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THE IMMEDIATE ELECTROCARDIOGRAPHIC EFFECTS OF CIRCUMSCRIBED MYOCARDIAL INJURIES: AN EXPERIMENTAL STUDY

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THE electric phenomena associated with the heartbeat have been analyzed with skill and thoroughness by a number of investigators versed in the physical laws which govern them.[3-9,13,18,20,21] These investigators have done their work so well that the primary task of those whose interest is engaged by these phenomena is no longer the creation of new hypotheses but rather the construction of a rational and consistent system of electrocardiography on the basis of the principles already established. This will require the testing and retesting by experiment and observation of every prediction that these principles suggest, to the end that the limits within which they apply may be defined.

Unless novelty of method affords a fresh approach, any study of the electrocardiographic consequences of myocardial injury is almost certain to be both derivative and repetitive. The methods of the present investigation represent no

radical departure from those applied by others. If justification for this report is
to be found, it must be sought in more commonplace qualities. It may be that
some of the results recounted here define more boldly the structure of the theory
to which they afford little needed confirmation; others may establish the con-
ditions which must obtain in order that the results predicated by that theory
may evolve; and finally, a report of the initial confusion provoked by certain
findings and resolved by more extended investigation may help others to avoid
like dilemmas. We are deeply indebted to Dr. Frank N. Wilson and Dr. Frank-
lin D. Johnston for counsel and suggestions in the course of our experiments.

Development of the membrane theory, elaboration of the laws governing
the flow of electric currents in volume conductors, and integration of these con-
cepts with the body of electrocardiographic knowledge lie beyond the scope of
this report. An extended survey of these and related problems may be found in
an earlier paper which, in conception and expression, bears the mark of finality.[20]
It is pertinent only to review aspects of earlier studies which are related directly
to the problem of myocardial currents of injury.

Essential to the production of a current of injury is the existence in the
myocardium of a region on one side of which the cell membranes are damaged
more severely than on the other. The side of this zone where the injury is most
severe may be bounded by a layer of muscle which has been destroyed completely.
If dead, this muscle layer has no part in the reactions under consideration and
acts only as a portion of the volume conductor surrounding the injured tissue.
On the other side of this zone of injury are fibers which may be termed normal in
respect to three arbitrarily defined criteria:

1. When the fibers are in the resting phase, a potential difference is main-
tained across the cell membrane. This potential difference is the product of an
orderly orientation of ions disposed in such a way that the external surface of the
membrane is positive relative to the internal surface.

2. On the arrival of the excitatory process, a redistribution of ions occurs
at the cell membrane attended by a profound alteration of the potential dif-
ference between the internal and external aspects of that membrane. This re-
action is called depolarization.

3. Following the response to the excitatory impulse with depolarization of
the cell membrane, a reorientation of ions occurs with the restitution of the
original potential difference across the membrane. This reaction is called re-
polarization.

Characteristic, then, of fibers lying just outside the zone of injury is the
maintenance of a fully polarized membrane during diastole, the occurrence of
depolarization on arrival of the excitatory impulse and the restitution of a state
of full polarization of the cell membrane following response to the excitatory
process.

In what respect does muscle within the zone of injury differ from that which
responds to excitation in a manner considered characteristic of the normal myo-
cardium? Two variations may be defined:

1. The voltage across the membrane of the injured fibers may be zero or
may reach any fraction of its normal value. The degree of polarization may

vary not only in different portions of the region of injury but also over different portions of the membrane of one and the same fiber. The potential difference across the membrane will, in general, be greatest in the fibers or parts of fibers which have been injured least.

2. On arrival of the excitatory impulse the injured tissue may respond, undergoing the changes of ionic distribution characteristic of this reaction. The possibility exists, however, that some of the fibers in the area of injury do not respond or that only a part of the cell membrane becomes depolarized, the remainder retaining across its surface the potential difference which existed during the resting state.

Muscle within the zone of injury exhibits, therefore, in comparison with that within the "normal" region a reduction, variable in degree, of the voltage across the cell membranes during the resting phase. In addition, some of the injured fibers or portions of fibers may display a state of refractoriness to the excitatory impulse. In a diagrammatic way, the difference between the fibers in the "normal" region and those in the injured region relative to the state of polarization of the cell membrane may be represented as in Fig. 1. In the un-
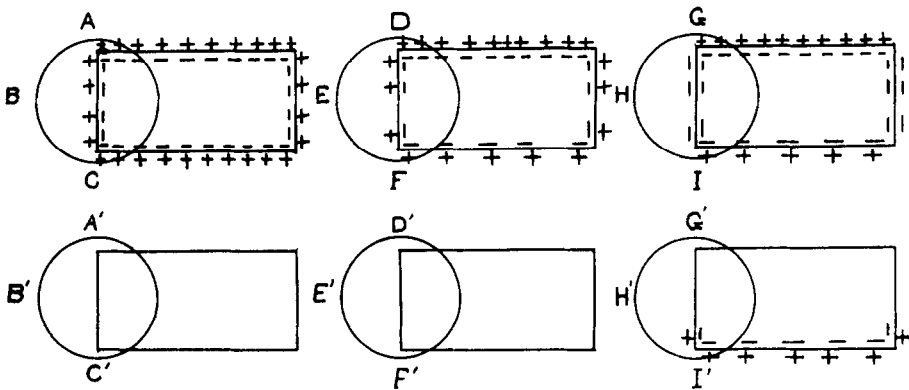

Fig. 1.—Diagrammatic representation of normal and injured cells with respect to the state of polarization existing at the cell membranes during the resting and active stages. For explanation, see text.

injured resting fibers, the voltage across the cell membrane is maximal for cells of this type. The potential difference between the inside and outside of that membrane is the same for all its parts. Hence any possible circuit, ABC, passing through the cell necessarily includes potential drops of which the algebraic sum is zero. This condition which exists in the resting normal fiber obtains also when that fiber has responded to the excitatory process and its membrane is depolarized. Any potential differences maintained at the cell membrane are the same for all its parts and no electromotive force is contributed to any circuit, $A'B'C'$, passing through it.

Only under two circumstances does the normal cell generate an imbalanced electromotive force. It does this as it passes from the resting into the active state, during which time depolarization occurs, and when it passes back from

the active into the resting state during the repolarization process. The normal cell does not contribute to the production of the current of injury.

