff attributes a great significance to the reticulo-endothelial apparatus in metaplastic bone formation.

Case Report

A.G., male, aged 46, family history unimportant. Has never been seriously ill. During the last two years of war he was obliged to walk mush through mountainous territory. After each long march he felt pain in the anterior upper third of the right thigh. After some rest the pain disappeared. At various medical examinations nothing abnormal

could be found in the ailing region. On his return from war
(1918) the trouble disappeared. He was quite well, working
as a joiner until last year, when the pain appeared again.
Three months ago he noticed in the upper third of the right
thigh an induration in the painful region. The extremity
deviated outward and he began to limp. Two months ago he
noticed in the painful region a swelling gradually increas-
ing in size. There has never been a direct injury to the
now painful region. The physical examination after his ad-
mission to the clinic was essentially negative.

The X-ray examination revealed just below the anterior
superior iliac spine a shadow about one centimeter in dia-
meter and about fifteen centimeters long, well limited,
showing in its center a lighter space like bone-marrow, un-
attached to the femur. Diagnosis at this time; myositis
ossificans.

He was operated upon. A bony mass was removed that
was irregularly quadrangled, about fifteen centimeters long
and one centimeter in diameter, surrounded by a strong fib-
rous capsule. Microscopical examination; transverse sect-
ion of the mass showed at one side of the periphery of
the section, an island of well preserved skeleton muscle
was to be seen, surrounded by fibrous connective tissue,
some of them degenerated and atrophied. In other parts
fibrous connective tissue, partially hyaline changed, with
only slight amounts of nuclei and very few blood vessels,
containing here and there small plates of osteoid tissue,

surrounded by osteoblasts. The connective tissue near these bone islands appeared more loose and showed many nuclei, arranged concentrically along the osteoid plates, so that their limits were not very sharp. It appeared as if the osteoid tissue originated directly from the connective one. The bony trabeculae were either homogeneous or there in their center distinct spaces filled with fat or loose connective tissue forming bone-marrow. Near the described plates at the other side of the section one met with a large island of typical spongy bone tissue sharply limited from the neighborhood. This island of typical spongy bone had an oval outline, size .6 by 1 centimeters. The trabeculae of typical bone structure were surrounded by an abundance of osteoblasts. The bone marrow contained, as above an abundant amount of fatty or loose connective tissue. Cartilage traces were found in the middle of some bony plates. Nowhere were inflammatory symptoms apparent.

Case Report

S.K., eighteen years old, school boy. No constitutional disease among the members of his family. Has never been seriously ill, excepting measles ten years ago. During the last four years, while playing football, received several blows on both legs without any complication. Thirty four days ago he was struck by a thick iron tube upon his left thigh. The pain it caused was so trifling that he could walk till evening, feeling no special discomfort.

The next day the contused region became swollen and discolored, tender on pressure but not especially painful when he was walking. The knee could be flexed only to about 135 degrees. Within five days the tenderness disappeared almost completely, conly a circumscribed swelling remained. The flexion of the knee returned also to normal limits. After a week he played football again, feeling no discomfort. Two days later, however, a severe pain on movement reappeared suddenly, forcing him to keep at rest for eight days. The mentioned swelling increased gradually and at the same time the knee became stiff again. Since two weeks ago he has been walking about. The pain on movement decreases slowly. The swelling remained unchanged.

X-ray photograph shows at the damaged region a spotted shadow, indistinctly and irregularly limited, separated from the femur by a narrow zone of light. The femur is unchanged; Diagnosis at this time, myositis ossificans.

Summary of Pathological Discussion.

From the study of the literature of these conditions and from observations of mixed cases (79) it is impossible to escape the conviction that either they are all parts of one disease, or each is a clinical manifestation rather than a morbid entity. One may occur alone or is associated with one or more of the other entities.

It appears that underlying these disorders lies a single

morbid process, at present unknown. When it produces an
acute reaction in the body there are numbered among its
symptoms fever, edema, skin eruptions, muscle tenderness
and pain, a liability to recrudescence and a danger of
death. Revealed by the microscope is parenchymatous de-
generation of muscle, cellular infiltration in subcutaneous
tissue, between muscle fibers and about the vessels, and some
excess of fibrous tissue in the same situations. When the
disease is more protracted or produces a less acute tissue
reaction, sclerosis predominates over the round-celled ex-
udation, producing hardening of skin and subcutaneous tissues
and of the muscles. Both may be affected together, either
may precede the other or either may occur alone. There is
also obliterating arteritis of the supplying vessels, which
possibly causes or enhances the atrophy of the skin and mu-
scles, and provides an explanation for the Reynaud's phen-
omena. Arthritis is an occasional associate. In the fibrous
tissue formed in the skin or subcutaneously and probably
also in that which is perivascular, calcareous salts may be
deposited, thus changing the diagnosis(12).

Summary of Histological Discussion.

From the foregoing discussion it can be seen that the dogmatism of many writers must be taken with reserve. From a histological standpoint the basic factors of the components of a muscle fiber are not clearly understood. The contraversy centers around the existance or non-existance of striations as observed in fixed and fresh preparation. The question of the innervation of muscle can be said to be fairly on the road to understanding when the recent work of Tower (73) is considered. She has shown fairly conclusively that sympathetic innervation of muscle does not exist.

If, however, we go back to a consideration of Haycraft's work a complete new foundation for muscle histology, from the standpoint of the sarcomere, must be undertaken.

Summary of Physiological Discussion

In essence contraction is a matter of the equal division of the dark, stainable materials of the Q discs (81) and the movement of the resultant semidiscs in opposite direction against the limiting telophragmata of the sarcomere. Relaxation is the reversal of this process, the halves of respective Q discs returning to their originally bisecting mesophragmata. Thus, two limiting membranes (terminal Z and median M), a laterally confining pellicle (sarcostylic membrane) and a dark substance (salts of Q) moving through a colloidal clear substance, are the only essential morphologic elements involved in contraction. How this shuttlelike movement of a dark substance between successive telophragmata effects contraction and relaxation would seem to be the central problem of the physiologist in his efforts to formulate an adequate explanation of muscle contraction.

The "all-or-none" law is not free of more detailed understanding as evidenced by work of numerous English physiologists.

Summary of Present Concept of Muscle.

To scientifically treat a condition the physiology, pathology, chemistry and histology of that morbid process should be thoroughly understood. From the foregoing discussion it can be assumed that what treatment is undertaken to relieve muscle pain is done purely from a palliative standpoint. The largest single tissue in the body, the one second in order for frequency as far as pathologic manifestations are concerned, and no phase of its normal or abnormal function is understood. With no portion of this subject understood completely no attempt to correlate the different phases with an attempt of better understanding of treatment will, therefore, be undertaken.

To stress this statement a recent article appearing in a reputable journal will be cited to show what is done for injuries to muscle.

"All injuries without fracture (82) must be treated intensely and vigorously from the beginning, except those of the elbow-joint, for fear of myositis ossificans developing. The essential factor is the working out of the muscle the product of injury immediately. When a muscle is bruised, torn or partially ruptured a hematoma forms - this becomes organized and results in fibrous tissue binding surrounding structures."

However, there is every reason to believe that research works are pointed in the right direction. The works of Tower,

Millar, Mathews, Gillespie, Sherrington, Eggleton and many others promise to be a definite advancement in the understanding of muscle, both normal and abnormal.

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