

insuficiente irrigación del miocardio que se manifestó por los cambios electrocardiográficos anotados.

R. Linión Lasón.

KOLETSKY, S. *Gross vascularity of the mitral valve as a stigma of rheumatic heart disease.* (Vascularización macroscópica de la válvula mitral como estigma de reumatismo cardíaco). *Am. Journ. Pathol.*, 22: 351, 1946.

En 150 corazones con vascularización macroscópica completa de la válvula mitral anterior y en 50 testigos se estudiaron con técnica histológica cuidadosa: las cuatro válvulas, el músculo papilar posterior del ventrículo izquierdo y la pared posterior de la aurícula derecha, en busca de signos de reumatismo.

En todos los casos se encontraron nódulos de Aschoff, exudados celulares, engrosamientos del endocardio, placas subendoteliales o vascularización de las válvulas en uno o varios sitios, proporcionalmente al grado de alteración de la válvula mitral. Las lesiones eran mayores y más extensas en el grupo con estenosis mitral clara, menores en el grupo de lesión mitral sin deformación, más discretas y localizadas en el grupo de válvulas vascularizadas sin alteración aparente.

Los vasos neoformados son en su mayoría pequeñas arterias, situadas bajo el endotelio del lado auricular. Proviene de preferencia de la comisura posterior en número de una o dos ramas delicadas, abarcan toda la válvula y se ramifican profusamente hacia el borde libre. Se aprecian con facilidad a la simple inspección o a la luz transparente, sobre todo al encontrarse congestionadas. Microscópicamente tienen pared gruesa musculoesférica, el diámetro de la mayoría varía entre 150 y 250 micras. Su luz es estrecha, a veces excéntrica. La lámina elástica interna está mal definida y puede faltar. El endotelio se adosa directamente a la capa muscular. Las fibras musculares tienen casi todas dirección longitudinal y la capa circular es rudimentaria, cuando existe. El citoplasma de estas fibras es muy claro o vacuolado. No hay capa adventicia bien definida.

Esta clase de vasos se diferencia con claridad de los capilares que pueden haber en el tercio basal de algunas válvulas normales y de las descritas en las valvulitis no reumáticas. Se forman probablemente durante el ataque agudo de reumatismo, ya sea a partir de elementos mesenquimatosos que se transforman en parte en fibras musculares, ya por la concurrencia de los haces de fibras musculares lisas que se encuentran normalmente en la base de algunas válvulas.

Los autores concluyen que, en los corazones estudiados, la diferencia entre aquellos que presentaban alteraciones macroscópicas y los que carecían de tales alteraciones era puramente cuantitativa. Green, por lo tanto, que la vascularización de la válvula mitral es un estigma de reumatismo cardíaco de gran valor, sobre todo si se hace a expensas de arteriolas musculoesféricas semejantes a las observadas por ellos.

F. von Lichtenberg.

## THE MATHEMATICAL FORMULATION OF THE PROBLEM OF CONDUCTION OF IMPULSES IN A NETWORK OF CONNECTED EXCITABLE ELEMENTS, SPECIFICALLY IN CARDIAC MUSCLE

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This study was made during Dr. Wiener's stay in Mexico as a guest of the Instituto Nacional de Cardiología.

### I

#### INTRODUCTION

Nervous elements and cardiac and other striated muscle fibers are excitable — that is, they respond characteristically to an appropriate stimulus. This response is conducted from the stimulated points to the rest of the fibers. In somatic striated muscle the individual fibers do not interconnect. In cardiac muscle, on the other hand, the structure is syncytial — i.e., the fibers interconnect abundantly so that the muscle may be considered, from the standpoint of function, as a single sponge-like structure; in other words, stimulation of any part of the muscle may spread to all of it.

Conduction in nervous tissue resembles that in somatic striated muscle in cardiac muscle. The laws which apply to the muscle fibers are also applicable to the nerve fibers. In both instances the propagation is active, with energy supplied locally. In both cases an impulse travels with a nearly uniform velocity. In both cases the excitation and transmission are all-or-none and do not allow for impulses of

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varying degrees of strength. In both cases activity is followed by an inexcitable period of definite duration, the absolutely refractory period; and this stage is followed in turn by a relatively refractory period, during which the tissues have subnormal excitability.

In nervous structures, however, conduction is more complicated than in cardiac muscle. Although impulses spread uniformly along axons, there is no anatomical or physiological continuity from neuron to neuron. The regions of connection between one neuron and another are called synapses. When an impulse reaches a synapse it does not necessarily stimulate the following neuron. Transsynaptic stimulation of a neuron requires usually either a repetition of impulses in time at the same synapses (temporal summation) or the simultaneous arrival of impulses at a sufficient number of adjacent synapses to make the "density" of excitation high enough at some region of the neuron.

When synaptic excitation takes place, the passage of the impulse across the synapse consumes time. This time is called the synaptic delay. The arrival of impulses at synapses may have other effects than the stimulation, subliminal or liminal, of the postsynaptic element. It may have the opposite effect, i.e., it may render the element less excitable to other stimuli. This decrease of excitability is called inhibition.

In spite of the greater complexity of conduction in the nervous tissue, compared with the cardiac muscle, one may select out of the responses mediated by the nervous system some which bear a close formal analogy to those of the heart. Thus, a stimulus applied to a centripetal nerve may cause a progressive wave of excitation of many elements connected synaptically. This response is formally analogous to a beat of the heart. Similarly, stimulation at any point on the surface of the cerebral cortex will usually elicit a wave which spreads in all directions for some distance, the counterpart of a beat. This wave usually degenerates within a short distance of the stimulated point; but under certain experimental conditions, say during the clonic stage of a widespread tonic-clonic response (experimental epileptic seizure) it is usual to find many cortical elements coupled physiologically so that stimulation of one of them activates the rest in a relatively orderly fashion.

Let us return to the heart. Besides its physiological beat, it can exhibit two other quite different types of contraction. If a turtle's ventricle is overdistended or stimulated with rapidly repeated electrical shocks, a continuous cyclical wave appears, running along a definite closed path. In this condition, unlike physiological beating, the whole muscle is never at rest (in diastole). Similar activity has been observed in human auricles. The conditions which initiate this activity are not known. The phenomenon is called flutter.

A type of nervous conduction quite like cardiac flutter is well known in the umbrella disc of the coelenterates. Appropriate stimuli to the quasi-circular nerve net of a medusa or of an anemone will start a circulating wave which may keep going around for many hours. Although neither the anatomical structure nor the physiological organization of this network is adequately known, the analogy to flutter in cardiac muscle is striking.

In the central nervous system of the mammal, circulating impulses of this same type have often been invoked to explain prolonged nervous discharges. Closed chains of neurons have been demonstrated anatomically. The assumption is made that these chains may reverberate and thus provide a mode of conduction like flutter.

The third type of cardiac contraction and conduction is known as fibrillation. Rapidly repeated stimulation of the mammalian ventricle will again set up circulating waves, as in flutter. These waves, however, do not seem to progress in an orderly fashion but rather to follow random paths. Several waves may progress simultaneously. The ventricle looks like a quivering mass of worms.

In the mammalian cerebral cortex, the tonic and phasic stages of the tonic-clonic response have many features reminiscent of fibrillation. In monkeys under chloralose anesthesia it is possible to start a long lasting activity which resembles the human "status epilepticus" (Rosenblueth and Cannon, 1942). During this state there is a slowly spreading activity along an apparently random path without any well defined periodicity.

The diversity of the few nervous responses mentioned is associated with the complex histological organization of the higher nervous systems. There are special long connections or pathways between remote regions, but the cerebral cortex has also what may be spoken of as the "nerve felt" — neurons with short processes

which connect with neighbouring elements in an apparently random fashion.

The following analysis will deal with the problem of conduction in cardiac muscle. It is obvious, however, from the above account, that the methods we use can be applied directly to the central nervous system.

## II

### THE DYNAMICS OF STIMULATION AND PROPAGATION

In order to treat the physiological problem mathematically we shall adopt certain postulates, simplified for mathematical convenience. These postulates are as follows.

1) The cardiac impulses, once started, spread with a constant velocity equal in all directions as far as the network continues. This assumption implies that cardiac muscle is homogeneous, that is, that the fibers which compose it have similar properties throughout the tissue. Heterogenous muscle will only be considered for special purposes.

This postulate simplifies the cardiac structure in two ways. First, it dismisses the heterogeneity which exists between the three main conducting tissues that constitute the heart: auricular muscle, Purkinje tissue, and ventricular muscle. The distinction between auricle and ventricle is not important, since, as is well known, flutter and fibrillation remain localized to either auricle or ventricle, but do not flow from one into the other. In other words, by *cardiac muscle* is meant here either auricular or ventricular tissue, but not both together. The role of the Purkinje tissue in ventricular flutter or fibrillation in those hearts where it exists is not known.

Second, the definition of homogeneity adopted here implies isotropy, although the fibrillar structure of cardiac muscle, with some orientation of fiber bundles in certain regions, makes absolute isotropy unlikely.

2) The amplitude of the process, whereby the activity of one region spreads by stimulating adjacent regions of a fiber, remains constant and exceeds the threshold of the adjacent regions when these regions are in the "resting condition" (to be defined later).

3) There are three conditions in which any given region of a fiber can exist. *a)* The active state. We shall suppose that this state occurs only at the instantaneous wave front. *b)* The refractory state, to which we assign a constant duration — probably an unimportant simplification. During this state the region of the fiber will neither receive nor transmit impulses. Although the regions in this state may not receive impulses from other regions, toward the end of the period they can be stimulated by a sufficiently strong electric pulse; in other words, the refractory period considered is that which is functional from the standpoint of conduction. *c)* The resting state, which follows immediately the termination of refractoriness and lasts until the next excitation. In this state the fiber is fully accessible to stimulation.

To these three states we assign "epoch numbers" as follows: to the instant of activity, the epoch number 0; to any instant during the refractory period, an epoch number between 0 and 1, representing the elapsed fraction of that period; to the resting state, an epoch number 1. The laws that govern the flow of epoch numbers are the following. *a)* Any number less than 1 grows at a constant rate equal to the reciprocal of the refractory time. *b)* Any epoch number 1 remains unchanged until the passing of a wave front. *c)* At any point where an epoch number 1 is in contact with a 0 there is a wave front moving toward the region with number 1 with a constant velocity  $v$ , which is the velocity of propagation. These laws of conduction will be applied in all the cases to be considered.

As a corollary of these postulates, behind every wave front moving freely there will be a band of fixed width within which the recovery process is taking place. This may be spoken of as a "wave length", even though this is not the standard definition of the term. The wave length is obtained by multiplying the conduction velocity by the duration of the functional refractory period.

These laws of propagation will cover all the cases that can arise; the simplifying assumptions made are minimal. The laws may be expressed symbolically as follows:

Let  $n$  be the epoch number as a function of the points of space  $x, y, z$  (or fewer dimensions, as the case may be) and time  $t$ . Then

$$(1) \quad du = k_1 dt \quad \text{when } 0 \leq u < 1$$

Finally, if the second stimulus follows the first within an interval  $l/v$ , the two impulses will meet somewhere in the interior of the fiber, but cannot cross each other because the two refractory waves will meet, that is, because there will be no epoch 0 in contact with a 1. The same argument applies to trains of impulses.

Similar reasoning shows that, with the assumptions made, there can not be any returning wave at the end of a fiber — i.e., no echo, since the back of a wave has no 0 epoch in contact with a 1.

These remarks are made for two reasons. First, there is no indefinitely self-sustained activity in an open unidimensional circuit under the assumptions adopted, which prohibit spontaneous firing, since the epoch 1 remains an epoch 1 indefinitely unless an epoch 0 approaches it. Second, the activity of a fiber without internal stimulation can be prescribed by considering only the epochs at the ends. This apparently trivial inference will be important in the discussion of the behaviour of fiber-nets.

Next consider a one-dimensional closed path. A narrow ring of auricular tissue is an example, as is the perioral, discal part of the nervous system of a coelenterate, e.g., medusa or sea anemone.

If a single stimulus is applied to any point of the path, the situation is essentially the same as that which would ensue were the two ends of an open circuit to be stimulated simultaneously: impulses will start in opposite directions, meet at the antipodes, and cancel.

In order to have self-perpetuating, steady-state waves moving around the closed path in one direction — that is, in order to have flutter — the distribution of epochs must be as follows. There will be one or more points at which an epoch number 1 abuts against an epoch 0, always in the same sense of rotation. On the other side of 0 the epoch is represented by a straight line rising to the value 1 at a distance from the 0 point equal to the wave length. This pattern is followed by an arbitrary length over which the epoch is equal to 1 and it may be repeated several times. Figure 1 illustrates this condition. It follows that the number of traveling impulses which can exist in a pathway of length  $l$  is  $[l/w]$  where  $w$  is the wave length and  $[x]$  is the largest integer not exceeding  $x$ .

The preceding statements demonstrate the possibility of self-perpetuation, but do not answer the question how such one-way waves

where  $k$  is the reciprocal of the refractory period.

$$(2) \quad du = 0 \quad \text{when } u = 1$$

except that when at a certain point  $(x_0, y_0, z_0)$   $u=0$ , and at a neighbouring point  $(x_1, y_1, z_1)$  placed within a sphere with center at  $x_0, y_0, z_0$  and with radius  $vdt$  (where  $v$  is the conduction velocity)  $u$  is at the same time  $= 1$ , then over the whole segment between these two points.

