matites of Madagascar with those of other countries (Vol. II, pp. 334–362). This embraces a careful description of these pegmatites in New England and in California, the greater part of the deposits having been studied in 1888 and in 1913 (pp. 334–346); in the last-named year Professor Lacroix was actively engaged in completing the great collection of American gems so generously donated to the Muséum d'Histoire Naturelle in Paris by J. Pierpont Morgan. He was accompanied on several of his excursions by the writer of the present notice and by Mr. Howe. He notes the striking resemblances between the pegmatites of California and those of Madagascar, the association in both regions of lithia tourmalines, notably of rubellite, caesium beryls, kunzite and spessartite, and the existence of native bismuth, of maganocolumbite. On the other hand, mineralogical differences must be noted.

The special attention here given by Professor Lacroix to these analogous formations in the United States is well worthy of remark in view of the fact that in but too many mineralogical handbooks composed by Europeans rather scant notice is taken of the United States.

Within the restricted limits of the present review we can only indicate the chief divisions of the section Lithography in Volume II, as follows:

FIRST DIVISION, INTRUSIVE ROCKS

Chap. I. Quartzite Rocks, pp. 229–243.
Chap. II. Pegmatites, pp. 244–376.
Chap. III. Syenites and Nephelinic Syenites, pp. 377–397.
Chap. IV. Rocks with Plagioclase, pp. 398–438.
Chap. V. Deformations and Transformations of the Eruptive Rocks, pp. 439–455.
Chap. VI. Contact Phenomena of the Eruptive Rocks, pp. 456–472.

SECOND DIVISION, CRYSTALLINE SCHISTS

Chap. I. Gneisses and Micaschists, pp. 479–522.
Chap. II. Quartzites, pp. 523–539.
Chap. III. Essentially Magnesian Rocks, pp. 540–545.
Chap. IV. Essentially Calcareous Rocks, pp. 546–574.
Chap. V. Exclusively Ferriferous or Aluminous Rocks, pp. 575–578.

THIRD DIVISION, INTRUSIVE POST-LIASSIC ROCKS

Chap. I. Quartzite Rocks, pp. 579–604.
Chap. II. Syenites and Nephelinic Syenites, pp. 605–622.
Chap. III. Syenito-Theralitic Series, pp. 623–643.
Chap. IV. Rocks with Feldspathoids without Feldspar, pp. 643–648.
Chap. V. Plagioclasites, pp. 649–655.
Chap. VI. Contact Phenomena of the Intrusive Post-Liassic Rocks, pp. 656–666.

The third and concluding volume[1] of Professor Lacroix's great work has been received since the review of the first two volumes was in type. This comprises the following petrographic sections: Post-liassic Volcanic Rocks (pp. 2–66); Sedimentary Rocks (pp. 67–91); Alteration of Rocks (pp. 92–149); Sketch of the Leading Lithological Characteristics of the Island (pp. 151–224). This is succeeded by a division devoted to a comparison of certain eruptive regions with those of Madagascar (pp. 227–294), and in the following brief section (pp. 295–334) the writer has grouped, in alphabetical arrangement and as an appendix, a series of mineralogical items which did not reach him until the earlier volumes were in press. The volume then concludes with a Bibliography (pp. 335–349), and an extensive Geographical Index of about 70 pages, succeeded by a Geological, Lithological and Mineralogical Index (pp. 421–431) and 4 pages of Errata. This truly monumental work is destined to remain an authority for a very long time.

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SPECIAL ARTICLES

THE GENESIS OF NORMAL AND ABNORMAL CARDIAC RHYTHM

THE story of the development of the modern ideas concerning the cause of the heart beat constitutes an interesting chapter in medical history. Haller,[1] in 1757, was apparently the first to conceive that the rhythm of the heart was dependent upon the blood flowing through it. To quote:

> Qui hos experimentorum nostrorum eventus pensitaverit, is quidem non dubitabit nobiscum pronunciare, causam quae cor in motum ciet, omnino sanguinem venosum esse. Nam enata ea causa cor movetur, subtracta quiescit, diminuta motus cordis languet, aucta motus intenditur.
>
> Id si verum est, si porro cordis admotum major, quam aliorum musculorum, promtitudo est, si praeterea cordi perpetuus, dum vivimus sanguis advenit, non mirum est, perpetuum cordis motum esse.