The source of the current of injury lies within the traumatized tissue. Its existence depends on the first of those two characteristics peculiar to injured fibers. It flows because of variations of voltage across different portions of the cell membranes in the damaged muscle. When traumatized myocardium is included between the terminals of the galvanometer, that part of the current of injury flowing through the instrument is neutralized by a compensating current. Hence, if the current of injury flowed uninterruptedly, its existence would have no effect on the electrocardiogram. The immediate source of the changes in the part of the electrocardiogram inscribed after myocardial excitation is completed must be sought in that second characteristic of traumatized fibers, the peculiarities in their response to the excitatory impulse. If a response occurs in these cells and their membranes are depolarized in greater or lesser degree, then all or part of the current of injury will disappear (Fig. 1, circuits DEF and $D'E'F'$). A corresponding fraction of the neutralizing current introduced in the galvanometer will flow unopposed until repolarization occurs. If, on the other hand, certain fibers or parts of fibers in the traumatized muscle are refractory to the excitatory impulse, the situation represented in Fig. 1, circuits GHI and $G'H'I'$, may develop. Because the more strongly polarized portion of the cell membrane responds while the remainder does not, an electromotive force will be generated directed in a sense opposite to that of the voltage responsible for the current of injury.

The displacement of the RS-T segment commonly occurring in the presence of acute myocardial injury is a manifestation of the flow of current produced by the electromotive force derived from the refractory portion of the cell membrane combined with some portion of the neutralizing current. The exact importance from the quantitative standpoint of each of these sources of current remains unknown. That monophasic curves can be recorded in the absence of significant myocardial injury has been demonstrated by Ashman and Woody.[1] Deflections of this kind developed when the spread of excitation was blocked at a junction between uncooled and cooled tissue, probably as a result of prolongation of the refractory period in the cooled fibers of the heart muscle. Furthermore, Eyster and associates[10] observed that the displacement of the RS-T segment which occurred at the inception of a myocardial injury exceeded the coincident shift in the diastolic base line of the electrocardiogram. This latter alteration is produced by the current of injury prior to its neutralization by the compensating current and is a measure of its intensity.

These observations afford support to the conclusion that the displacement of the RS-T segment following acute myocardial trauma is not dependent solely on a reduction of the intensity of the current of injury when excitation is complete. It is possible that this displacement is unrelated to alterations of the flow of the current of injury, and is a manifestation only of the imbalance of electromotive forces at the cell membranes within the injured region consequent to variations of their response to the excitatory impulse.

Both the direction and the amount of RS-T displacement produced by an acute myocardial injury depend on the spatial orientation of the injured tissue relative to the electrodes of the galvanometer.   If the potential at the indifferent electrode is not influenced significantly by voltages generated within the heart, then the electrocardiogram will afford an uncomplicated record of the changes of potential at the exploring electrode.   If the solid angle subtended at the exploring electrode by the bounding surfaces of the damaged muscle includes only portions of those surfaces on which lie the more severely injured cells, the potential at the electrode will be positive during inscription of the RS-T segment. The potential at this period will be negative if the angle subtended at the exploring electrode includes only the less severely injured cells (Fig. 2).   If the configuration and orientation of the zone of injury is such that the angle subtended at the exploring electrode by the bounding surfaces of the lesion includes cells of both types, then the potential at the electrode will be the algebraic sum of the electric forces which would be produced by each group of cells in the absence of the other.
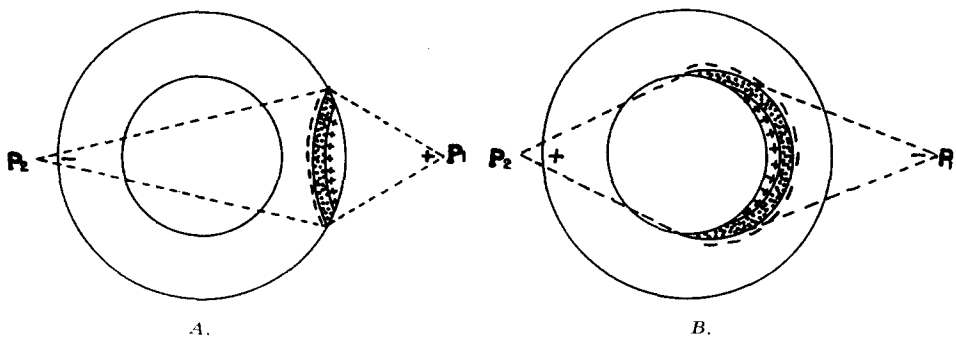

Fig. 2.—A, Diagrammatic representation of the electric field produced at the end of the QRS interval by a region of injured muscle on the epicardial aspect of the ventricular wall.   The field is similar to the one which would be produced if the injured muscle (dotted zone) were polarized in the sense indicated.   (After Wilson, Hill, and Johnston,[18] 1934.)   B represents the field produced by a layer of injured muscle confined to the subendocardial region.

In so brief and dogmatic a statement of the conceptions of the dipole theory as they are related to myocardial injury, accuracy has been sacrificed and ignorance has been veiled.   An attempt has been made to arrive at certain points of departure, points which are fundamental in the realm of theory and points which may be tested experimentally.

EPICARDIAL LESIONS

The electrocardiographic phenomena produced by injuring the heart have been investigated carefully.[6,18,20-22]   Wilson and associates[19] in 1934 burned the subepicardial muscle of the ventricle of turtle hearts.   Electrocardiograms were recorded with the indifferent electrode placed at a point remote from the heart and with the exploring electrode near or in contact with the ventricular surface. They observed that, apart from a difference of magnitude, the variations of po-

tential at a given point on the ventral surface of the beating heart were similar in all respects whether this surface was exposed to air or was in contact with an external conducting medium. When the muscle beneath the exploring electrode was injured, pronounced displacement of the RS-T segment occurred and the ventricular complex often became monophasic. With connections made so that relative negativity of the exploring electrode produced an upward deflection, the direction of the RS-T displacement was downward. When the subepicardial muscle was injured over a wide area and the injury and the exploring electrode were on opposite sides of the heart, the RS-T displacement was upward and was less pronounced. These investigators analyzed the electric field produced by the injury. It is their conception of this field which forms the basis for Fig. 2, A.

During the course of studies designed to ascertain the effects of lesions involving only the subendocardial layers of muscle, occasion arose to repeat certain procedures of these earlier investigations. In several experiments, observations were made on lesions involving the subepicardial muscle of that portion of the ventral surface which was exposed to air. Electrocardiograms in which relative negativity at the exploring electrode was represented by a downward deflection showed pronounced upward displacement of the RS-T segment when the exploring electrode was on the epicardial aspect of the lesion. However, curves derived from an exploring electrode in the ventricular cavity did not show the distinct downward displacement of the RS-T segment that had been anticipated.

In the experiments of Wilson and associates, the potential inside of the ventricular cavity was not recorded. However, when the subepicardial muscle of the dorsal myocardial wall was burned, relative negativity of the epicardium on the ventral wall was recorded during the RS-T period. If the conductivity of the body tissues is relatively uniform, the electric field corresponding to the forces arising within the injured muscle should be approximately symmetric with respect to the bounding surfaces of that damaged tissue. This being the case, one would expect that in the presence of an acute lesion of the dorsal epicardium, negativity of the ventral epicardium would be attended by negativity of the ventricular cavity (Fig. 2, A).