We have thus defined an infinitesimal transformation changing  $u$  into  $u + du$ .

$$(3) \quad du = -1$$

### III

#### CONDUCTION IN A ONE-DIMENSIONAL SYSTEM

By this expression is meant conduction in a structure in which two of the dimensions are negligible because they are much smaller than the wave length.

First consider an "open circuit", such as a single fiber with two free ends; and, in the first instance, impulses originating at the ends of the fiber. As a consequence of the laws formulated, any number of impulses started at one end will proceed with a constant separation and will arrive at the other end without interference at the same intervals as those at which they were set up. This inference illustrates one of the simplifications in the assumptions, for experiments have shown that in nerve fibers two impulses started very close together will not remain at the same distance, since conduction is slowed during the relatively refractory state.

If impulses are sent from the two ends in opposite directions, they will not interfere with each other if the second is started after a time  $l/v + A$ , where  $l$  is the length of the path, and  $A$  is the functional refractory period. If the second stimulus is applied at a time between  $l/v$  and  $l/v + A$  after the first, it will not set up an impulse because the fiber will be refractory at the stimulated region.



$$(5) t < \frac{1+2w}{2v}$$

The previous analysis shows that one-way waves can be started only where there is an asymmetry of the two sides of the region to which the second stimulus is applied. This asymmetry was obtained here by a displacement of the stimulated regions; but it is clear that the displacement can be very small if the temporal interval is suitable — i.e., in the neighbourhood of the functional refractory period. It is known that flutter may be initiated by two shocks applied to electrodes which have not been displaced. Since the tissues which have been thus studied are not mathematically homogeneous it is quite likely that the refractory periods are not the same for all the elements on both sides of the stimulated region. Under the circumstances, it is easy to see how stimuli applied in the conditions mentioned may start flutter.

#### IV

##### CONDUCTION IN A HOMOGENEOUS, ISOTROPIC, TWO-DIMENSIONAL SYSTEM

In such a system the phenomena of conduction are identical at all points and in all directions from each point. The case approximates some of the large scale phenomena, while it does not cover phenomena whose physical dimensions are not large compared to the reticulations of the tissue concerned. The propagation of a beat and the development of flutter in a segment of auricular muscle does fall under this head. It is reasonable to suppose that impulses propagate from any stimulated point with equal velocities in all directions. But in the case of fibrillation, we can not ignore the heterogeneity of the muscle, if fibrillation is a random, small scale, series of wavelets. Under these conditions the specific connections between neighbouring fibers become more important than the way in which the tissue made out of these fibers approximates to a homogeneous structure. A statistical treatment of fibrillation in two-dimensional and three-dimensional systems is presented in a later section.

To clarify the differences between flutter and fibrillation consider an analogous situation which arises in a classical problem of waves and vibrations. A telegraph or telephone line may be described by the distribution of certain constants: resistance, capacitance, inductance and leakage to ground. These may be distributed continuously, or else lumped discretely. It is a common procedure to lump inductances in order to produce an approximate Heaviside's distortionless line. Now, the lumped line behaves like a homogeneous one for large enough wave lengths. When the wave lengths are of the order of magnitude of the distance between lumpings, however, the line will not transmit the messages. It was on this basis that the wave-filter was invented. For large wave-lengths such a line may be treated as homogeneous, but that treatment fails for phenomena of small spatial scale.

The law of the propagation of impulses in a homogeneous two-dimensional system is Huyghens' principle in its simplest form: the successive wave fronts are perpendicular to a system of rays which represent the position which may be assumed by stretched cords starting from the stimulated point and passing around all obstacles. The back of the refractory wave is another curve of the same form, which follows the wave front at a distance  $w$  measured along these rays. As before, a wave front can only propagate into a region in the resting state.

It is stated that the rays are equivalent to the stretched cords; and that, since the velocity of propagation is constant, all the points of the wave front at a given time are at a constant distance along the corresponding stretched cord from the source of the impulse. In an infinite sheet with no holes or obstacles, the wave front from single point stimulation will be a circle about that point, and will recede to infinity. In a finite convex region, single point stimulation will again give an expanding circular wave front which disappears without reflection wherever it reaches the boundary.

Two factors will deflect the stretched cords and hence alter the circular pattern of the wave front: obstacles — i.e., holes in the sheet — and certain concavities of the boundary.

Consider first a single convex obstacle within a convex region. Figure 3 illustrates successive wave fronts after stimulation of the point A. The convex outer boundary of the region is not shown

since it merely cuts off the wave fronts wherever they touch it. The two lines  $AT_1$  and  $AT_2$  are the two tangents from A to the obstacle. In the region containing A and bounded by the dotted line, the wave fronts are circles or segments of a circle. Outside that region the curves are formed as follows. From any point P let the tangent be drawn to the obstacle; then the length  $AT_2 + T_2P$

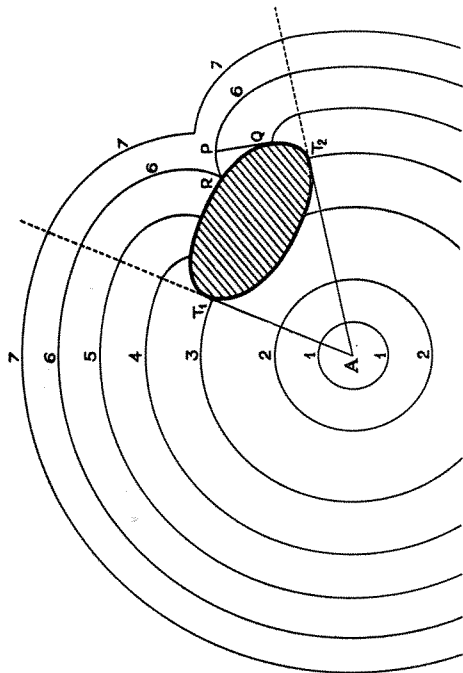


Figure 3.—The influence of a convex obstacle (e. g., a hole) on the propagation of impulses in a homogeneous two-dimensional conducting system. The obstacle is represented by the hatched area. A single stimulus was applied at A. The lines represent successive wave fronts. For further explanation see text.

$Q + QP$  is constant and equal to the radius  $AT_3$  of the circular segment which comprises part of the same wave front; in other words, the locus of P is the involute of the obstacle. There are two sets of segments of involutes, one about  $T_1$  the other about  $T_2$ . There is only one point R where the stretched string distance from A by way of  $T_1$  and of  $T_2$  are the same — i.e., the distance along the radius  $AT_1$  and from  $T_1$  to R on the curved edge of the obstacle, and the corresponding distance by way of  $T_2$ . If these distances are less than that corresponding to R, then the wave front intersects the obstacle at two points. If these distances are larger, the two involute segments of the wave front intersect with a progressively larger

angle as the distances increase. The portions of the involutes inside the intersection do not form wave-fronts because that would only happen if they should advance in refractory territory.

Some cases arising when either the boundary or the obstacle has a concavity are illustrated in the diagram in figure 4. On the left side of the diagram are indicated the deformations corresponding to a concavity in the obstacle, while to the right are shown those

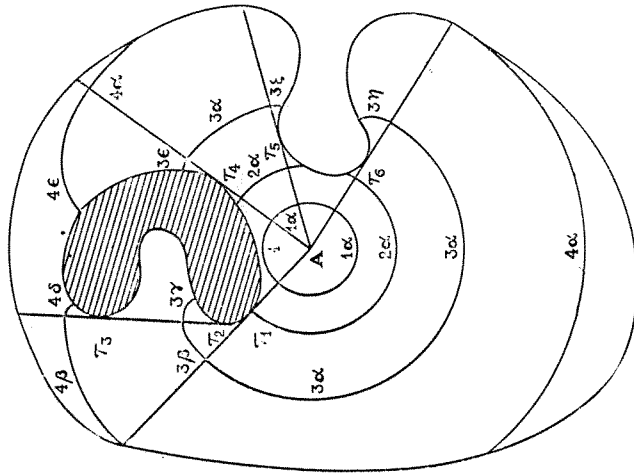


Figure 4.—The influence of concavities in an obstacle and in the boundary on the propagation of impulses in a two-dimensional system. The conventions for this diagram are the same as those in figure 3.

corresponding to a concavity in the boundary. The numbers 1, 2, etc. correspond to different instantaneous wave fronts after stimulation of the point A. The letter  $\alpha$  indicates the part of the wave-fronts

which are segments of circles about  $A$ ;  $\beta$  marks the involutes of the arc  $T_1 T_2$ ;  $\gamma$ , those of the part of the boundary of the obstacle beyond  $T_2$  up to the point of inflection in the concavity;  $\delta$  those of the convex part beyond  $T_3$ ; etc.

V

FLUTTER IN A TWO-DIMENSIONAL SYSTEM

First the external boundary will be neglected and a single convex obstacle will be considered. The only periodic solutions for self-sustained waves are those in which the wave-fronts, and hence the wave backs, are involutes of the obstacle. Since the wave-back must not interfere with the front for propagation—in other words, since there must be a gap of recovered tissue between the two limits of the wave—the perimeter of the obstacle must exceed a wave-length. This statement implies, first, that there is no self-sustained propagation in a simply connected sheet; and, second, that the obstacle which destroys the simple connectivity, if convex, must exceed a minimum perimeter equal to the wave length.

If the obstacle has concavities the previous statement need not be modified except to replace the perimeter by the effective perimeter, defined as that of a string stretched around the obstacle. In other words, the concavities are replaced by tangents. Between the tangents and the concavities there will be complex wave fronts, but the influence of the obstacle on the persistence of flutter is not modified.

If there is only one wave front at any time—in other words, if there is only one flutter wave,—the perimeter of the obstacle is the pacemaker. An involute will always move parallel to itself in a homogeneous and isotropic conducting sheet. Hence, if it is possible to stimulate along an involute, it will always be possible to start flutter in a sheet with a single obstacle of the appropriate perimeter, regardless of the extent of the sheet.

Now we examine the problem of initiating flutter by stimulation of small regions in rings of this type—i.e., two-dimensional rings. First, consider an infinite sheet without obstacles, stimulated successively by two shocks at a suitable interval, applied to two neighboring

regions. The diagrams in figure 5 show the subsequent events. In A the region R was stimulated; the wave front is marked by the arrows, and the whole hatched circle is refractory. B represents the situation when the back of the original wave coincides roughly with the region originally stimulated. A second stimulus is now applied to the region  $R_2$  slightly to one side, but overlapping  $R_1$ . The response to this stimulus can not progress to the right, where the tissue is refractory, but can progress to the left. A wave front appears in the form of a segment of a circle and expands, always cutting the back of the initial wave in points along a fixed vertical line, namely the perpendicular bisector of the line connecting the centers of the two regions stimulated,  $R_1$  and  $R_2$ .

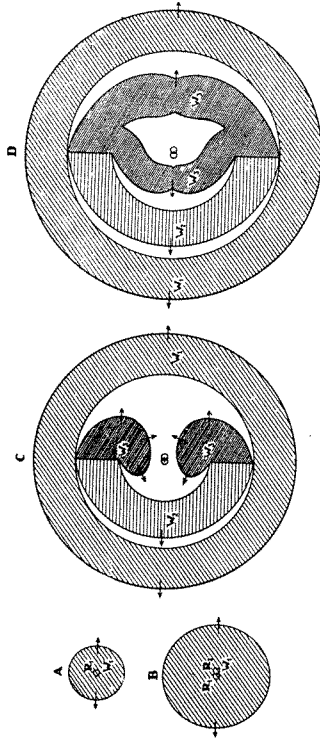


Figure 5.—The initiation of a one-way wave by successive stimulation of two overlapping small regions of a two-dimensional system. For explanation see the text.

In addition to this new wave front (as shown in C, which depicts a later stage) the activity at the points of intersection of these two circles must spill into the regions to the right and center, where the tissue is already fully recovered. Two arcs of active front will thus be formed, which will expand in all directions except at the boundary with the rear of the second crescent wave (boundary between the regions  $W_2$  and  $W_3$  in the diagram). These new wave-fronts remain initially separated until  $R_2$  recovers. Then, as shown in D, the two arcs join. Three wave-fronts are now traveling to the left and only two to the right. A new resting region has developed in the center, but this is not in contact with any epoch number 0.



Now let us consider an obstacle in the sheet with a sufficiently great effective perimeter. The simplest case is a circle with its center on the perpendicular bisector to the line of the centers of  $R_1$  and  $R_2$ . In figure 6A are shown merely the wave fronts corresponding to figure 5D some time after the impulses have reached the obstacle. Figure 6B represents a still later stage. It is clear in figure 6B that the waves meeting from opposite directions in the shadow of the obstacle will cancel by pairs. Since the number of waves is odd, however, there is a fifth front traveling clock-wise around the obstacle, it does not meet an antagonistic wave and will therefore persist.