Subsequently, in the early nineteenth century, arose the argument as to the neurogenic or myogenic origin of the beat with the evidence then considered to be in favor of the former. The work of Gaskell,[2] in 1881–83, cleared much of the confusion and laid the foundation for subsequent work by pointing out the control

[1] Tome III. Lithologie, Appendice-Index Geographique; Paris, 1923, 437 pp.; 28 text figures, 8 plates, and a colored geological map, 4to.

[1] Haller, Elementa Physiologiae Corporis Humani., 1757, tome I, p. 493.

[2] Gaskell, *Journ. Physiol.*, 1883, *4*, 43.

of the rhythm by the "pacemaking" venous end of the heart. At about the same time Langendorff[3] pronounced the theory that the tissue found its stimulus in the products of its own metabolism, and this view was later adopted by Englemann.[4] Ringer,[5] in 1883, perfused the isolated heart with artificial inorganic solutions and with his work there began extensive researches along this line.

An adequate review is not within the scope of this note. Through the work of many observers the cardiac muscle has come to be regarded as an irritable, conducting, contractile tissue mass which normally responds rhythmically to a so-called "inner stimulus." These fundamental properties, and the "inner stimulus" as well, have been shown to depend upon the composition of the fluid bathing the muscle tissue. Particular importance has been attached to the chlorides of sodium, calcium and potassium. More recently the significance of the reaction of this fluid has been pointed out.

For several years we have been interested in developing an approach to the problem of the cardiac arrhythmias by way of the origin of the normal rhythm. We have studied the isolated, perfused hearts of cold-blooded animals and of dogs. These observations, together with a review of the literature, have led us to advance a conception of the genesis of the heart beat which seems to explain the normal rhythm as well as many of the irregularities. The theory is not entirely a new one. It consists, in part, of the application to the excitatory process in the heart muscle of the results of the study of this phenomenon in other irritable tissues.

Simply stated, our conception is as follows:

The cardiac rhythm is due to the rhythmic building up and discharge of a potential difference across a semi-permeable membrane. The rate of development and magnitude of this potential difference are dependent fundamentally upon the difference in hydrogen ion concentration within the cells of the cardiac tissue and in the fluid bathing them. The level of potential difference at which discharge takes place is determined by the permeability of the interposed membrane. This, in turn, is dependent upon the concentration of sodium, calcium and potassium salts an either side of that membrane.

The muscle cell is essentially made up of an aqueous solution of colloids, certain organic compounds and electrolytes. It is surrounded by tissue fluid of a similar composition but differing from it in the concentration of certain ions. Thus, the muscle cell contains more potassium and less sodium and calcium than the tissue fluid. The concentration of hydrogen ion appears to be greater within the muscle cell than without. This ion is being constantly set free in the cell metabolism. On the other hand, the reaction of the tissue fluid is more rigidly fixed by "buffer" salts.

At the interface between two such phases such substances from each as lower surface energy tend to concentrate. Hence colloids, proteins and lipoids form a surface film which comes to assume definite characteristics as the cell membrane. Space does not permit a detailed description of this membrane, but the studies of Loeb,[6] Osterhout[7] and others assign to it special properties of permeability. It seems established that the membrane is impermeable to colloids. As regards crystalloids the situation is complicated by the presence of compounds of electrolytes and colloids. In addition, the properties of the membrane are such that a more or less constant difference is maintained in the concentration of the inorganic ions within and without the cell. Moreover, the degree and type of semi-permeability appear to vary with the cell and to depend upon the concentration of sodium, calcium and potassium salts in the immediate vicinity.

Since the ionic concentration is not the same within and without the muscle cell a definite potential difference develops across the surface film in accordance with the formula:

$$E = \frac{RT}{F} \cdot LN \cdot \frac{C}{C_1}$$

where C_2 and C_1 represent the concentration of the diffusible ion in the more concentrated and the more dilute phases, respectively. The cell membrane is thus polarized with the outer surface positively charged. Inasmuch as the hydrogen ion is by far the most rapidly moving ion concerned and experimental evidence shows that the polarization of the membrane is not due to the other cations it is to be inferred that the degree of potential difference existing across the surface film is dependent upon the difference in the hydrogen ion concentration in the muscle cell and in the fluid bathing it.

In 1911 Lillie[8] elaborated the "membrane theory" in explanation of the excitatory process in nerve. This theory, originally suggested by Hermann* and Brunings,† has since been shown to be in accord with the experimental evidence in this regard not only in nerve but in other irritable tissues as well. It may reasonably be applied to cardiac muscle. According

[3] Langendorff, *Arch. f. Anat. & Physiol.*, 1884 (supp. vol.), p. 1.

[4] Englemann, *Arch. f. d. ges. Physiol.*, 1897, *65*, 109.