An obvious discrepancy existed between the preliminary observations of the present investigation and the results predicated on the basis of the conceptions of Wilson and associates. The experiment of the earlier investigation, therefore, was repeated with the intent of recording simultaneously the potential changes in the ventricular cavity and those at the epicardial surface.

Method. Experiments were performed on turtles (*Graptemys geographica*). The animal was pithed, the heart was exposed by removing the plastron and the preparation was placed with the dorsal side down in a large shallow dish filled with Ringer's solution. A Sanborn Tribeam electrocardiograph was used to obtain two simultaneous records on the same strip of paper. One terminal of each circuit of the instrument was attached to a copper disk 5 cm. in diameter. This electrode was placed in the Ringer's solution at a point as remote as possible from the heart. The other terminal of each circuit was attached to one of the

exploring electrodes. When points on the surface of the heart were to be explored, the electrode consisted of a small glass tube stoppered with salted kaolin and filled with 20 per cent copper sulfate solution into which was thrust a coil of copper wire. Contact with the heart was made by a wick of cotton embedded in the kaolin plug and enclosed in a small rubber tube so that it was insulated to within 1 or 2 mm. of its exposed end. When the potentials within the ventricular cavity were to be recorded, the electrode consisted of a filiform catheter with a core of copper wire. The insulation of the catheter covered all but the tip of the copper wire. The lesions produced in the subepicardial muscle were burns made with a high frequency electrocoagulation unit (Bovie).

Experiment 1.—The turtle was prepared in the usual manner. The filiform electrode was introduced into the ventricular cavity. This was accomplished by making a small incision in the lateral subdivision of the right aorta. The tip of the electrode was slipped into the ventricular cavity and a ligature encircling the artery in which lay the shaft of the electrode was drawn tight. The soft-tipped electrode was placed on the part of the ventral surface exposed to air and simultaneous records were made of the ventricular cavity and epicardial potentials. The epicardial electrode was then removed temporarily. With the electrocoagulation unit, a burn was made on the dorsum of the ventricle. This lesion covered the left half of the basal portion of the dorsal epicardial surface. The soft-tipped electrode was replaced on the epicardium and another set of electrocardiograms was recorded immediately. Subsequent electrocardiograms were made five minutes, twenty-five minutes, and forty minutes after production of the lesion.

The electrocardiograms recorded in Experiment 1 are reproduced in Fig. 3. Downward displacement of the RS-T segment is present in the curves obtained after production of the lesion with the exploring electrode in the ventricular cavity and also in those taken with this electrode on the portion of the ventricular surface which was exposed to air. The amount of displacement is greatest in records obtained immediately after the lesion was produced. Within twenty-five minutes the RS-T segment had returned almost to the isoelectric line in both the epicardial and the cavity leads.

These results are in complete accord with those reported by Wilson and associates and with the conception of the electric field which they advanced. But this confirmation of their observations defined with even greater precision the problem which remained unsolved. Why should the potential within the ventricular cavity be made negative during the inscription of the RS-T segment by an acute lesion affecting the dorsal subepicardial muscle, but remain unchanged when a similar lesion of the ventral subepicardial muscle was produced? The major difference between the two lesions did not appear to be an intrinsic one. In each instance the orientation of the injured and the uninjured muscle relative to the exploring electrode in the ventricular cavity was the same. But a major difference did exist in the environment of the lesion. The injured area on the dorsal surface was completely surrounded by a conducting medium

whereas that on the ventral surface was bounded on one side by air. Determination of the effect of eliminating this difference afforded an attractive approach to the problem under investigation.
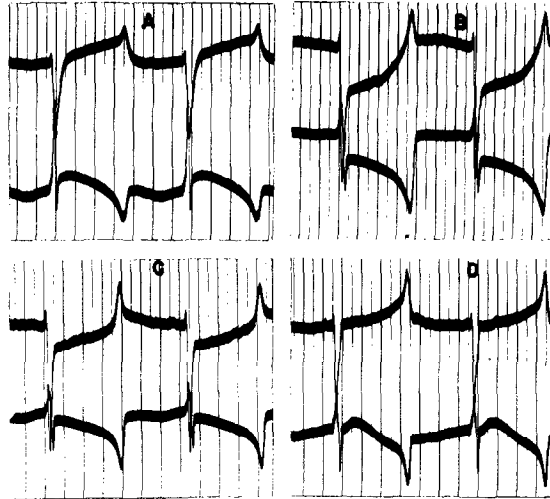

Fig. 3.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on the portion of the ventricular wall exposed to air. Exact sensitivity is uncertain but it approximates 3 millivolts per centimeter on the ordinate scale. *A*, Control; *B*, after burning dorsal surface of the ventricle; *C*, five minutes after burn; and *D*, forty minutes after burn.

Experiment 2.—The turtle was prepared in exactly the same manner as in Experiment 1. Electrocardiograms were taken with the exploring electrode of one circuit in the ventricular cavity and that of the other on the portion of the ventral surface exposed to air. A circular pad of cotton, approximately 3 mm. thick and large enough to cover the ventral surface of the heart and extend into the surrounding medium, was soaked in Ringer's solution and laid over the heart. The soft-tipped electrode was placed in contact with the surface of this pad at a site as near as possible to its previous point of contact with the ventricular surface. Another set of electrocardiograms was made. When the pad lay on the heart, the size of the deflections of the ventricular complex was reduced to approximately a fifth the amplitude of the deflections obtained when the exploring electrode rested on the exposed surface of the heart. In order to maintain approximate constancy of the size of the deflections recorded under the two sets of conditions, the sensitivity of the circuit was increased fivefold when curves were taken with the pad covering the heart.

The pad was then removed and with the electrocoagulation unit a burn was made on the exposed portion of the ventral surface of the heart. Thereafter, electrocardiograms were recorded in the same manner and in the same order as the curves taken before the burn. Additional sets of electrocardiograms were made ten minutes, twenty minutes, and fifty minutes later.