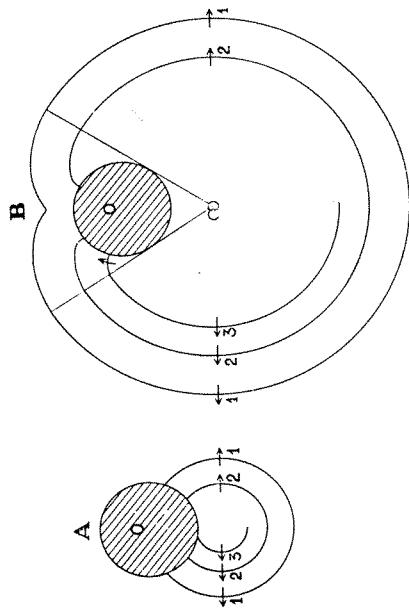


Figure 6.—The influence of an obstacle on waves such as those of figure 5.

The two outside enveloping waves of figure 6B recede to infinity; or, if the sheet is finite, vanish at the boundary. The unpaired wave will always have an edge touching the obstacle; in the finite case it will ultimately have another edge touching the boundary of the sheet; after a sufficient interval of time it will take the shape of one of the family of involutes corresponding to the pattern of the obstacle. Hence, flutter will always follow appropriate repeated stimulation of an arbitrarily small region in a sheet with an obstacle of sufficiently large effective perimeter, independently of the extent

of the sheet. Here an appropriate repeated stimulation must be such that the direction of the line joining the centers of  $R_1$  and  $R_2$  is so oriented that the fifth wave front hits the obstacle end on, and not tangentially, when they meet. In the latter case two waves would be started traveling in opposite directions around the obstacle. They would meet somewhere on the other side, cancel there, and leave as a residue a wave traveling away from the obstacle.

VI

FLUTTER IN A TWO-DIMENSIONAL SYSTEM WITH TWO OBSTACLES

1. Two equal circular obstacles with circumference greater than a wave length. a) Stimulation applied within a small region with center in line with the centers of the obstacles and generating a fifth

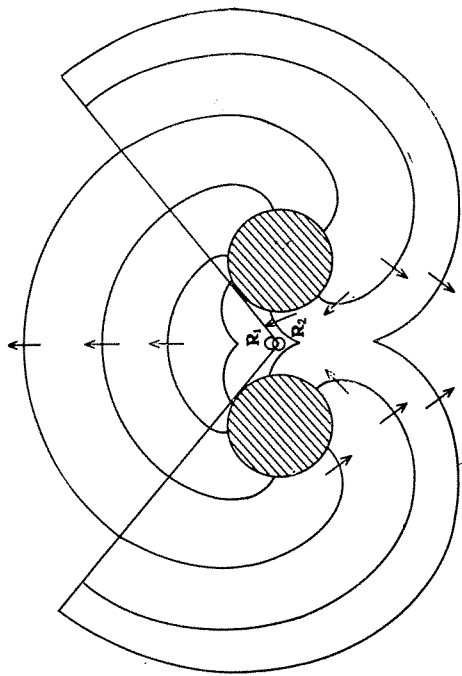


Figure 7.—Symmetric stimulation (at  $R_1$  and then  $R_2$ ) of a two-dimensional system with two equal circular obstacles with circumferences longer than a wave-length. The arrows indicate successive wave-fronts.

wave (see above,) symmetrical with respect to the obstacles. Figure 7 illustrates this case. It is clear that the original fifth wave travel-

ing upward continues to span the two obstacles in a symmetrical manner. In the course of time the lobe that has gone around the first obstacle will meet the lobe that has gone around the second one at some point on the perpendicular bisector of the line of centers. Then the wave fronts break up into two others, one downward and surrounding the obstacles, which recedes from them, and one upward which again spans the distance between them and repeats the cycle. Thus we get flutter.

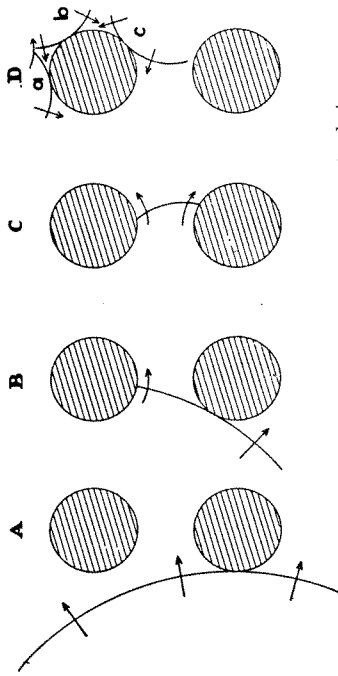


Figure 8.—As in figure 7, but asymmetric stimulation.

b) *Asymmetric stimulation.* Figure 8 illustrates several cases. In all the diagrams only the front of the effective fifth wave is shown as it meets the obstacles. In A there will be two waves in opposite directions around each obstacle. They will cancel for each obstacle and the activity will lose its contact with the obstacles and recede. No flutter will ensue.

In B, the wave around the lower obstacle will cancel and not recur, but that around the upper will return and establish a cycle. The steady state will in general not be symmetrical with respect to the two obstacles, but will recur regularly — i.e., flutter will take place. In C the situation is not significantly different from that in figure 7, but leads to skewed results as in case 8B.

In D are illustrated three more cases, a, b and c. The case a will not lead to flutter. The case c, will lead to flutter, for it is like case B, except that the wave front will only touch end — on the lower

obstacle later. Case b is indeterminate; for some orientations the wave front will meet the lower obstacle end on, and for some it will meet it tangentially, or clear it completely if the two obstacles are sufficiently far apart. If it meets it end-on there will be flutter, and not otherwise.

2. *Unequal circular obstacles, both longer than a wave length.* The only case to consider in detail is symmetrical stimulation between the two unequal obstacles. At first the situation is like that of figure 7. The recurring wave front will arrive sooner around the smaller obstacle than around the other one. After several of these waves have passed, the wave front around the larger obstacle may precede that from the smaller. Thus, there will be between the two obstacles a complex succession of waves, some of which will come around one, some around the other. The general result will be the appearance of beats; a harmonic analysis of flutter in this generalized sense is likely to show periods which are integral combinations of the periods of rotation around the two obstacles except that periodicity is replaced by quasiperiodicity the situation is not fundamentally different from what it was with equal obstacles.

We shall not consider in the present study the cases of asymmetric stimulation of these systems.

3. *Unequal circular obstacles with perimeters respectively greater and less than a wave-length.* This case need not be considered in detail. Whenever a wave will travel around the larger obstacle it will recur cyclically and the smaller obstacle has little or no influence on the length of the cycle, although it modifies the shape of the wave in its neighbourhood.

4. *Two obstacles both with perimeter smaller than a wave length.* In the case illustrated in the diagram in figure 9 the two obstacles are equal, with circular radius  $r$ . The perimeter of one obstacle plus twice the distance between the centers is of length  $w + \epsilon$ , where  $\epsilon$  should be less than  $\pi r$ . The dimensions of the obstacles are unimportant otherwise. The diagram A illustrates a steady state condition which will flutter. The solid left hand line with the arrow represents part of the wave-front and its direction of progression; the dotted right hand line represents the corresponding position of the wave-back. All the shaded region is refractory at the instant

represented in the diagram; the unshaded region between the two obstacles (R) may be partly or wholly refractory or not refractory at all. When the wave front reaches that region it either finds it

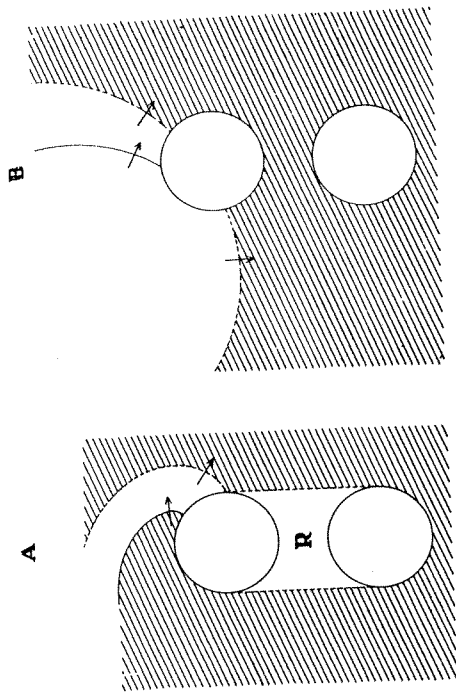


Figure 9.—Flutter in a two-dimensional system with two equal obstacles of perimeter smaller than a wave-length. For explanation see text.

refractory and keeps on toward the other object, or else it penetrates. But when it penetrates, it cannot go beyond R to the left because that part will still be refractory. The left boundary of R can only be reached around the lower obstacle. When the wave has reached this left boundary, the same conditions will then hold for the right part of the boundary of R. The wave will therefore repeat along a path surrounding the two obstacles. Every part of R will fire once in every cycle.

In order to start the proper wave it is sufficient to first set up a wave such as that whose receding back is shown in figure 9B by the dotted line, and then to start a one-way wave, e.g., a fifth wave, as indicated by the solid line with the arrow.

Essentially the same situation as that of figure 9A is more simply illustrated by the line diagram of figure 10. The solid lines represent transmitting fibers and the dotted arrow spans the region between

the wave-front and wave-back. The state of the conducting line *a b* has no effect on the rest of the system. It will be activated from one direction only, i.e., it will have the same frequency as the rest of the system.

VII

FLUTTER IN A TWO-DIMENSIONAL SYSTEM WITH MANY OBSTACLES

The cases where the obstacles have effective perimeters greater than a wave length do not present any difficulties from the standpoint of the initiation and maintenance of flutter. The line diagrams introduced in figure 10 are convenient for the study of several obstacles with perimeters less than a wave length.

Figure 11 represents a simple case. The conventions are similar to those in figure 10. It is clear that provided that the width of the gap between the wave rear and the wave front is less than the width of any of the obstacles in the figure, flutter can be started and maintained as in figure 10.

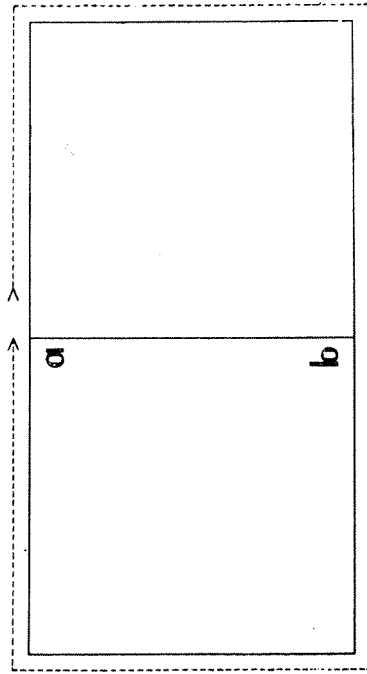


Figure 10.—Line diagram of the same case of figure 9.

That several independent flutter waves can occur in such a system is shown in figure 12A, which is self explanatory. More complex

VIII

TWO-DIMENSIONAL CASES OF HOMOGENEOUS AND ISOTROPIC TRANSMISSION ON SURFACES OTHER THAN A PLANE

These cases are important to consider because the auricle may be regarded as an example.

The fundamental differences between these cases and those in a plane, are as follows. 1) The shortest distance between two nearby points is no longer a straight line but a geodesic. 2) The simple convexity and the effective perimeter have to be replaced by geodesic convexity and geodesic effective perimeter. 3) The simple involute of the plane becomes a geodesic involute, or in other words, the curve obtained by the end of a string wrapped around an obstacle on the surface and unwound tightly while it always stays on the surface. 4) The surface may not be topologically equivalent to a segment of a plane. Thus, in the anchor ring there are closed geodesics. Hence, it is possible to obtain flutter waves in the absence of any extrinsic obstacles or any boundary. The conditions in which flutter would occur in an anchor-ring shaped

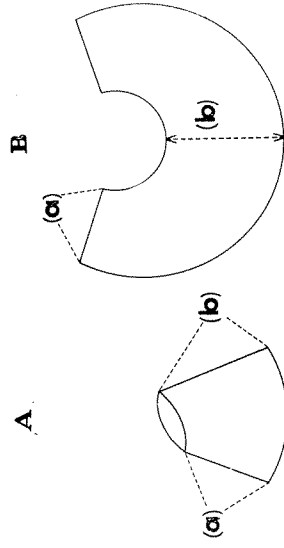


Figure 13.—Flutter in a conical frustum surface.

conducting tissue, if it existed, are easy to understand in view of the previous analysis.