[5] Ringer, *Journ. Physiol.*, 1880–82, *3*, 380.

[6] Loeb, J., *Journ. Gen. Physiol.*, 1922, *5*, 225.

[7] Osterhout, *Journ. Gen. Physiol.*, 1922, *5*, 220.

[8] Lillie, R. S., *Am. J. Physiol.*, 1911, *28*, 197.

* Hermann, L., Handbuch der Physiol., 1879, II, 194.

† Brunings, W., Arch. f. d. ges. Physiol., 1903, C, 367.

to the "membrane theory," the process of excitation involves changes in the permeability of the cell membrane at the point of stimulation and simultaneous depolarization. Since the remainder of the cell surface is positively charged, a current will at once begin to flow towards the stimulated area; this point becomes electronegative to the rest of the cell surface. This constitutes the action current and its strength depends, obviously, upon the potential difference existing across the membrane at the time of stimulation.

Nernst,[9] considering the effect of electrical stimuli, brought forward the view that stimulation involved a critical increase in concentration of ions on either side of a semi-permeable membrane. In other words, if a certain potential difference were developed across a membrane in a certain time that very potential difference would cause changes in the membrane which would constitute stimulation. Upon this conception he showed that any current to stimulate must fulfill certain relations of intensity and duration, as expressed in the formula:

$$I\sqrt{T} = c$$

where I represents intensity and T duration of current, and c denotes the threshold of the tissue involved. With minor modifications this relation has been shown by Lucas[10] to hold over a wide range of tissues. Lapicque[11] has shown that this formula applies to the polarization of artificial membranes as well.

Lillie has developed the conception that the process of conduction depends upon the excitation of the adjacent area by the action current developed at the point of stimulation. The action current from each excited point causes excitation in its neighborhood and the process is thus propagated in a wave over the tissue. The distance over which the action current can fulfill the requirements of Nernst's formula and so produce stimulation is determined by the potential difference existing at the point of stimulation and by the permeability of the cell membrane. Both of these circumstances are dependent, as we have outlined, upon the relative ionic concentration within and without the cell.

The heart is made up of a mass of tissue similar in composition to the muscle cell described. It is our conception that, under optimum conditions, the difference in hydrogen ion concentration within this muscle mass and in the tissue fluid bathing it, and the proportion of sodium, calcium and potassium are such that a potential difference is built up at a characteristic rate. When this potential difference has reached a certain level changes are thereby produced in the cell membrane which allow a transfer of electricity and stimulation. Once so initiated the excitatory process is propagated over the heart as described above, the action current from each excited point stimulating adjacent areas. It is this wave of negative potential difference which is registered as the electrocardiogram. A most important corollary to such a conception is this: No fiber of cardiac tissue can conduct the excitatory process unless it is itself excited.

Abnormalities of rhythm may thus be due to either or both of two derangements in this scheme: (1) To a change in the development of the excitatory process, (2) to a variation in the mechanism of its conduction, or (3) to a combination of these conditions.

First to consider derangements of impulse formation. Lewis[12] has pointed out quantitative differences in function of the four types of cardiac tissue, nodal, auricular and ventricular muscle, and Purkinje fibers corresponding to differences in structure. These tissues may be regarded as differing in the properties of their limiting membranes and hence in the rate of development of potential difference and in the level at which discharge takes place. Each type of tissue possesses an inherent rhythm. Normally, as Gaskell conceived, the rhythm of the sino-auricular node is most rapid and hence governs the rhythm of the heart. It has been shown that if the sino-auricular rhythm is eliminated some lower rhythmic center takes over control. In terms of our theory the condition of the cell membrane is such in the node that a potential difference is there built up more rapidly, or that discharge takes place at a lower level. Conversely, the same takes place at a relatively much higher level in the ventricular muscle and the inherent rhythm of the ventricle is much slower.

Alteration in the process of impulse formation may be produced either by alteration in the permeability of the interposed cell membrane through a change in the relative concentration of sodium, calcium or potassium, or by a change in the potential difference across the membrane. Our studies have recently been confined to alterations in the hydrogen ion concentration.

It is apparent that as the hydrogen ion concentration of the perfusate is increased the amount of the diffusible ion in the more dilute phase is raised. In other words, the potential difference across the cell membrane is diminished. Theoretically, such a reduced potential difference requires longer to effect stimulation. A priori, therefore, an increase in the hydrogen ion concentration of the fluid bathing the cardic tissue should slow the rhythm of the islolated

[9] Nernst, *Ztschr. f. Elektrochem.*, 1904, p. 665.