The electrocardiograms recorded in Experiment 2 are reproduced in Fig. 4. Examination of these curves reveals that upward displacement of the RS-T

segment is present in those derived from the epicardial electrode after production of the lesion whether the ventral surface was or was not immersed in the conducting medium.   On the other hand, downward displacement of the RS-T segment is present in the leads from the electrode in the ventricular cavity only when these were taken while the ventral surface of the heart was covered by the pad soaked in Ringer's solution.
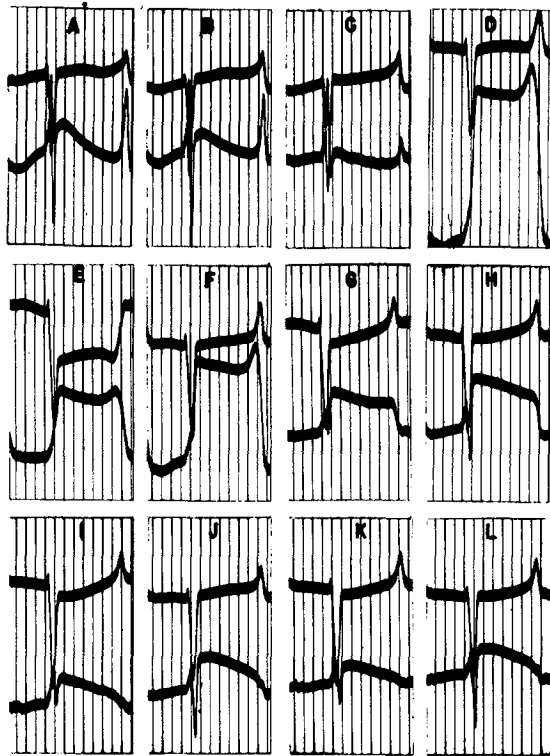

Fig. 4.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on or adjacent to the epicardial aspect of the ventral wall of the heart.   A, Control prior to immersing the dorsal surface of the heart in Ringer's solution; B, control after immersion of the dorsal surface; C, control with ventral surface of the heart covered by a pad soaked in Ringer's solution; D, after burning ventral surface of heart, lesion and ventral wall of heart exposed to air; E, immediately after D, ventral surface of heart covered with a pad soaked in Ringer's solution; F, immediately after E, pad removed from ventral surface of heart; G, ten minutes after burn, pad over heart; H, immediately after G, pad removed from surface of heart; I, twenty mintues after burn, pad over heart; J, immediately after I, pad removed from surface of heart; K, fifty minutes after burn, pad over heart; and L, immediately after K, pad removed from surface of heart.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except when ventral surface of heart was covered by pad, then 0.5 millivolt per centimeter.

It has been observed by others that the distribution of electric forces arising within a region of injury is dependent on environmental factors.   Craib[4] found that the potential at the surface of a partially immersed strip of injured skeletal muscle varied with the position of the injured tissue relative to the conducting medium.   Eyster and associates[10] in 1938 commented on the minor changes in the potential of the medium surrounding an isolated quiescent tortoise heart

following injury if the heart were not immersed or if the plane of injury corresponded to that of the field.

It is questionable how much will be gained from an effort to conceive the exact origin and distribution of potential variations within an electric field under the circumstances described in Experiment 2. An analysis will be presented only after according recognition to the fact that it is an explanation designed to fit a limited set of circumstances.

Suppose that a sheet of heart muscle could be isolated in an untraumatized state and then injured in such a way that the cells on one side of the sheet were damaged more severely than those on the other side. A gradient of injury would then exist across the muscle, and current* would flow from the least injured cells on one side to the most injured cells on the other. Within this isolated strip of muscle there must be complete circuits containing the algebraic sum of all the potential drops between the least injured side of the least injured fibers and the most injured side of the most injured fibers. If one electrode were placed on one surface of the sheet and the second electrode on the other surface, the potential difference between the two sides could be measured. Immersion of the muscle in a conducting medium would not be essential to any of these developments.

Suppose the surface of this muscle on which lay only the least injured aspects of the least injured cells was placed in contact with a conducting medium of large extent. All points on this surface would be at the same potential and hence no current would flow between them.

Finally, suppose that both surfaces of the injured muscle were immersed in the conducting medium. Innumerable circuits would now exist, running from the least injured fibers through the conducting medium and back into the muscle sheet on the side where lay the most injured cells.

Thus, if an acutely injured muscle in which a gradient of injury exists is to create an electric field in a conducting medium of large extent, cells lying at different levels on the gradient of injury must make contact with the medium.

Under the circumstances existing when the electrocardiograms reproduced in Fig. 4, *D* were recorded, only the least injured fibers made contact with the medium. Hence, no significant amount of current flowed from the injured tissue into the conducting medium. When one electrode of the galvanometer was connected to the most severely injured cells and the other terminal to the reference electrode in the medium, a circuit was completed and the potential difference across the traumatized tissue was recorded. However, only after the more severely injured fibers were immersed in the medium did any appreciable fraction of the current of injury flow through the ventricular cavity and thence into the circuit of the galvanometer to which the electrode in the cavity was connected.

This analysis appears to afford a reasonably satisfactory explanation for the developments in Experiment 2. It does not lend itself easily to the explanation of even minor alterations in the conditions which existed in that experi-

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*In this description, the term "current of injury" is used in the broadest sense. The exact source of the current responsible for RS-T displacement in the electrocardiogram is immaterial to the argument.

ment. In order to arrive at a method more generally applicable, it is necessary to adopt a procedure commonly utilized in computing electric fields in heterogeneous media.[15] This approach, known as the method of images, may be applied in the analysis of problems in which two media are separated by a plane boundary. In Fig. 5, part 1, let the line AB represent a plane surface
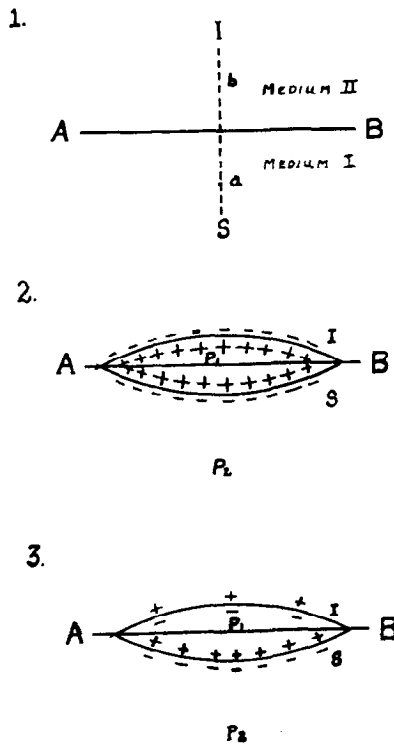

Fig. 5.—The method of images as it applies to the solution of the problem presented by the results of Experiment 2.   In all three diagrams, the line AB represents a plane which forms the boundary between two mediums of different conductivities. S represents a source of electricity in Medium I and I represents its image forces in Medium II.   For further discussion, see text.

which constitutes the boundary between two media.   Let us suppose that there is a source S of electricity in Medium I at a distance a from the plane surface. Let I in the second medium be the image of S, and let k_1 be the resistance of Medium I and k_2 the resistance of Medium II.   It can be demonstrated that the flow of current at any point in the first medium is the same as would be produced by the source S, together with a source $\dfrac{k_2 - k_1}{k_1 + k_2} S$ placed at I, if the first medium were infinite in all directions.   The current at a point in the second medium is the same as would be produced by a source $\dfrac{2k_2 S}{k_1 + k_2}$ placed at S if the second medium were infinite in all directions.