The geometry of the auricles is much too complex for detailed

patterns and combinations are illustrated in figure 12 B and C. The essential feature in all these cases is the existence of a number of paths which are in length only slightly in excess of an integral

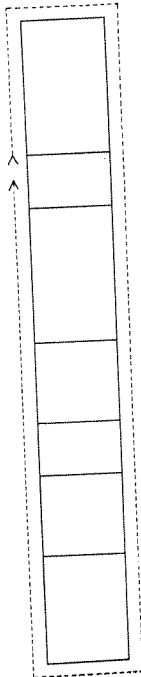


Figure 11.—Line diagram of flutter in a two-dimensional system with several small obstacles.

number of wave lengths, combined with the absence of short paths in the interior which are not substantially shorter in length than the paths between corresponding points by the boundary. Individual and not necessarily similar paths of this sort may be combined into structures of any degree of complexity, as long as where they impinge on one another the direction of traversing the boundary is concordant. It is important to note that the several waves in B and

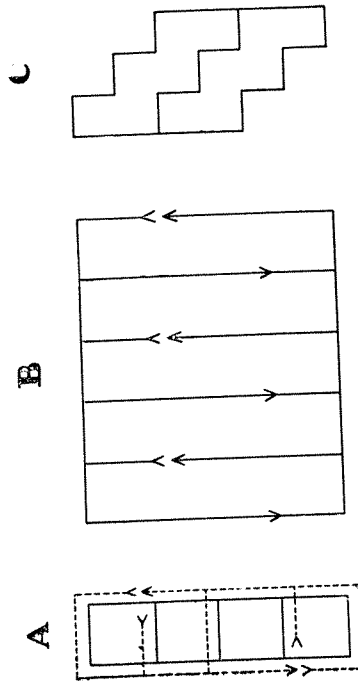


Figure 12.—Combinations of several flutter waves such as those of figure 10.

C must be in phase over the common part of their path, since the first to arrive there will occupy this path, that is, it will suppress the later arrival.

IX

SPECIFIC THREE-DIMENSIONAL CASES WITH HOMOGENEOUS CONDUCTION

A solid anchor ring can readily flutter if the lesser or inner equator is longer than a wave-length. The wave-front will be a complicated involute surface.

In general, for multiply-connected regions such as the anchor ring, with at least one hole with a minimum convex line of striction longer than a wave length, it is likely that flutter can be maintained.

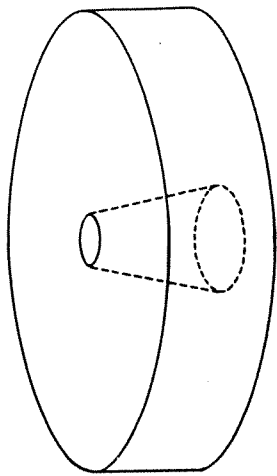


Figure 15.—A three-dimensional system where flutter may be initiated and maintained.

Figure 15 illustrates a solid of this type. The pace-maker for the flutter will be the line of striction — i.e., in this case, the upper aspect of the conical hole.

It is quite doubtful whether any simply connected homogeneous and isotropic solid region can exhibit flutter in the steady state. This case is particularly important, since a turtle ventricle may be represented in first approximation as a thimble-shaped simply connected solid such as that illustrated in a meridian section in figure 16. The situation is in many respects like that of the spherical surface with one hole (fig. 14 C). Reflected waves from the apical region are possible and they may invade the resting regions near the opening, thus canceling a flutter wave around that opening. A series of spiral waves around the opening may take place, but they might cease spontaneously.

analysis at present. The following remarks, however, show a way to approach the problem. Figure 13B illustrates the development of the conical frustum surface 13A on a plane. The involute indicated in B maps in A into a curve which represents the steady-state wave front of a flutter wave around the upper obstacle. Here again, for flutter to take place, it is necessary that the perimeter of the upper obstacle exceed a wave length. It is clear that for more complex combinations of obstacles in such a surface the general principles enunciated for the plane hold *mutatis mutandis*. In other words, there are no reasons to believe that the complexity of the structure of the auricle will significantly change the rules obtained in the cases in a plane.

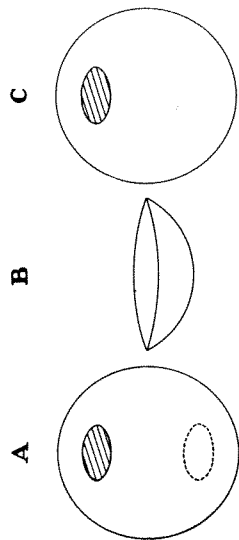


Figure 14.—Spherical surfaces with holes. See text for a discussion of the possibility of developing flutter in such surfaces.

The only other cases that need be considered in detail are those illustrated in figure 14. A, B and C are spherical surfaces with holes. In A there are two circular holes, diametrically opposite and of equal perimeter, greater than a wave length. In this case the geodesic involutes run spirally from hole to hole and are perpendicular to both holes: clearly flutter is possible. In B the hole removed more than a hemisphere; the situation is here essentially that of a plane convex disc without a hole and there can be no flutter. In C there is a single circular hole smaller than a hemisphere, with a perimeter greater than a wave length. We have not worked out this case in detail. One sees that an incipient flutter around the hole may be abolished by a returning wave from the antipodes.

A turtle ventricle, isolated from the atrium, will usually flutter for long periods if subjected to a relatively high internal hydrostatic pressure. This pressure probably acts as a continuing stimulus so that the situation does not correspond to the one we have considered

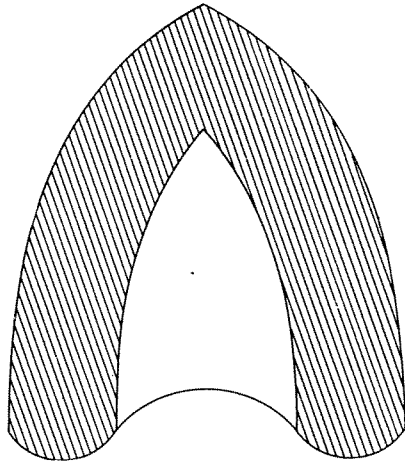


Figure 16.—Sagittal section of a three-dimensional thimble-shaped solid, grossly similar to a turtle's ventricle. See text for a discussion of the development of flutter in such a system.

above. It would be interesting to find out whether the flutter of those ventricles consists of a cyclical series of sequences of diverse waves in other words, a modulated series.

Two other important cases are those of fine "alveolar" and fine "trabecular" structures. By alveolar structure is meant one similar to that of a Gruyère cheese, where there are a large number of small holes or bubbles which do not connect with each other. In the trabecular structure, on the other hand, there is really a single highly multiplyconnected hole. A sponge is a good example of a trabecular structure.

Two simple cases of these structures are given respectively by regular cubic nets in space, in which the conducting elements will be in one case the faces of the cubes (alveolar), and in the other the edges (trabecular). As shown by the line diagram in figure 17, multiple flutter waves are possible in a trabecular structure. A

perspective view of a parallelepiped with 8 confluent holes is shown and the wave fronts and backs are indicated after the convention of figure 12. In addition, the direction of flow in lines common to several paths is indicated by arrowheads. It is obvious that this pattern can be repeated *ad libitum*. It is also obvious that complicat-

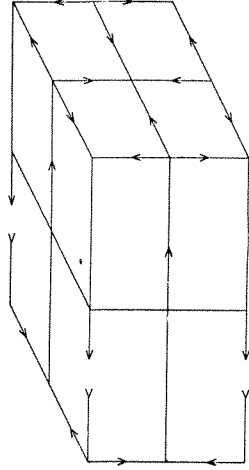


Figure 17.—Line diagram of a system of flutter-waves such as those of figure 12, but in a three-dimensional system. This network illustrates a trabecular structure.

ed paths, such as those in figure 12 C, could have been used instead of the simple pattern adopted.

The corresponding alveolar network will not flutter because it consists essentially of a series of intersecting planes without obstacles in which flutter is impossible.

X

THEOREMS CONCERNING FLUTTER IN HOMOGENEOUS ISOTROPIC NON-SPONTANEOUSLY ACTIVE CONDUCTION MEDIA

The following theorems are indicated by the previous analysis and are proved here.

1) *A single stimulus applied to a single point or region can never result in flutter.*

*Proof.* Consider a given time  $t$  after the application of the stimulus. The medium can then be divided into two parts with a boundary between them which is the wave-front; these are, respectively, the regions which have been traversed by a wave-front by

time  $t$ , and those which have not yet been reached by any front. All portions of the wave-front are advancing into the regions last mentioned. Between the wave-front and the originally stimulated region there is a continuous barrier of refractory tissue which represents earlier positions of the wave-front and which entirely separates all points active before time  $t$  from those beyond the wave-front. It is therefore impossible at any time for any part of the wave-front to retrace its steps. Whenever two segments of the wave-front meet, they meet head on; the colliding parts disappear and the remaining parts become confluent. Since the wave-front progresses as long as there is non-refractory tissue available it will always recede from the stimulated region, to infinity or the boundary of the tissue, as the case may be.

The above proof is valid for one-, two- or three-dimensional systems or combinations thereof, and is not affected by the presence of obstacles, whatever their size and shape.

2) *Simultaneous single stimulation of any number of points or regions can never result in flutter.*

*Proof.* The proof is similar to that of theorem 1. There will be several independent wave-fronts which cannot retrace their way. Whenever two of these meet, they will cancel or merge but each will be unable to penetrate territory passed over by the other one.

3) *For the production of flutter at least two stimuli are indispensable, separated by an appropriate time-interval. The second stimulus must be applied to a region overlapping a wave-rear. The two stimuli are therefore such that the time interval separating the two is equal to the functional refractory period plus the conduction time between the two stimulated regions.*

*Proof.* If the second stimulus is applied to a not yet activated region it generates a wave-front of its own and the situation will be equivalent to that considered in theorem 2. If the second stimulus is applied between wave-front and wave-back, the tissue will be refractory and nothing will happen. If it is applied entirely inside a recovered region, it will set up another wave front which can never catch up with the receding wave back which resulted from the first stimulus. If it is applied to a region overlapping the wave-front of the first stimulus it will merely modify the pattern of that

wave front by adding a segment which will merge with it. By exclusion, therefore, the only possible effective region of application of the second stimulus is as stated in the theorem. This itself determines the timing.

4) *At any time subsequent by at least the duration of the refractory period to the application of the last stimulus to any two-dimensional system, any wave-front existing is either an open or a closed path. If it is open then the free ends must lie either on geometrical boundaries or on wave-rears.*

*Proof.* The closed circuit case needs no comments, nor do the cases where a wave rests on one or two boundaries. There are only four possible types of boundary to a refractory region: a) the geometrical boundary of the system if it exists; b) wave-fronts; c) wave-rears; d) incompletely recovered boundaries. The last can not progress and will recover within one refractory period; there is no mechanism in propagation which will introduce new boundaries of this character. All wave fronts and wave rears are boundaries of a refractory region. Hence, at the end of a refractory period all the boundaries of type  $d$  will have disappeared and wave-fronts must about as stated in the theorem.

5) *After the last stimulus has been applied and one refractory period has elapsed there cannot be an increase in the number of wave-front to wave-back junctions in the system.*

*Proof.* No matter what the direction of approach, a wave-rear will recede from an advancing wave-front at the same rate at which the advance takes place.

6) *The number of wave-front to wave-back junctions in a system may decrease.*

*Proof.* There are at least two ways in which this decrease can happen: A) by impingement upon a geometrical boundary; B) by confluence. The two mechanisms are self-explanatory.

7) *In any simply connected region in which at any time greater than a refractory period after the end of stimulation there are no wave-front to wave-back junctions, flutter is impossible; that is, activity will die out.*

*Proof.* The wave-front must then be either closed or open, and the open fronts lie on the boundary at both ends. As shown in the

diagram in figure 18, all the regions between wave-fronts may be numbered beginning arbitrarily with 0 at any one of them and increasing the number by one when a wave-front is crossed in the sense of progress of the wave, and decreasing by one when fronts

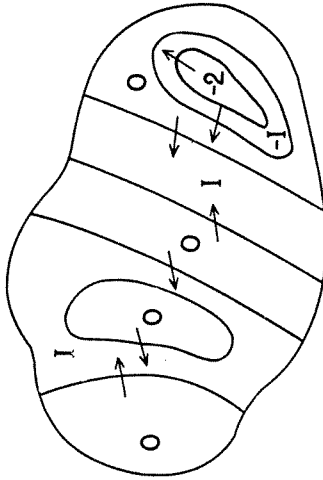


Figure 18.—Diagram to illustrate the proof of theorem number 7.

are crossed in the opposite direction. The simple connectivity of the regions makes this numbering unique. Now consider only the region or regions of lowest number. These can never be penetrated by any front corresponding to any region of higher number. If there are two or more of these lowest number regions, they will eventually fuse and if the system is finite they will ultimately sweep it out entirely.

## XI

### FLUTTER IN A SIMPLY CONNECTED TWO-DIMENSIONAL REGION

Theorem 7 makes it clear that flutter can only endure in a system of this type if there are permanent wave-front to wave-back junctions. Theorem 5 shows that the number of these junctions cannot increase while theorem 6 indicates that it can decrease. We have not proved that the number of those junctions must decrease; we suggest, however, that such is the case, and that sustained flutter is therefore impossible in these systems. We also consider it pla-

visible that the same will be true in simply connected three-dimensional systems. We suggest further that for enduring flutter there must always exist at least one non self-intersecting closed path which is the shortest of all paths topologically equivalent to it and which is of length not less than a wave-length.

## XII

### FIBRILLATION

A sufficiently complicated aggregate of flutter circuits such as those in figures 12 and 17 will simulate in many respects the picture of fibrillation, much as a crystal simulates in several features an amorphous substance. Given the irregularity of structure of cardiac muscle we cannot expect to find regularity of geometric pattern for fine scale phenomena; not only will there be differences from region to region within one heart, but there will be no accurate constancy from heart to heart. The approach to the problem of fibrillation from the standpoint of regularly or semiregularly repeated short paths is contradicted by the lack of periodicity indicated by the electrograms recorded under the conditions.