[10] Lucas, K., *Journ. Physiol.*, 1908, *37*, 459.

[11] Lapicque, *Compt. rend. d. l. Soc. d. Biol.*, 1907, *63*, 37.

[12] Lewis, *Quart. Journ. Med.*, 1921, *14*, 339.

heart; and it does so consistently. Conversely, an increase in alkalinity, by increasing the potential difference across the cell membrane, should cause a more rapid rate. All our records show that this is also the case.

With the heart in situ the vagus and accelerator nerves may be considered as operating upon the permeability of the cell membrane. The vagus, by decreasing permeability, slows the rate while the accelerator increases the rate of discharge by increasing the permeability. In this connection the work of Howell[13] showing the allied effects of the vagus and potassium is significant.

In experiments with the perfused heart it is possible to control only the hydrogen ion concentration in the fluid bathing the tissue of the heart as a whole. In pathological conditions, however, many other possibilities arise as regard an increase in the hydrogen ion concentration within the cell. The heart is a unique organ in that it is dependent upon itself for its own circulation. The conception is not a new one that with cardiac failure the myocardium suffers for want of a sufficient circulation. Under such circumstances, or even in the absence of clinical evidence of failure of the systemic circulation, local areas of deficiency in the intrinsic myocardial blood supply may conceivably arise. Such local failure of circulation must result in insufficient oxygen supply for the proper oxidation of the lactic acid formed in that area, in short, in a local increase in the hydrogen ion concentration within the tissue. The conditions are thus fulfilled for the development and discharge of a potential difference locally, for the genesis of a so-called ectopic focus of rhythm. The duration and rate of the development of the excitatory process in this focus are determined by the degree of local oxygen deficiency and by the condition of the cardiac tissue as a whole. A minor disturbance may give rise to arrhythmic or rhythmic extrasystoles which may or may not interrupt the dominant rhythm. A more severe change may produce a paroxysm of rapid excitations which may for a time command the rhythm of the whole heart, as illustrated by the onset of ventricular tachycardia following ligation of a coronary artery.

Secondly, arrhythmias may be due to variations in the process of the propagation of the excitation wave. As we have pointed out, according to the "membrane" theory, the rate of propagation of the excitatory process is determined by the area over which the local action current is effective in producing stimulation. Furthermore, this distance is dependent upon the magnitude of the potential difference and the permeability of the membrane. An increase in the hydrogen ion concentration without the cell results in a diminution in the potential difference across the cell membrane and hence a reduction in the intensity of the action current. Such a condition must reduce in extent the area over which the action current from any excited point can produce stimulation. Thus, such a change in the perfusate should slow the rate of propagation of the excitatory process.

Experimental evidence is entirely in harmony with this conception. The prolongation of conduction time in hearts perfused with acid perfusates has been noted by many observers. We have many records to show this. Heart block has been produced in animals by asphyxia and with narcotics. Clinically it is not unusual, in cases of heart failure, to meet with evidence of delayed conduction which disappears with the return of more normal circulation or upon the administration of oxygen.

Finally, more complex abnormalities of rhythm may involve changes both in the development of the excitatory process and in its propagation. If we suppose a local circulatory change giving rise to an ectopic focus of impulse formation, and, in addition, diffuse or local changes in conduction we have those conditions which, through the work of Mines[14] and of Garrey,[15] have been shown to be at the basis of the circus movement involved in flutter and fibrillation.

To summarize briefly: We have outlined a conception of the genesis of the cardiac rhythm as based upon the rhythmic development and discharge of potential difference across a semi-permeable cell membrane. We have described this potential difference as due to the difference in the hydrogen ion concentration within and without the cell, and its discharge as regulated by sodium, calcium and potassium through their effect upon the cell membrane. We have pointed out that local areas of circulatory deficiency in the myocardium may give rise to ectopic foci of impulse formation, and that diffuse changes in conduction may result from an increase in the hydrogen ion concentration of the perfusate. That gaps exist in the chain of evidence we are well aware. We hope, however, that we may have shown it possible to consider the cardiac arrhythmias as no more mystical than the normal rhythm and to offer an explanation common to both.

This communication is in the nature of a preliminary note. A complete account of our work will appear in an early publication elsewhere.

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[13] Howell, *Am. J. Physiol.*, 1905–6, *15*, 280.

[14] Mines, *Journ. Physiol.*, 1913, *46*, 349.

[15] Garrey, *Am. J. Physiol.*, 1914, *33*, 397.