If the second medium is a perfect insulator, then k_2 is equal to infinity and by the first equation the image at I would be equal to the source at S and of the same sign.

In Experiment 2 the source S in the first medium was represented by the injured layer of muscle, one aspect of which was bounded by a volume conductor of large extent and the other by a nearly perfect insulator, air. The effect of this environmental situation on the distribution of electric forces produced by the lesion may be estimated by applying the method of images. Because the medium on one side of the boundary was a nearly perfect insulator, the images at I and the forces at S would be of the same sign and of equal magnitude. In Fig. 5, part 2, the forces produced by the lesion are represented diagrammatically by a polarized surface S, seen in section. The image forces I are indicated in the same way. It will be seen that the polarized surface S and its image I form a closed space. The positive poles of the elementary voltages are inside this space, the negative poles outside.

At any point P_1 on the epicardial surface of the lesion, the solid angle subtended by the polarized surface S and that subtended by its image I have the same sign and equal magnitude. At any point P_2 which lies outside the injured muscle, the two angles are opposite in sign and equal in magnitude. The potential at any point due to an injured region is roughly proportional to the solid angle which the bounding surfaces of the lesion subtend at that point. It is clear, therefore, that the potential at the epicardial surface of the lesion under consideration would be positive and double what it would be if the medium surrounding the injured muscle were infinite in all directions. The potential at any point outside the zone of injury, on the other hand, would not be influenced significantly by electric forces produced within the damaged muscle.

When the surface of the heart was covered by a pad soaked in Ringer's solution, an environmental situation was created in which the injured layer of muscle was bounded on its epicardial aspect by a medium of higher conductivity than that which lay on the opposite side of the zone of injury. Under such circumstances, by equation 1, the images at I and the forces at S would be of opposite sign and of a magnitude determined by the relative conductivity of the mediums and their extent (Fig. 5, part 3). As a result, the degree of positivity at P_1 would be reduced greatly and significant negativity would develop at P_2.

An Experiment With Muscle Juice (Experiment 3).—This experiment does not constitute an integral component of the series. It is described because, to us, the results seemed particularly interesting.

The sequence of changes in myocardial injury probably includes (1) an increase of the permeability of the cell membranes; (2) a redistribution of the ions on either side of the cell membranes, and (3) a diminution of the voltage across these membranes, the degree of which is proportional to the severity of the injury.

There is reason to believe that, in these changes which occur after injury, potassium ions are involved. A consideration of the intimate nature of the part which these ions play would extend beyond the authors' knowledge. Two well-

established facts may be cited: (1) The concentration of potassium ions is much higher in intracellular than in extracellular fluids.   (2) If a solution containing potassium ions in relatively low concentration (0.1 molar potassium chloride) is applied to the surface of the heart and the exploring electrode is placed on the same area, ventricular complexes of a monophasic type are recorded.

If injuring the cell increases the permeability of its membrane, it undoubtedly leads to diffusion of potassium ions from the intracellular to the extracellular fluid.   These potassium ions may be expected to exert on the less severely injured and uninjured muscle an effect similar to that produced by a solution of 0.1 molar potassium chloride.   As a minor and perhaps repetitious study of this phenomenon, the following experiment was undertaken.

A turtle was prepared in the manner already described, and control electrocardiograms were taken in the usual way.   A small piece of skeletal muscle from the pelvic girdle of the same turtle was chopped into fine pieces and a few drops of juice were squeezed from the macerated tissue onto a piece of dry cotton 8 mm. in diameter.   This piece of cotton was laid on the air-exposed portion of the ventricle of the beating heart.   The wick of the soft-tipped electrode was placed in contact with the piece of cotton.   Two sets of tracings were made.   In a second piece of cotton, 3 cm. in diameter, a hole approximately 8 mm. in diameter was cut.   This pad was soaked in Ringer's solution and placed on the surface of the heart in such a way that the borders of the hole made con-
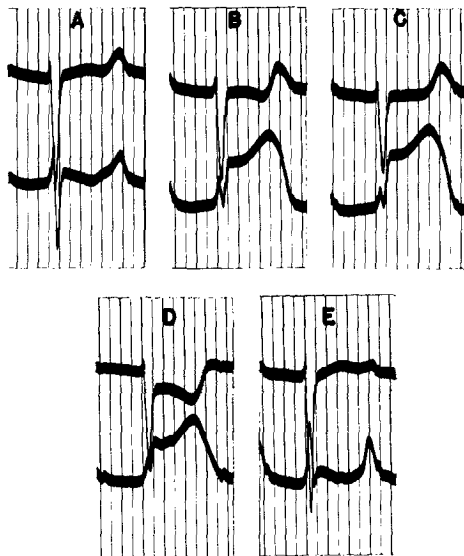

Fig. 6.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the exploring electrode on or adjacent to the ventral aspect of the heart wall.   A, Control; epicardial electrode resting on surface of heart; B, after placing small pad soaked in muscle juice between the epicardial electrode and the ventral surface of the heart; C, one minute after B, conditions unchanged; D, two minutes after B, air-exposed portion of ventral surface covered by a cotton pad soaked in Ringer's solution; and E, after both pads had been removed and surface had been rinsed repeatedly with Ringer's solution.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except in D, where a scale of 0.8 millivolt per centimeter existed.

tact with the margins of the pad soaked in cellular juice. Another set of electrocardiograms was recorded. Both cotton pads were removed and the surface of the heart was rinsed repeatedly with Ringer's solution. A final set of electrocardiograms was recorded.

The electrocardiograms recorded in Experiment 3 are reproduced in Fig. 6. In the curves derived from the electrode placed in contact with the small cotton pledget soaked in muscle juice, upward displacement of the RS-T segment was always present. Downward displacement of the segment occurred in leads from the electrode in the ventricular cavity only when the exposed surface of the heart was covered with a larger pad soaked in Ringer's solution. These findings are similar to those obtained when the subepicardial muscle at a comparable site was burned.

The results of this experiment indicate that in the fluid which can be squeezed from severely damaged muscle cells of a turtle there is a substance which, when applied to the beating heart of the same animal, will produce changes in its action currents like those which follow injury inflicted on the myocardial cells by mechanical or thermal means.