It is quite clear that, as opposed to flutter, fibrillation has not an anatomical but a histological basis. In other words, it is clear that the only uniformity from heart to heart in fibrillation is statistical and that the problem can only be approached, therefore, on a statistical basis.

For this statistical approach the heart is considered as a tangle of fibers distributed at random and anastomosing with one another. The anatomical pictures of a cardiac muscle, particularly of the ventricle, although they show some orientation of certain groups of fibers, display in general a picture of random anastomoses.

The mathematical theory of a random distribution of anastomosing fibers is not yet available. On the other hand, the foundation of a general theory for random distribution of points in space or time has been laid by Wiener and Wintner (1943), generalizing the particular case studied by Poisson. Starting with a distribution of points, a distribution of fibers may be obtained by making the appropriate assumptions with regard to the connections between



these points. Furthermore, conduction can be adequately described in terms of the nodal points of the network by specifying activity at successive epochs of the nodes. The analysis will be made therefore on the basis of a random distribution of the nodes. Since several simplifying assumptions are adopted in is not excepted that the formal model which will ensue will portray the conditions in the heart accurately. It is submitted, however, that the approach employed here may eventually furnish a satisfactory picture, once the simplifying assumptions will have been modified and corrected as physiological knowledge progresses.

A. *The Poisson distribution of points at random in space.* This distribution, the simplest known, is characterized by the following features: *a*, the points are distributed with the same statistical density over the whole region of space considered; *b*, the distribution in non-overlapping regions is completely independent, hence, when we consider joint probabilities over two such regions we multiply the probabilities for the individual regions.

The simplest contingency is that of an empty region. As is well known, the probability that a given region with measure  $m(R)$  should be empty, is

$$(6) \quad p_0^R = e^{-\lambda m(R)}$$

where  $p_0^R$  is the probability that  $R$  contain 0 nodes and  $\lambda$  is a constant which depends on the average density, but not on  $R$ . While a rigorous demonstration of this formula requires a theory of Lebesgue measure, its plausibility may be seen by considering a region formed by  $n$  congruent subregions; if the probability that one of these be empty is  $p$ , then the probability that they should all be empty is

$$(7) \quad P_0 = p^n = e^{n \log p} = e^{-\lambda n} = e^{-\lambda m(R)}$$

where  $\lambda = -\log p$ .

Let us now consider the probability that a region  $R$  contains  $k$  nodes. This is true if whenever the region is divided into  $n > k$  blocks then exactly  $k$  are occupied and the rest empty. The probabilities of this last contingency are

$$(8) \quad P_k^R = \frac{n(n-1)\dots(n-k+1)}{k!} \left( e^{-\frac{\lambda m(R)}{n}} \right)^{n-k} \left( 1 - e^{-\frac{\lambda m(R)}{n}} \right)^k$$

The first fraction is the number of ways that  $k$  terms can be drawn from  $n$ . The next exponential represents the conditions in which exactly  $n-k$  blocks will be empty; and the last, the probability that the remaining  $k$  be occupied. As  $n$  becomes infinite.

$$(9) \quad (n-k)/n \rightarrow 1, \text{ and}$$

$$(10) \quad (n-j) \left( 1 - e^{-\frac{\lambda m(R)}{n}} \right) \rightarrow \lambda m(R)$$

for any fixed  $j$ .

Hence,

$$(11) \quad P_k^R = \lim_{n \rightarrow \infty} P_k^R = \frac{[\lambda m(R)]^k}{k!} e^{-\lambda m(R)}$$

Now

$$(12) \quad \sum_{k=0}^{\infty} P_k^R = \sum_{k=0}^{\infty} \frac{[\lambda m(R)]^k}{k!} e^{-\lambda m(R)} = e^{\lambda m(R)} e^{-\lambda m(R)} = 1.$$

This means that the sum of the probabilities for each  $k$  that the region  $R$  contains exactly  $k$  points is 1; or that the probability that the region be occupied in any other way than by a finite number of points is 0.

Consider now the probability that in a large region  $R_0$  there be exactly  $k$  occupying points, and that the first shall lie in a subregion  $R_1$ , the second in a subregion  $R_2$ , etc. This probability is

$$(13) \quad \frac{\lambda^k m(R)^k}{k!} e^{-\lambda m(R)} \frac{m(R_1) m(R_2) \dots m(R_k)}{m(R)^k} = \frac{\lambda^k}{k!} e^{-\lambda m(R)} m(R_1) \dots m(R_k).$$

This formula does not require that the subregions  $R_1 \dots R_k$  be mutually exclusive — i.e., that they do not overlap. In the exclusive case, when the points need not be taken in a particular order, but may each lie in any of the subregions, the probability (13) is multiplied by  $k!$

With these formulae it is possible to give a complete character-

ization of all the statistical properties of a Poisson distribution of points. If these points are taken as the nodes for a net of fibers one may suppose the fibers straight between nodes. In this case the characterization of the net depends on the assumptions made concerning the connections of nodes. The final determination of the assumptions appropriate for the heart will depend on a statistical study of histological specimens. Until that is available, we shall use theoretical models which are mathematically manageable and bear a sufficient similarity to the gross organization of cardiac muscle.

A simple assumption is that each node connects with all those lying within a certain fixed distance. That assumption can be made in either two or three dimensions. The first may be used as an approximate representation of the auricle, the second as one of the ventricle. A better representation might be obtained by connecting every node with all those within an ellipse or ellipsoid centered on the first node, and with determined shape and orientation. This picture takes account of the fact that fibers of cardiac muscle tend to be parallel in certain regions.

B. *The distribution of activity in time.* The Poisson distribution furnishes only a spatial model of the heart. In order to deal with the spread of activity in the tissue it is necessary to introduce quantities distributed in time. A reasonable model may be obtained by considering the successive excitation of neighboring nodes, eliminating from consideration the conducting process in the connecting fibers. Activation of nodes may be assumed to take place at discrete instants. The events in the network cannot be covered by a Poisson distribution, since this distribution assumes complete independence of the events. It is necessary, therefore, to use the more general theory of statistical distributions elaborated by Wiener and Wintner (1943).

The temporal history of a single node may be represented graphically by a straight line, and the times of activation by points on that line. The problem is then the characterization of the distribution of sets of discrete points on a line; it requires the determination of the probability that for a set of non-overlapping intervals  $I_1, \dots, I_k$  there be corresponding numbers  $n_1, \dots, n_k$  of active instants in each interval, respectively. This probability will be symbolized as

$$(14) p_{n_1, n_2, \dots, n_k}^{I_1, I_2, \dots, I_k}$$

It must be a positive number not exceeding 1. It must also be invariant under any simultaneous permutations of the  $I$ 's and the corresponding  $n$ 's.

The consistency relationships which must hold for the probabilities are the following:

$$(15) \begin{cases} a) \sum_n p_n^I = 1 \\ b) \sum_n p_{n_1, \dots, n_k}^{I_1, \dots, I_k} = p_{n_1, \dots, n_k}^{I_1, \dots, I_k} \\ c) \sum_{n_1, n_2, \dots, n_k} p_{n_1, \dots, n_k}^{I_1, I_2, I_3, \dots, I_k} = p_{n_1, n_2, \dots, n_k}^{I_1 + I_2, I_3, \dots, I_k} \end{cases}$$

Equation (15a) states that the interval  $I$  contains at most a finite number of active instants. Equation (15b) states the fact corresponding to (15a) for combined probabilities instead of simple probabilities. Equation (15c) states that if a combination of intervals  $I_1 + I_2$  is occupied by  $n_0$  active instants, then there is a number  $n_1 < n_0$  of active instants in  $I_1$  while the remaining  $n_0 - n_1$  instants are in  $I_2$ . This equation (15c) may be regarded as a definition of the probabilities  $p$  in the cases where some intervals are replaced by sums of finite numbers of intervals.

It is a familiar mathematical procedure to replace certain sequences of numbers by functions in which these numbers appear as coefficients. This procedure is useful in bringing the formulac of consistency (15) into more convenient forms. The functions in question are:

$$(16) f(\xi_1, \dots, \xi_k) = \sum_{n_1=0}^{\infty} \dots \sum_{n_k=0}^{\infty} p_{n_1, \dots, n_k}^{I_1, \dots, I_k} \xi_1^{n_1} \dots \xi_k^{n_k}$$

This series will converge if

$$(17) |\xi_i| < 1, \dots, |\xi_k| < 1.$$

It will be shown later that in the cases treated here the series is

convergent for all values of the  $\xi$ 's and represents an entire function. Equations (15) now become

$$(18) \begin{cases} a) f\left(\begin{matrix} 1 \\ 1 \end{matrix}\right) = 1 \\ b) f\left(\begin{matrix} l_1, l_2, \dots, l_k \\ \xi_1, \xi_2, \dots, \xi_k \end{matrix}\right) = f\left(\begin{matrix} l_2, \dots, l_k \\ \xi_2, \dots, \xi_k \end{matrix}\right) \\ c) f\left(\begin{matrix} l_1, l_2, \dots, l_k \\ \xi_1, \xi_2, \dots, \xi_k \end{matrix}\right) = f\left(\begin{matrix} l_1 + l_2, \dots, l_k \\ \xi_2, \xi_3, \dots, \xi_k \end{matrix}\right) \end{cases}$$

By differentiating equation (16)  $l$  times with respect to  $\xi_1, \dots, l_k$  times with respect to  $\xi_k$ , we obtain.

$$(19) \left(\frac{\partial}{\partial \xi_1}\right)^{l_1} \dots \left(\frac{\partial}{\partial \xi_k}\right)^{l_k} f\left(\begin{matrix} l_1, \dots, l_k \\ \xi_1, \dots, \xi_k \end{matrix}\right) = \sum_{n_1=1}^{\infty} \dots \sum_{n_k=1}^{\infty} n_1(n_1-1) \dots (n_1-1+l_1) \dots n_k(n_k-1) \dots (n_k-l_k+l_l) \times p_{n_1, \dots, n_k}^{l_1, \dots, l_k} \xi_1^{n_1-1} \dots \xi_k^{n_k-l_k}$$

If we now make all  $\xi$ 's = 1, we get

$$(20) \left(\frac{\partial}{\partial \xi_1}\right)^{l_1} \dots \left(\frac{\partial}{\partial \xi_k}\right)^{l_k} f\left(\begin{matrix} l_1, \dots, l_k \\ \xi_1, \dots, \xi_k \end{matrix}\right) = \sum_{n_1=1}^{\infty} \dots \sum_{n_k=1}^{\infty} n_1(n_1-1) \dots (n_1-1+l_1) \dots n_k(n_k-1) \dots (n_k-l_k+l_l) \times p_{n_1, \dots, n_k}^{l_1, \dots, l_k}$$

This equation represents the average number of ways of selecting simultaneously  $l_j$  active instants from the interval  $I_j$  where  $j$  runs from 1 to  $k$  in order. If we assume, as we should for the heart, that the active instants cannot be closer together than a fixed interval — in other words, that there is a refractory period — then the members of (20) are not greater in absolute value than a finite quantity of the form

$$(21) A^{l_1 + \dots + l_k} m(I_1)^{l_1} \dots m(I_k)^{l_k}$$

Under these conditions the series

$$(22) \sum_{l_k=0}^{\infty} \dots \sum_{l_1=0}^{\infty} \frac{\left[\left(\frac{\partial}{\partial \xi_1}\right)^{l_1} \dots \left(\frac{\partial}{\partial \xi_k}\right)^{l_k} f\left(\begin{matrix} l_1, \dots, l_k \\ \xi_1, \dots, \xi_k \end{matrix}\right)\right]_{\xi_1=1, \dots, \xi_k=1}}{l_1! \dots l_k!} (x_1-1)^{l_1} \dots (x_k-1)^{l_k}$$

will be term by term less in absolute value than

$$(23) \sum_{l_k=0}^{\infty} \dots \sum_{l_1=0}^{\infty} \frac{A^{l_1 + \dots + l_k} m(I_1)^{l_1} \dots m(I_k)^{l_k}}{l_1! \dots l_k!} (x_1-1)^{l_1} \dots (x_k-1)^{l_k} = \sum_{\alpha \in J^k} A^\alpha m(\alpha_j)(x_j-1)$$

and will hence converge for all values of  $x_j$ . On the basis of the ordinary theorems on multiple Taylor series, the series (22) will then be identical with

$$(24) f\left(\begin{matrix} l_1, \dots, l_k \\ x_1, \dots, x_k \end{matrix}\right)$$

which is defined for all values of the  $x$ 's.

Because of the refractory period, there cannot be more than a fixed finite number of active instants in a finite interval. Hence, the generating function (16) is a polynomial of finite degree. If the  $I$ 's are sufficiently small, it is in fact a multilinear polynomial.