ENDOCARDIAL AND SUBENDOCARDIAL LESIONS

Large myocardial infarcts which involve only the subendocardial muscle occur very rarely in man and lesions of this kind are difficult to produce in animals. Hence, the electrocardiographic changes related to acute injuries in the subendocardial region have remained problematic. It seems to be generally agreed that such lesions produce depression of the RS-T segment in the standard limb leads and often in the precordial leads as well. Wolferth and associates[22] recently have proposed certain generalizations in explanation of this phenomenon. They divided RS-T displacements into primary and secondary types, defined as follows: displacement of the primary type results from physicochemical disturbances in the fibers directly beneath the exploring electrode; displacement of the secondary type is recorded over the surface of uninvolved muscle as a result of changes of potential produced at that surface by forces generated in injured muscle elsewhere in the heart. In the language of Lewis and Rothschild, the first is intrinsic and the second extrinsic in origin. In the experimental results reported by Wolferth and associates,[22] primary RS-T displacement, with one possible exception, was always positive and secondary displacement always negative. Since endocardial lesions consistently bear a secondary or extrinsic relation to an electrode placed on the epicardial surface of the heart, the resulting displacement of the RS-T segment is downward.

Between the predictions based on these generalizations and those derived from the concepts of the dipole theory outlined, there is seldom a significant difference. However, on the basis of the dipole theory, an endocardial lesion may produce upward displacement of the RS-T segment in a lead from an electrode placed on an uninjured epicardial surface. This possibility is illustrated in Fig. 2, B, in which a subendocardial lesion is represented. An electrode placed at P_1 lies in a portion of the cardiac field which should be at a negative potential

at the end of the QRS interval.   Under the circumstances postulated, an electrode placed at P_5 on the epicardial wall opposite the lesion would lie in the positive portion of the field and in a lead from this point the RS-T segment would be displaced upward.

Consideration of these relationships identifies one requirement which should be satisfied in an investigation of the electrocardiographic changes produced by acute subendocardial injuries.   Curves should be recorded not only from points on the epicardium overlying the injured muscle but also from the epicardial surface of uninvolved parts of the ventricular walls.

The difficulties encountered in attempts to produce endocardial lesions justify extended consideration of other aspects of this problem.   If the effects of damage to tne ...ndocardial and subendocardial tissue on the potential at an electrode outside the heart are to be ascertained, then the lesion must be satisfactory in certain respects.

1.   It should be large enough and severe enough to generate an electric field of measureable intensity in the conducting medium surrounding the heart.

2.   The boundaries of the lesion should meet the following specifications: first, the zone of damage should be thin, so that a layer of uninjured cells lies between the traumatized tissue and the epicardium; and second, the injured cells should be oriented in such a way that all the electric forces produced by them have a similar effec on the potential of an electrode placed on one side of the lesion.

The production of a lesion which meets these requirements is not accomplished easily nor frequently.   The very architecture of the heart renders difficult their fulfillment.   The epicardium presents a relatively broad smooth surface readily accessible to traumatizing procedures.   The area of the endocardial surface is much smaller, its configuration is irregular and its approach is difficult. If a lesion is to be large and still meet the demand that all its parts contribute forces of like sign to the electric field, then it must involve most of the endocardial aspect of either the ventral or the dorsal wall of the ventricle without extending into the endocardial tissues on the opposite side of the ventricular cavity.   Experience soon reveals that in the production of so large a lesion on one wall, injury to the other wall is likely to occur, particularly near the apex.

Limitation of the thickness of the traumatized zone can be achieved more satisfactorily by the electrocoagulation technique than by any other method which we have devised.   Yet an unusually prolonged or intense flow of the traumatizing current may result in extension of the injury to the epicardial tissues.

The two experiments described here were selected from a series of thirty-five.   In these two instances among all the experiments the electrocardiographic changes were greatest, but in them also the criteria defined in the preceding paragraphs were most nearly fulfilled.

Method.—Turtles were used.   The earlier experiments were undertaken on small specimens (*Graptemys geographica*) measuring 6 to 8 inches (15 to 20 cm.) in diameter.   In such animals the heart is small and the production of a well-localized subendocardial lesion was found to be exceedingly difficult.   Large

snapping turtles (*Chelydra serpentina*) were then secured. Each of these animals measured 12 to 14 inches (30 to 36 cm.) in diameter and weighed approximately 10 pounds (4.5 kilograms). Following an initial series of experiments on twenty small turtles, a second series was carried out on fifteen of the larger animals. An endocardial lesion of some type was produced in all except two of these turtles.

The myocardium was injured by electrocoagulation. The method was identical with that employed in damaging the subepicardial tissues. In the experiments on small turtles, the filiform electrode previously described was introduced into the ventricular cavity by way of the lateral branch of the right aorta. This electrode was used both for recording potentials in the ventricular cavity and for applying the electrocoagulating current. In the experiments on the larger turtles, an enameled copper wire 1.2 mm. thick with a rounded tip was substituted for the filiform electrode.

The large turtles were not placed in a dish filled with Ringer's solution. In the experiments performed on them, the indifferent electrode was a copper disk, 2 cm. in diameter, placed on the subcutaneous tissues of the left hind leg.

Experiment 4.—This was an experiment on a small turtle. The animal was prepared in the usual manner. Two leads were taken simultaneously; one recorded the potential of the ventricular cavity, and the other, the potential at a point on the central portion of the exposed ventricular surface. With the filiform electrode attached to the electrocoagulation unit, an endocardial burn was made. Electrocardiograms were made in rapid succession under conditions noted in the legend of Fig. 7.

Post-mortem examination of the heart revealed a lesion involving the entire endocardial aspect of that portion of the ventral wall lying to the left of the band of muscle which represents the primordial septum. The apparent thickness of this lesion was 1 mm. or less.

Electrocardiograms recorded in Experiment 4 are reproduced in Fig. 7. The results of this experiment are presented for two reasons. The first of these is that the curves obtained exhibit displacement of the RS-T segment induced by extensive injury of subendocardial tissues of the ventral wall of the heart. The contrast between the electric field on one side and that on the opposite side of the injured region is illustrated. The RS-T displacement in the leads from the epicardial electrode is downward, whereas, in those from the cavity electrode, the RS-T displacement is upward. These findings are consistent with the postulates of the dipole theory.