If we now take the functions (16) and replace the  $\xi$ 's by  $x$ 's, and then combine them with formulae (22) and (24), we see that

$$\begin{aligned}
 (25) \quad & \sum_{n_1=0}^{\infty} \dots \sum_{n_k=0}^{\infty} p_{n_1, \dots, n_k} x_1^{n_1} \dots x_k^{n_k} = \\
 & = \sum_{l_1=0}^{\infty} \dots \sum_{l_k=0}^{\infty} \frac{\left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1}}{l_1! \dots l_k!} \\
 & \quad \times \sum_{n_1=0}^{l_1} x_1^{n_1} (-1)^{l_1-n_1} l_1! \dots \sum_{n_k=0}^{l_k} x_k^{n_k} (-1)^{l_k-n_k} l_k! \\
 & = \sum_{l_1=0}^{\infty} \dots \sum_{l_k=0}^{\infty} \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1} \\
 & \quad \times \sum_{n_1=0}^{l_1} \frac{x_1^{n_1} (-1)^{l_1-n_1}}{(l_1-n_1)! n_1!} \dots \sum_{n_k=0}^{l_k} \frac{x_k^{n_k} (-1)^{l_k-n_k}}{(l_k-n_k)! n_k!}
 \end{aligned}$$

$$\begin{aligned}
 & = \sum_{n_1=0}^{\infty} \dots \sum_{n_k=0}^{\infty} x_1^{n_1} \dots x_k^{n_k} \sum_{l_1=n_1}^{\infty} \dots \sum_{l_k=n_k}^{\infty} \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} \right. \\
 & \quad \left. \times f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1} \frac{(-1)^{l_1-n_1} \dots (-1)^{l_k-n_k}}{(l_1-n_1)! n_1! \dots (l_k-n_k)! n_k!}
 \end{aligned}$$

By equating coefficients in (25) we finally get

$$\begin{aligned}
 (26) \quad & p_{n_1, \dots, n_k} = \sum_{l_1=n_1}^{\infty} \dots \sum_{l_k=n_k}^{\infty} \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1} \\
 & \quad \times \frac{(-1)^{l_1-n_1} \dots (-1)^{l_k-n_k}}{n_1! (l_1-n_1)! \dots n_k! (l_k-n_k)!}
 \end{aligned}$$

This is a generalized alternating series for the  $p$ 's. For a probability  $p$  to have any meaning it must be positive. There is no simple way of determining the positivity of (26) in terms of the quantities

$$(27) \quad \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1}$$

If these quantities are used to determine the system of probabilities it must be with the proviso that they are positive.

The question now arises under what conditions on the quantities in (27) the conditions of consistency (15) will be satisfied. First, let us consider the cases where all the  $l_j$ 's are 1. Suppose that  $l_1 = 1, l_2 = 1, \dots, l_k = 1$ , where  $l_1'$  and  $l_1''$  are non-overlapping sets of intervals. Then, since,

$$(28) \quad f \left( \xi_1, \xi_2, \dots, \xi_k \right) = f \left( \xi_1, \xi_2, \dots, \xi_k \right)$$

according to (15c); and since by (15b)

$$(29) \quad f \left( \xi_1, \xi_2, \dots, \xi_k \right) = f \left( \xi_1, \xi_2, \dots, \xi_k \right)$$

and also

$$(30) \quad f \left( \xi_1, \xi_2, \dots, \xi_k \right) = f \left( \xi_1, \xi_2, \dots, \xi_k \right)$$

it follows from the formula for the total derivative of a function that

$$\begin{aligned}
 (31) \quad & \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1} \\
 & = \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \xi_2, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1} \\
 & \quad + \left[ \left( \frac{\partial}{\partial \xi_1} \right)^{l_1} \dots \left( \frac{\partial}{\partial \xi_k} \right)^{l_k} f \left( \xi_1, \xi_2, \dots, \xi_k \right) \right]_{\xi_1=1, \dots, \xi_k=1}
 \end{aligned}$$

That is (27), is an additive functional of the set  $l_1$ . It is similarly an additive functional of the sets  $l_j$ . In other words, it is an

additive functional in the product space of these sets. It is non-negative since it represents a series in the probabilities with positive coefficients. Such a positive additive functional of sets of points can always be represented by a generalized Stieltjes integral in the appropriate space (see Saks, 1937). We may write the differential of this Stieltjes integral in the form

$$(32) \quad d_t_1 \dots d_{t_n} \varphi(t_1, \dots, t_n).$$

Knowing the additive functionals (27) in the case where the  $I$ 's are all 1 we can express the more general quantities (27), with unrestricted  $I$ 's, in terms of the same additive functionals.

Suppose each region  $I_j$  is divided into subregions  $I_{jk}$  of shorter length than the refractory period. Then each  $I_{jk}$  will contain either no active instants or only one active instant. Consider then the expression

$$(33) \quad f(I_1, \dots, I_k) = f(\xi_1, \dots, \xi_k).$$

This can be written as follows

$$(34) \quad f(I_1, \dots, I_k) = f(\xi_1, \dots, \xi_k),$$

where

$$(35) \quad \xi_{11}, \dots, \xi_{1n_1} = \xi_1 \quad \text{and}$$

$$(36) \quad \xi_{k1}, \dots, \xi_{kn_k} = \xi_k.$$

The function (34) will be multilinear in the variables

$$(37) \quad \xi_{11}, \dots, \xi_{kn_k}.$$

Consider next the expression

$$(38) \quad \left[ \frac{\partial^{m_1}}{\partial \xi_1^{m_1}} \dots \frac{\partial^{m_k}}{\partial \xi_k^{m_k}} f(I_1, \dots, I_k) \right]_{\xi_1=1, \dots, \xi_k=1}.$$

This can also be expressed in the form

$$(39) \quad \sum \left[ \frac{\partial}{\partial \xi_{1t_1}} \dots \frac{\partial}{\partial \xi_{1t_{m_1}}} \dots \frac{\partial}{\partial \xi_{kt_1}} \dots \frac{\partial}{\partial \xi_{kt_{m_k}}} \right] \times f(I_1, \dots, I_k)_{\xi_1=1, \dots, \xi_k=1},$$

where the sum is taken over all selections of

$$(40) \quad \xi_{1t_1}, \dots, \xi_{1t_{m_1}},$$

from among the variables

$$(41) \quad \xi_{11}, \dots, \xi_{11},$$

and so on, until we select

$$(42) \quad \xi_{kt_1}, \dots, \xi_{kt_{m_k}}$$

from among the variables

$$(43) \quad \xi_{k1}, \dots, \xi_{kn_k}.$$

In doing this all the partial derivatives are reduced to partial derivatives of the first order in each variable independently; these have already been defined as integrals of densities. In this way, once more compounding  $I$ 's with one index, out of the  $I$ 's with two indices, it follows that

$$(44) \quad \left[ \frac{\partial^{m_1}}{\partial \xi_1^{m_1}} \dots \frac{\partial^{m_k}}{\partial \xi_k^{m_k}} f(I_1, \dots, I_k) \right]_{\xi_1=1, \dots, \xi_k=1} = \int_{I_1} \dots \int_{I_1} \dots \int_{I_k} \dots \int_{I_k} d_{\xi_{11}} \dots d_{\xi_{1m_1}} \dots d_{\xi_{kn_k}} \times \varphi^k m_j (\xi_{11}, \dots, \xi_{kn_k}).$$



$$(50) \nu_{k_1}, \dots, \nu_{m_1}$$

active instants, . . . , and that finally, at Pk, the intervals

$$(51) I_{k_1}, \dots, I_{k n_k}$$

shall contain respectively

$$(52) \nu_{k_1}, \dots, \nu_{k n_k}$$

active instants. Under the assumption that the space distribution of the nodes is of the Poisson type, the combined probability of the conditions leading to the system of probabilities (48) and the condition that P1 lies in R1, . . . , Pk in Rk will be:

$$(53) \lambda^k \int_{R_1} \dots \int_{R_k} dV_{P_1} \dots dV_{P_k} p \left( \begin{matrix} P_1, \dots, P_k, \dots, P_k, \dots, P_k \\ I_{k_1}, \dots, I_{k n_1}, \dots, I_{k_1}, \dots, I_{k n_k} \\ \nu_{k_1}, \dots, \nu_{k n_1}, \dots, \nu_{k_1}, \dots, \nu_{k n_k} \end{matrix} \right) \\ = \lambda^k \int_{R_1} dV_{P_1} \dots \int_{R_k} dV_{P_k} \sum_{m_{k_1}} \dots \sum_{m_{k n_k}} \frac{(-1)^{m_{k_1} + \dots + m_{k n_k}} \nu_{k_1} \dots \nu_{k n_k}}{(m_{k_1} - \nu_{k_1})! \dots (m_{k n_k} - \nu_{k n_k})! \nu_{k n_k}!} \\ \times \int_{I_{k_1}} d_{T_{k_1}} \dots \int_{I_{k m_k}} d_{T_{k m_k}} \dots \int_{I_{k n_k}} d_{T_{k n_k}} m_{k_1} m_{k_2} \dots m_{k n_k} \\ \times \left( \varphi_{n+1}^{P_1, P_2} (t_{k_1}, m_{k_1}, j, \dots; t_{k n_1}, \dots, t_{k n_k}, m_{k n_k}) \right)$$

D. *The statistical conditions for fibrillation.* We have now reduced all probabilities in time and space connected with the structure of the fundamental heart-net and the distribution of its moments of activity to probabilities that may be expressed in terms of the  $\varphi$ 's. These  $\varphi$ 's depend on the time variables  $t_{ij}$ , the space variables  $P_i$ , and the multiplicities  $m_{ij}$ . Now let us consider the possibility of fibrillation. In this case, the heart-net is stimulated in a way in which there is statistical invariance both under translations in space and in time, and in which the stimulation does not reduce to 0. Neither a simultaneous uniform translation of all the P's in space,

nor of all the  $t$ 's in time, will change the statistical state of the system.

Let us now discuss the dynamics of fibrillation. The first dynamical condition concerns the refractory period. If the length of this period is A, it says merely that

$$(54) \int_{t_1} d_{t_1} \int_{t_2} d_{t_2} \varphi^P (t_1, t_2) = 0$$

if I1 and I2 do not overlap, and no instant of I1 is more than a time-distance A from any instant of I2.

The second condition asserts that if P2 is connected with P1 — that is if it lies within the sphere or ellipsoid of connection about P1 —; and if P2 fires between

$$(55) \frac{-\bar{P}_1 \bar{P}_2}{v} \text{ and } \frac{-\bar{P}_1 \bar{P}_2}{v} + \epsilon,$$

where v is the velocity of the muscle impulse; and finally, if P1 fires between -t and -t +  $\epsilon$ ; then P1 must fire between -t +  $\epsilon$  and 2 $\epsilon$ . By (48) this becomes:

$$(56) \int_{-\frac{P_1}{v}}^{-\frac{P_2 + \epsilon}{v}} dt_1 \int_{-t_1}^{-t_1 + \epsilon} dt_2 \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \int_{-t_1 + \epsilon}^{-t_1} d_{s_1} \dots \int_{-t_1 + \epsilon}^{-t_1} d_{s_n} \\ \times \varphi_{n+1}^{P_1, P_2} (t_2, s_1, \dots, s_n; t_1) = 0$$

The final fundamental equation on the  $\varphi$ 's in the case in which all nodes within a distance  $\rho$  from one another are connected will be given below. Let us suppose: a) that P1 has fired between -t and -t but has not fired between -t and 0; b) that no Pj among the points P2, . . . , Pk has fired between the appropriate

$$(57) \frac{-\bar{P}_1 \bar{P}_2}{v} \text{ and } -\frac{\bar{P}_1 \bar{P}_2}{v} + \epsilon;$$

c) that St is a sphere of radius  $\rho t$  about P1, where  $\rho t$  is 0 if  $t \leq A$  and otherwise is the smaller of the two quantities  $\rho$  and  $v(t-A)$ ; d) that within this sphere St there are, besides possible Pj's, the nodes

$Q_1 \dots Q_n$ . Then  $P_1$  fires between times 0 and  $\epsilon$  when, and only when, some  $Q_j$  fires between

$$(58) \quad -\frac{P_1 Q_j}{v} \text{ and } -\frac{P_1 Q_j}{v} + \epsilon_1.$$

In this formulation we are supposing  $\epsilon$  and  $\epsilon_1$  to be small quantities and are considering as negligible all probabilities of smaller order than these quantities.

The probability that  $St$  contains just  $n$  points  $Q_j$  is

$$(59) \quad \frac{[\lambda m(S_t)]^n}{n!} e^{-\lambda m(S_t)}$$

and each of these points is distributed uniformly and independently within the sphere. Thus, if  $tn+1, \dots, tm$  lie outside the interval  $(0, t)$ , and if no  $s_{jk}$  is such that

$$(60) \quad s_{jk} - t = \frac{P_k Q_j}{v}$$

our condition becomes:

$$(61) \quad \frac{\partial}{\partial T} \left( \sum_0^\infty \frac{(-1)^n}{n!} \int_0^t \dots \int_0^t dt_1 \dots dt_n \right) \times \varphi_{\substack{P_1, P_2, \dots, P_k \\ m+1, n_2, \dots, n_k}}(0, T, t_1, \dots, t_m, S_{21}, \dots, S_{2n_2}; \dots; S_k; \dots; S_{kn}) \tau = t \\ = \frac{\partial}{\partial T} \left( \lambda \int \int \int dV_a \sum_0^\infty \frac{(-1)^n}{n!} \int_0^t \dots \int_0^t dt_1 \dots dt_n \right) \times \varphi_{\substack{P_1, P_2, \dots, P_k \\ m+1, n_2, \dots, n_k}}(0, t_1, \dots, t_m; S_{21}, \dots, S_{2n_2}; \dots; S_k; \dots; S_{kn}) \tau = t \\ \dots S_{kn} ; \tau - \frac{P_1 Q_j}{v} \tau = t.$$

Here the

$$(62) \quad \lambda \int \int \int dV_a \sum_0^\infty \frac{(-1)^n}{n!} \int_0^t \dots \int_0^t dt_1 \dots dt_n \times \varphi_{\substack{P_1, P_2, \dots, P_k \\ m+1, n_2, \dots, n_k}}(0, t_1, \dots, t_m; S_{21}, \dots, S_{2n_2}; \dots; S_k; \dots; S_{kn}) \tau = t$$

comes from the fact that we have to add up  $n$  identical probabilities when  $St$  contains  $n$  points  $Q_j$ , so that we have to multiply an average over  $St$  in a single  $Q_j$  by  $\lambda m(S_t)$ , the average number of  $Q_j$ 's.

These formulae are of course to be supplemented by others which result from the positivity of the fundamental probabilities. How to solve them, and what they lead to, is a question for further and difficult mathematical work.

XIII

THE BEARING OF THE PRESENT STUDY ON THE DATA AVAILABLE ABOUT FLUTTER AND FIBRILLATION

In Lewis' lucid book "The Mechanism and graphic Registration of the Heart Beat" (1925) there is an excellent review of the experimental and clinical data and an equally excellent discussion of the current theories on flutter and fibrillation. To our knowledge, few data and no new theoretical concepts have appeared since the date of publication of that book. We shall use it mainly, therefore, as the basis for this and the next sections.

Our analysis of the mechanism of flutter is in agreement with the data, as follows. We have concluded that in a two-dimensional system such as the auricle, an obstacle or system of obstacles is necessary for flutter; this system should have an effective perimeter greater than a wave length. According to Lewis, the propagation velocity in the dog's auricle is normally 1m/sec.; it slows, however, with increasing heart rate, and at the rates corresponding to auricular flutter (5.7 to 9.6/sec.) it decreases to about 0.5 m/sec. The



absolutely refractory period, which decreases considerably with fast rates, is about 0.095 sec. The functional refractory period cannot be much longer than that of absolute refractoriness; let us assign it a value of 0.1 sec. The wave-length is therefore approximately 5 cm.

In one of the cases analyzed in detail by Lewis he was able to trace the path of flutter around the orifices of the two venae cavae. The length of the path was 13.7 cm., there was obviously ample perimeter for a wave length; indeed, the perimeter was sufficient for two waves following each other. Lewis decided that there was only one wave, and that the gap between wave-front and wave-rear (in the direction of the circus movement) was quite narrow. Had there been only one wave traveling around a closed path 13.7 cms. long with a velocity of 0.5 m/sec. the rate of flutter would have been 3.8/sec., and the duration of the cycle 0.263 sec. Now, Lewis measured the cycle and found it to last 0.1600 sec.; in other words, the rate was 6.25/sec. This discrepancy in Lewis' measurements is readily explained if we conclude, as suggested, that there were two waves, and not one, traveling around the path he determined. An alternative possibility would be that the wave was traveling, not around both cavae, considered as a single obstacle, but around one of them. Lewis does not give the perimeter of the cavae in his experiment, but from the figure which he reproduces (fig. 290, p. 299) this perimeter would be about 47 mm. for the superior cava, and it should be even greater for the inferior — i.e., the perimeters could have been approximately the proper length to contain a wave. But this second alternative would invalidate the path which Lewis determined. It is interesting to note that in the calculations used for determining the path, Lewis (p. 297) assumed that the wave completed the path with the perimeter of 13.7 cm. in the duration of the cycle: 0.16 sec. This assumption implies a conduction rate of 0.856 m/sec., a very high velocity for a fluttering dog's auricle, according to Lewis' own measurements of propagation rate in those conditions.

In some measurements which we have carried out on adult human hearts, the diameter of the cavae were about 2.1 cm. for the superior and 3.1 cm. for the inferior. These give circumferences of about 6.6 and 9.7 cm., respectively. If the wave length in the fluttering human auricle is approximately equal to that of the dog's

auricle, it is clear that flutter is possible in man with only one of the cavae as the directing obstacle for the recurring wave. The rate of the human auricular flutter (usually about 5/sec.) also suggests the probability that it may often be due to a single wave around the inferior cava. Assuming a conduction velocity equal to that of the dog — i.e., 0.5 m/sec. — the distance traveled in a cycle (0.2 sec.) will be 10 cm. If we suppose that the effective obstacle is around the two cavae the perimeter is about 18.3 cm., since the distance between the two veins is about 2.5 cm. The cycle would then be 0.367 and the rate 2.72/sec., or 163/min., a rate much too slow. We should therefore have to assume again that there are two waves around the obstacle, if the path were around both veins.

Lewis agrees that flutter is possible in a flat sheet of muscle with only one hole of perimeter less than a wave-length, and Garrey (1924) reports that it is even possible in the absence of a hole. In

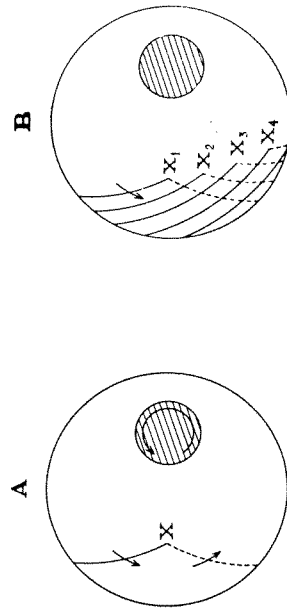


Figure 19.—A. A wave-front (full line with arrow) and wave-rear (dotted line), with  $x$  as the junction, in a two-dimensional system with an obstacle (hatched circle) of circumference less than a wave-length. Lewis assumes that flutter would take place — i.e., that  $x$  would rotate around the obstacle.  
B. The course (successive wave-fronts) which the wave in A will follow. Flutter will not take place.

figure 19 A is reproduced Lewis's diagram (his fig. 310 C, p. 322) with only insignificant changes to adjust to the conventions followed in this paper. Lewis assumes that the junction of wave-front to wave-rear  $x$  rotates around the obstacle. This assumption is erroneous. In B the progress of the wave in A is shown by successive wave fronts; it is clear that the junction  $x$  will not move around the

obstacle, but out, toward the boundary, and that the wave will therefore sweep away and not recur.

Garrey's observations (loc. cit., p. 236) were made on the auricle of large Selachians. He reports the possibility of setting up simple circuits (i.e., flutter waves) not only around the vessels but also around a stimulated region with no natural obstacle. It is difficult to evaluate these observations, since they are given with very little detail. An obscure aspect of the data is as follows. The three rings observed visually measured respectively 12, 6, and something like 3.2 cm. or more. Now the rates were respectively 60, 120 and 159/min. The first two rates are consistent with the sizes of the corresponding rings; but the third rate is grossly at variance with the others. Strong faradization of a region may render cardiac muscle non-conductive locally, much as it renders nerve non-conductive. It is possible that in Garrey's observations an artificial transitory obstacle was established unwittingly at the stimulated region. More precise observations than those available are necessary to prove experimentally that flutter waves may circulate in the absence of a central obstacle of the proper dimensions.

XIV

Comments

First let us state the definitions of flutter and fibrillation to which we have adhered in this study.

*Definition of flutter.* Flutter consists of a wave or waves of activity in a conducting system with a regular cyclic recurrence of paths, and therefore with a well-defined regular wave-front and period.

Flutter differs from the ordinary heart-beat in that flutter activity is continuous, while beats are separated by periods of total rest (diastole of cardiac muscle).

This definition agrees with both the clinical and the experimental observations; thus, Lewis emphasizes the regularity of the cycles and of the electric phenomena recorded.

*Definition of fibrillation.* Fibrillation consists of a continuous activity over randomly varying paths in a network of connected

conducting elements. That such fibrillation exists and is what we usually mean by the term is an assumption.

The main difference between flutter and fibrillation, according to these definitions, is the randomness of fibrillation as opposed to the regularity of flutter. Randomness precludes sharp, defined wave-fronts and cyclical regularity.

Lewis recognizes that one of the differences between auricular flutter and fibrillation is that the path in flutter is repeated accurately while in fibrillation it is not. The path here is uneven; it alters constantly in detail. Immediately thereafter he stresses, however, that the irregularities of auricular fibrillation are relatively slight, and that in general the same broad path is used over and over again. He infers that the course in fibrillation is not wholly erratic and that there is no evidence of several independent circuits. He concludes, therefore, that the mechanism of auricular flutter and

TABLE 1

Some data (taken from Lewis, 1925) on auricular flutter and fibrillation. The question marks indicate that the corresponding measurements are not available; the figures for man are then assumed equal to those for the dog.

	Auricular flutter		Auricular fibrillation	
	Dog	Man	Dog	Man
Rate (per sec.)	5.75 to 9.67	3.67 to 6.17	8.33 to 15	6.67 to 10
Average	8	5	12	8
Average cycle (sec.)	0.125	0.2	0.083	0.125
Refractory period (sec.)	0.1	0.1 (?)	0.1	0.1 (?)
Propagation velocity (m/sec.)	0.5	0.5 (?)	0.4-0.5	0.4-0.5 (?)
Length of path if single wave (cm.; cycle x velocity)	6.75	10	3.32-4.15	5.0-6.25

fibrillation is the same: a single wave of circus movement; and that the main difference — i.e., the higher cyclic rate of fibrillation — is due to a shorter gap between wave front and wave rear and to

decreases and the slight irregularities of fibrillation tend to dissipate. Quinidine slows the conduction velocity, hence the decrease of rate. Quinidine also lengthens the refractory period; the regularization of the wave, when it takes place, is probably due to a greater influence of the drug on the velocity than on the refractoriness.

We now state and answer some objections, based on clinical experience, that have been raised against the view that auricular flutter and fibrillation are the result of a single mechanism.

a) Significant irregularities of pattern and rhythm are characteristic of fibrillation, as opposed to flutter. If the superior cava were the usual effective obstacle in fibrillation irregularities should be the rule, because of the presence of the additional obstacle constituted by the inferior cava (see section VI, 2).

b) Sudden transitions from fibrillation to flutter are not uncommon. We attribute those transitions to a progressive or sudden change in either the refractory period, or the conduction velocity, such that the superior cava no longer provides an effective perimeter and the pacemaker shifts accordingly to the inferior cava.

c) Both flutter and fibrillation appear generally in patients with lesions in the left, not in the right auricle; this fact has been considered opposed to the role attributed to the cavae. The circuit of a flutter wave is independent of the site and mode of initiation. The possibility that the pulmonary veins, singly or jointly, may provide effective obstacles for flutter or fibrillation has not been discussed here, but should be investigated.

d) Quinidine, which is usually effective in stopping fibrillation, fails often to stop flutter. There is probably a limit to the changes that the drug causes in the conduction velocity and the refractory period. In fibrillation, with the relatively small obstacle of the superior cava, the suppression of the sufficient perimeter should be easier than in flutter, where the obstacle has a longer perimeter.

If there is only a quantitative difference between the two auricular conditions it seems advisable to use a single term for both with the proper adjective to distinguish the two; thus the term flutter might be retained and we would have a *slow* and a *fast* flutter, the latter expression replacing the term auricular fibrillation as used now.

a shorter path. The gap in flutter would be grossly 1/5 to 1/6 of the total ring; a shorter gap in fibrillation would explain the greater irregularity, since the wave front would always be meeting many insufficiently recovered fibers.

TABLE 2

Approximate perimeter (in cm.) of the superior and inferior venae cavae, and of a tight string around both. The figures are based on Testut's data for the human, Lewis's illustrations of dog's auricles, and some measurements of our own. These figures are meant to apply to average adults; it is clear that the variability of size of different dogs makes the figures for that species very grossly approximate.

	Dog	Man
Superior cava	4.5	6.6
Inferior cava	6.0	9.7
String around both	13.5	18.3

In table 1 are summarized some of Lewis's data pertinent to this problem, and in table 2 are given some approximate measurements of the perimeters of the obstacles in the auricle around which flutter or fibrillation waves could flow. A comparison of the lengths of path in table 1 with the perimeters of table 2 shows that, given the necessary approximate character of the figures, the inferior cava alone is a possible obstacle for flutter, not the superior cava. For fibrillation the superior cava alone has the sufficient dimensions. Indeed in both species, man and dog, as well as in our measurements of cats' hearts, the perimeter of the inferior cava is to that of the superior approximately as the rate of fibrillation is to that of flutter. This relation suggests strongly that if we follow Lewis's views on auricular flutter and fibrillation, the sole difference between the two conditions would be a difference in the obstacles around which a circus wave would be traveling.