The second reason for presenting these data is that they illustrate a problem which arose frequently in this series of experiments; namely, the effect on the form of the electrocardiogram of changes in the electrical properties of the immediate environment of the heart. In Experiment 2, an example of this effect as it occurs in epicardial lesions was presented and discussed at length. Review of the electrocardiograms reproduced in Fig. 7 indicated to the observers that in the presence of endocardial injury an abundance of free fluid on the surface of the heart has an effect similar to that produced by covering the air-exposed

portion of the surface with a thin cotton pad soaked in Ringer's solution. Either of these environmental factors could be effective in one or both of two ways: either by altering the distribution of cardiac currents or by changing the nature of the contact between the soft-tipped electrode and the ventricular surface. When all free fluid is removed from the air-exposed portion of the ventral surface of the heart and from the cotton wick at the tip of the exploring electrode, the area of contact between the epicardial surface and the wick is small and is subject to variations during different portions of the cardiac cycle. A relatively constant contact can be effected only by pressing the wick of the electrode firmly
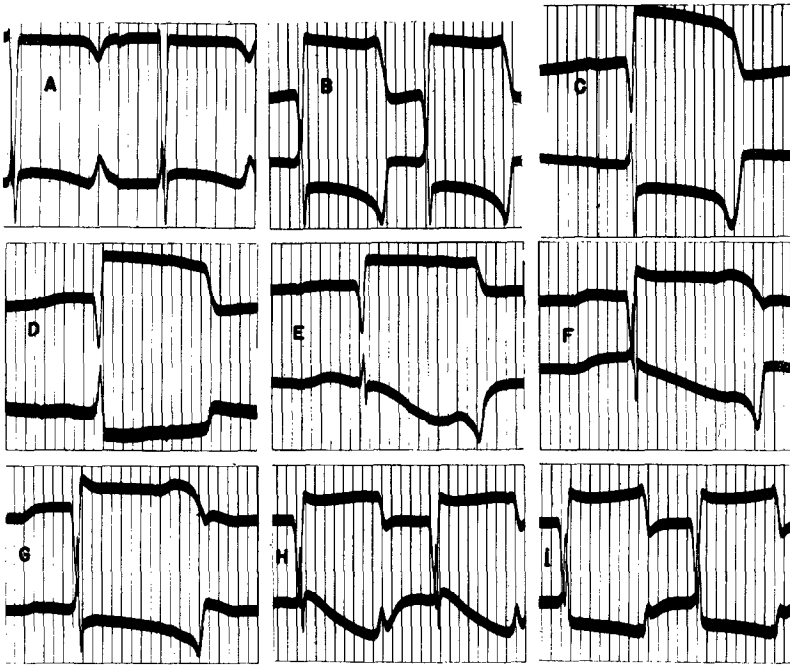

Fig. 7.— Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart. *A*, Control; *B*, after making a burn on the endocardial aspect of the ventral wall of the heart, ventral surface of heart partially immersed in Ringer's solution; *C*, immediately after *B*, 2:1 auriculo-ventricular block had developed and persisted until curves reproduced in *H* were recorded; *D*, air-exposed portion of ventral surface of heart covered by a pad soaked in Ringer's solution; *E*, after removing all fluid from ventral surface of heart; *F*, five minutes after burn, no free fluid on ventral surface of heart; *G*, immediately after *F*, pad covering heart; *H*, ten minutes after burn, all free fluid removed; and *I*, immediately after *H*, pad covering ventral surface of heart.

Sensitivity of galvanometer circuit was increased approximately fivefold in recording curves from epicardial electrode when pad soaked in Ringer's solution covered ventral surface of heart.

against the epicardium. However, this procedure may itself injure the subepicardial muscle and produce changes in the form of the electrocardiogram. Covering the heart with a pad soaked in Ringer's solution or immersing it in free fluid permits the establishment of a constant contact between the heart and the exploring electrode.

It is difficult to ascertain whether the changes in the electrocardiogram which attended immersion of the heart in Experiment 4 were related primarily to alterations of the electric field produced by the injured muscle or to the establishment of a better contact between the electrode wick and the cardiac surface. These changes were not striking in leads from the electrode within the ventricular cavity. In such curves the upward RS-T displacement was slightly greater when a pad covered the heart than it was when the ventricular surface was exposed to air (Fig. 7, *H* and *I*). With the same variation in the environmental circumstances a greater change occurred in leads from an electrode placed at a point outside the heart. When the ventral surface of the heart was bounded by air, the junction of the S wave and the S-T segment was above the isoelectric line in an epicardial lead from the exposed region. In a similar lead taken with a pad covering the heart, this junction was on a level below the isoelectric line near the point occupied by the spike of the S wave in the preceding curves.

It appears probable that most of these changes in the ventricular complexes of leads from the epicardium were due to variation in the contact made by the electrode with the heart. The conclusion is not justified, however, that all of them certainly were related to this factor. If an alteration of the electric field produced by the lesion did occur, the origin of the change may have been similar to that postulated in the discussion of a similar situation which obtained in Experiment 2.

Experiment 5.—This experiment was performed on a large turtle. The animal was prepared in the usual manner. In order to obtain electrocardiograms from the dorsal epicardial surface, a piece of enameled copper wire was used. The distal end of the wire was rolled into a coil 8 mm. in diameter, from one side of which the enamel was removed. The surface of the coil was flat and smooth. The coil was placed in the pericardial sac, resting lightly against the epicardium of the dorsal ventricular wall near the base of the heart. The shaft of this electrode was sutured firmly to the adjacent tissues. Electrocardiograms were taken by leading from electrodes placed on the dorsal and ventral epicardial surfaces and from an electrode in the ventricular cavity. A second set of curves was recorded after the ventral surface of the heart was covered with the pad soaked in Ringer's solution. A lesion was produced with the electrocoagulation unit. Thereafter, electrocardiograms were recorded in the manner and at the times designated in the legend of Fig. 8. Post-mortem examination revealed that the lesion involved the endocardial aspect of the entire ventral wall of the ventricle. Even the ridge of muscle which represents the primordial septum was burned. The apparent depth of the lesion was 1 mm.

The electrocardiograms recorded in Experiment 5 are reproduced in Fig. 8. After the subendocardial injury was produced, the changes in the QRS complexes of the leads from the dorsal and those of the leads from the ventral surface were opposite in character. Prior to the production of the injury, the QRS deflections had essentially the same form in leads of both kinds. A broad R wave was followed by an S wave of approximately equal amplitude. After the