If we accept the previous argument and the suggested hypothesis to which it leads, it follows that there is only a quantitative but no qualitative difference between what is called auricular flutter and auricular fibrillation. This inference is supported by the fact, stressed by Lewis, that under the influence of quinidine there is a gradual transition from fibrillation to flutter — i.e., the rate gradually

The question arises then whether fibrillation, as defined here, actually exists. We would answer that question in the affirmative, and cite the observations on ventricles of cats, dogs and men in support of that answer. It is of course well known that the ventricular response to faradic stimulation begins usually with relatively uniform electrical oscillations, but that state of flutter is usually promptly followed by another in which both the electrical and the mechanical records are quite erratic. This latter stage we designate as genuine fibrillation. The present confusion of terminology would be avoided if the suggestions offered here were followed; granting that complex mixtures of flutter and fibrillation are probably not uncommon, at least the typical pictures would be clearly separated. It is interesting to note that Lewis's admirable analysis of the problem does not mention once ventricular flutter. In other words, our suggestion is that flutter and fibrillation be distinguished not by the rate, but by the regularity, absolute or relative, of the one, and the ostensible irregularity of the other.

The question arises next whether fibrillation, in the strict present sense, is possible in the auricle. Observations mentioned by Garrey (1924) answer this question affirmatively. Finally, it is quite likely that flutter may appear in the ventricle.

It should be stated that with the data available it is not possible to distinguish phenomenologically fibrillation, as defined here, from fine grained flutter over a multiplicity of complicated fixed paths. A large number of flutter waves, if sufficiently out of phase, could produce a complicated pattern of beats and modulation indistinguishable by gross observation from multiple random waves.

*Alternative theories for flutter.* The following theories are suggested by the data.

- 1) Flutter may be due to circus movements of active waves. This theory, due originally and independently to Mines (1913) and Garrey (1914), is generally accepted. For this reason it was adopted here as the basis for the mathematical formulation of the problem.
- 2) Flutter may be due to continuous activity in circuits open from the standpoint of conduction, but closed by mechanical stimula-

tion of one end upon contraction of the other. This theory is a variant of the preceding one. It may be applicable to the ventricle, where the contraction of the papillary muscles could stimulate the base via the chordae tendinae.

3) Flutter may be due to one or more spontaneously active initiators of impulses, or pace makers. This theory, which has been considered in the past and has been dismissed (see Garrey, 1924), is unlikely but is not disproved by the data.

4) Flutter may be due to a continuous external stimulus causing the most excitable region or regions to become the initiators of regular, rapidly repeated activity as in (3). This theory may find an application in the flutter of a distended turtle ventricle.

There may be other alternative theories. These are suggested for the sake of completeness. Theory (2) would require only slight changes of the present analysis; theories (3) and (4) would require more radical modifications. All these theories are compatible with the definition of flutter adopted.

#### *Alternative theories of fibrillation*

1) Fibrillation may be due to random circus movements; this is the theory which has been favored here in order to permit a specific mathematical treatment, but the two following theories allow a treatment different only in details from that presented.

2) Fibrillation may be due to the appearance of multiple spontaneously active foci (Engelmann's theory, 1895; see Garrey, 1924).

3) Fibrillation may be due to the presence of a continuous external stimulus; if the elements have an approximately equal excitability numerous fortuitous waves should ensue.

#### XV

#### *Concluding remarks*

It is clear that the two main topics considered in this paper, namely cardiac flutter and fibrillation, bear not only a close relationship to each other, but also to the other physiological problems

mentioned in the introduction. All these cases concern continuous self-sustained transmission of impulses in physiologically connected non-spontaneously-active networks. It is also clear, therefore, that the method of approach used here is equally applicable, with the proper modifications of detail, to other networks, such as nerve-nets.

The importance of this type of study is that it exhibits the implications of the theories analyzed and supplies a basis for their adequate experimental test.

We have shown how mathematical models may be formulated for flutter and for fibrillation. As to models for flutter, we have only considered here the cases which appeared more important in a first study. The treatment is not exhaustive, but it seems best to postpone a further elaboration until more data are available, and there is a more complete factual picture of the phenomenon. The theory thus far developed suggests many observations and experiments pertinent to the problem.

With regard to fibrillation, we have taken the first step toward the building of an applicable mathematical theory. This step is the formation of a model of a statistically random network of fibers, and the establishment of equations for conduction over such a network. In this first step we have not made any attempt to secure a detailed verisimilitude in our model. That second step can only be taken later after the technique of manipulating relatively simple models, such as the present one has been mastered. We have not attempted to go beyond the mathematical formulation of the statistical problem.

This formulation shares a certain difficulty with the closely related problems of the equation of state of a gas and the equations of turbulence. That difficulty lies in the extreme multiplicity of the variable functions needed to characterize the situations mentioned. In all these cases we meet with constants, functions of one variable, functions of two variables, etc. The equations connecting the functions of lower order are not complete and adequate. We should, therefore, have recourse to some technique by means of which the total effect of the functions of higher order may be given

approximately by functions of lower order. That technique is not yet available, but a further study now being carried out by Walter Pitts and Norbert Wiener seems to show a great deal of promise.

## RESUMEN

Para poder formular un modelo matemático aplicable a los problemas del flutter y la fibrilación del músculo cardíaco se adoptan los siguientes postulados. 1) Una vez iniciado, el impulso cardíaco avanza con velocidad constante en todas direcciones en la aurícula o ventrículo. 2) La intensidad del proceso que determina la propagación es constante. 3) Cualquier región de una fibra puede estar en uno de tres estados: *a*, el estado activo (los puntos situados en el frente de una onda propagada); *b*, el estado refractario (se considera el funcional y se le postula de duración constante); *c*, el estado de reposo.

Se asignan a estos tres estados números que caracterizan su época: el número 0 corresponde al instante de actividad; los números entre 0 y 1 representan la fracción transcurrida del período refractario; el número 1 corresponde al estado de reposo. Las leyes de estos números son: *a*) los números menores que 1 crecen con velocidad igual a la reciproca del tiempo refractario; *b*) el número 1 no cambia si no llega una onda de actividad; *c*) en cualquier punto en que un número 1 está en contacto con un 0 hay un frente de onda que se mueve hacia la región con número 1 con una velocidad constante. Como consecuencia de estos postulados, detrás de cada frente de onda hay una banda de latitud constante, que se considera la "longitud de la onda".

La figura 1 ilustra la propagación de impulsos en un sistema cerrado de una dimensión (una fibra continua). La figura 2 muestra que es posible iniciar actividad recurrente (flutter) en estos sistemas por la estimulación apropiada de dos regiones.

La ley de la propagación de impulsos en los sistemas de dos dimensiones es el principio de Huyghens: los frentes de onda sucesivos son perpendiculares a un sistema de radios que representan la posición tomada por cordones tirantes que parten del punto estimulado y pasan alrededor de los obstáculos; los zagueros de las ondas son curvas semejantes que siguen a los frentes a una distancia

constante medida en esos radios. Las figuras 3 y 4 ilustran la influencia de obstáculos y de concavidades del perímetro del sistema sobre los frentes de onda. La figura 5 muestra la posibilidad de iniciar ondas unidireccionales por dos estímulos apropiados en un sistema de dos dimensiones. Las figuras 6 a 12 muestran la influencia de diversos obstáculos en la producción del flutter. En las figuras 13 y 14 se analiza la iniciación del flutter en sistemas de dos dimensiones en el espacio (suponiendo que no son planos). Diversos casos de flutter en sistemas de tres dimensiones están esquematizados en las figuras 15 a 17.

De este análisis se desprenden los siguientes teoremas, demostrados en el trabajo.

- 1.—Un estímulo único aplicado a un punto único de un sistema pasivo nunca puede producir flutter.
- 2.—La estimulación única de un número indefinido de puntos tampoco puede producir flutter si es simultánea.
- 3.—Para producir flutter son necesarios cuando menos dos estímulos separados por un intervalo apropiado. El segundo estímulo debe aplicarse a una región que incluya el zaguero de una onda. El intervalo entre los dos estímulos debe ser igual al período refractario funcional, más el tiempo de conducción entre las dos regiones estimuladas.
- 4.—En cualquier momento después de la aplicación del último estímulo a un sistema de dos dimensiones, y subsecuente por cuando menos la duración de un período refractario, cualquier frente de onda que existe representa una línea abierta o cerrada. Si está abierta sus extremidades tienen que estar en contacto o bien con los confines geométricos del sistema o bien con un zaguero de onda.
- 5.—Después de la aplicación del último estímulo y cuando ha pasado un período refractario no puede haber aumento en el número de uniones de frentes y zagueros en el sistema.
- 6.—El número de estas uniones puede disminuir.
- 7.—En cualquier sistema sin obstáculos (con conexiones simples) en el cual en cualquier momento ulterior por más de un período refractario al final de la estimulación no hay uniones de frentes con zagueros, el flutter es imposible; o sea, la actividad no recurrirá. El teorema 7 demuestra que no puede haber flutter en un sistema

de dos dimensiones sin obstáculos si no hay uniones permanentes de frentes con zagueros; el teorema 5 muestra que el número de estas uniones no puede aumentar, y el teorema 6 indica que este número puede disminuir. No hemos demostrado que tiene que disminuir; su verdadero es imposible en estos sistemas. Consideramos probable que la misma ley rige en los sistemas de tres dimensiones con conexiones simples. Sugerimos, por lo tanto, que para que haya flutter es preciso que exista un obstáculo de dimensiones apropiadas, o sea de perímetro efectivo mayor que la longitud de onda.

Para formular matemáticamente el problema de la fibrilación, definida como actividad *irregular* permanente, es preciso aplicar métodos estadísticos, como sigue. Las ecuaciones 6 a 13 describen la distribución de Poisson de puntos al azar en el espacio. Para convertir estos puntos en una red de fibras suponemos que cada punto está conectado con todos los que se encuentran dentro de una distancia fija. Las ecuaciones 14 a 45 describen la distribución de la actividad de los puntos en el tiempo. Las ecuaciones 46 a 53 describen a su vez la actividad de la red en el espacio y en el tiempo, suponiendo que cuando cualquier punto entra en actividad los puntos con los cuales hace conexión entrarán también en actividad al cabo de un intervalo de tiempo apropiado. Las ecuaciones 54 a 62 dan finalmente las condiciones estadísticas para que haya fibrilación en el sistema descrito por las ecuaciones anteriores. Estas condiciones requieren que el sistema sea invariante estadísticamente cuando se hacen translaciones en el espacio y en el tiempo, puesto que la actividad de la fibrilación es continua.

En seguida se procede a aplicar las teorías desarrolladas a los datos que existen acerca del flutter y la fibrilación. Se toman como base las observaciones de Lewis (1925). En un experimento hecho en un perro en el cual provocó flutter auricular, concluyó Lewis que el circuito recurrente circulaba alrededor de las dos cavas. El análisis numérico muestra que esta interpretación no concuerda con los datos y que el obstáculo efectivo era probablemente la cava inferior sola. Las tablas 1 y 2 resumen los valores de los factores importantes para la interpretación del flutter y la fibrilación. De estos valores se puede concluir que en los casos humanos tanto el flutter como la fibrilación auriculares se deben

al mismo proceso, con la única diferencia que en el flutter el obstáculo es la cava inferior, en tanto que en la fibrilación es la cava superior. Se discuten las diferencias clínicas entre el flutter y la fibrilación auriculares y se muestra que éstas no se oponen a la interpretación adoptada. Se sugieren las siguientes definiciones:

El flutter consiste en una o varias ondas de actividad en un sistema conductor, con recurrencia cíclica regular de las trayectorias, y por lo tanto con frentes de onda y periodos regulares y definidos.

La fibrilación consiste en la actividad continua con trayectorias que varían al azar en una red de elementos conductores conectados.

De acuerdo con estas definiciones, lo que se llama en clínica fibrilación auricular no es sino un flutter rápido. La fibrilación auricular propiamente dicha puede ser producida experimentalmente en animales, pero no ha sido descrita hasta ahora clínicamente. También es posible producir experimentalmente flutter ventricular, que tampoco ha sido descrito en clínica.

En las consideraciones finales hacemos notar que los dos temas abordados en este estudio no tan sólo tienen relaciones íntimas mutuas, sino que también están relacionados con diversos tipos de actividad del sistema nervioso central. El método de estudio que hemos empleado es por lo tanto aplicable, con pequeñas modificaciones, a otras redes de elementos excitables, tales como las redes nerviosas. La importancia de este tipo de estudio estriba en que saca a luz las implicaciones de las teorías que se analizan y proporciona así una base para su control experimental. Los modelos de flutter que hemos considerado abarcan sólo los casos que nos parecieron más importantes para un estudio inicial. La teoría sugiere observaciones necesarias y experimentos importantes para la solución completa del problema. Por lo que a la fibrilación se refiere, sólo hemos dado el primer paso hacia la construcción de una teoría matemática aplicable — a saber, la formación de un modelo de red de fibras estadísticamente caótico y la formulación de las ecuaciones que rigen la conducción en una red de este tipo. No hemos intentado ir más allá de la formulación matemática del problema estadístico. La aplicación de esta formulación requiere progresos matemáticos considerables y difíciles.

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