injury, the complexes of the leads from the ventral epicardium consisted of a small Q wave followed by a broad R wave. The S wave had disappeared. The complexes recorded from the dorsal epicardial surface also underwent alterations in form. The R wave became narrower and the S wave broader and deeper.
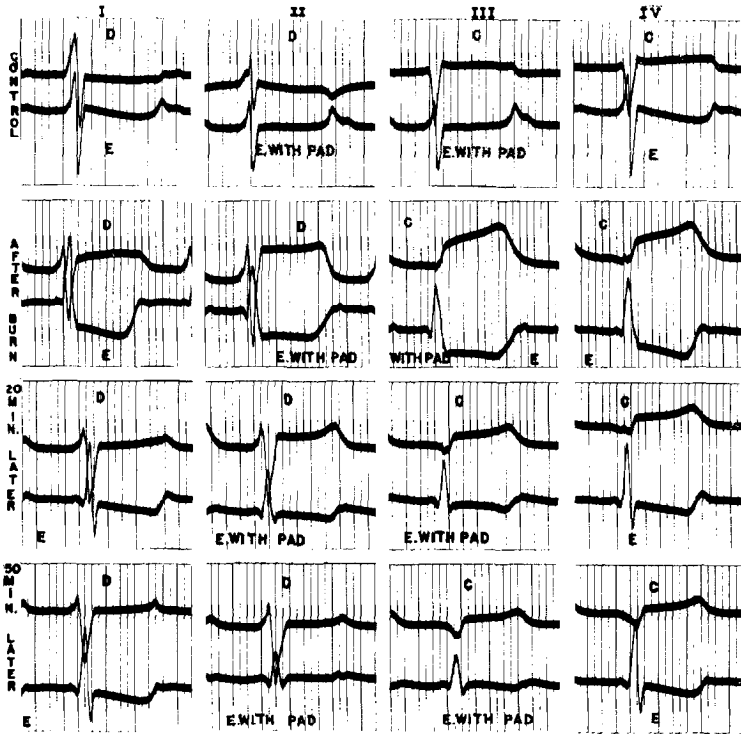

Fig. 8.— Upper curves in Columns I and II were recorded with the exploring electrode on or adjacent to the epicardial aspect of the dorsal ventricular wall (D); upper curves in Columns III and IV were recorded with the exploring electrode in the ventricular cavity (C). The lower curves were recorded with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart (E). In Columns I and IV, the ventral surface of the heart was exposed to the air; in Columns II and III the ventral surface was covered with a pad soaked in Ringer's solution. Records were made at times indicated along left hand margin of figure.

Ordinate scale: in curves derived from ventricular cavity, 5 millivolts per centimeter; in curves derived from dorsal surface and from exposed ventral surface, 3 millivolts per centimeter; in curves derived from surface of pad covering ventral wall of heart, 0.5 millivolt per centimeter.

These electrocardiograms suggest delayed activation of the ventral wall of the heart. Changes in the QRS complexes similar in character and magnitude to those recorded in this instance were not encountered in any other experiment of this series. Their occurrence may have been due to the large extent of the endocardial lesion or to the involvement of some portion of the heart wall essential to rapid propagation of the wave of excitation.

The RS-T displacements recorded in Experiment 5 are readily perceptible. Subsequent to the production of the endocardial lesion, upward displacement was present in leads from the ventricular cavity and in leads from the dorsal

epicardium. When the exploring electrode was on the ventral epicardium and, therefore, on the opposite side of the injured layer, the displacement was downward.

These results afford evidence that the direction of the RS-T displacement produced by injury to the endocardial and subendocardial tissues depends primarily on the orientation of the lesion relative to the exploring electrode. The presence of uninjured muscle between the electrode and the lesion is significant in determining the direction of the displacement only when the uninjured myocardium underlying the exploring electrode constitutes one boundary of the injured region. In this case the electrode lies on that side of the lesion where the injury to the muscle is least. From an electrode so located, downward displacement of the RS-T segment will be an invariable derivative.

The results of Experiment 5 suggest also that upward displacement of the RS-T segment may be recorded in the absence of significant injury to the muscle cells underlying the electrode. For the appearance of upward RS-T displacement, it is necessary and sufficient that the exploring electrode face the side of the lesion on which the injury was most severe. In lesions produced by traumatizing the subepicardial layers, the region of most intense injury is also the most superficial. From an electrode placed on the surface of such a lesion, curves will be derived in which the RS-T displacement is upward. But when a lesion is produced by traumatizing the endocardial and subendocardial layers of muscle, the most severely injured cells are on that aspect of the lesion which faces the ventricular cavity. An electrode placed on the epicardial aspect of the opposite ventricular wall may lie within the electric field of that lesion at a point where the potential at the end of the QRS interval is positive enough to produce significant upward displacement of the RS-T segment.

If, in the electrocardiograms commonly recorded, subendocardial injury is attended more frequently by depression than by elevation of the RS-T segment, the explanation must be sought in the orientation of the injured muscle relative to the leads used. Such an explanation may be derived from concepts compatible with the dipole theory.

In an earlier investigation by one of us, in association with Barnes and Essex,[17] changes in the electrocardiogram induced by injuries confined to the endocardial and subendocardial tissues were recorded in a series of experiments on dogs. Extensive lesions were produced by mechanical means. The leads used were from an exploring electrode on the thoracic wall at a point overlying the injured region to an indifferent electrode on the right foreleg. Displacement of the RS-T segment was neither a consistent nor an impressive feature of the records obtained. The explanation of its absence remained obscure. In the present series of experiments, the production in dogs of lesions restricted to the endocardial tissues was not undertaken. We feel, however, that a brief discussion of this unsolved problem of the earlier investigation and its relation to the findings just reviewed is desirable.

The electric manifestations of cellular injury appear to be similar in turtles and dogs. In contrast, the spread of the wave of excitation is significantly different in the two species. In the heart of the turtle, no system of tissue special-

ized for the conduction of this wave has been identified. Its spread occurs ordinarily in the direction of a line pointing from the left basal to the right apical region of the ventricle.[11,13,16]   Epicardial points are activated later than the endocardial points immediately underlying them. In the canine heart, a ventricular system for conducting the excitatory impulse is well developed. The entire endocardial aspect of the ventricular walls probably is activated almost simultaneously. The major portion of the QRS complex is formed while the wave of excitation is spreading across the wall from within outward. However, it appears unlikely that the course taken by this wave could influence portions of the electrocardiogram written after the impulse has completed its spread to all parts of the ventricular muscle. If valid, this principle would apply whether the heart under consideration was that of a dog or that of a turtle. Therefore, the effects of endocardial and subendocardial injury on the level of the RS-T junction and segment should not depend on the mode of propagation of the wave of excitation.

In all probability, the failure in the earlier experiments on dogs to record results similar to those subsequently obtained in turtles was dependent on some factor or factors other than the course pursued by the excitatory impulse. Two of these factors may be mentioned.

In the experiments on dogs, no effort was made to produce lesions so located that all of the resulting electric forces would have essentially the same orientation. In many of these experiments, the area of injury extended over the subendocardial muscle of the entire apical portion of the left ventricle including the septum. Under these circumstances the potential changes at a point on the thoracic wall overlying the lesion would represent the algebraic sum of electric forces of one kind from the injured region on one wall of the left ventricle and forces of inverse polarity from the injured region on the opposite wall. Because the traumatized muscle on the ventral side was nearer the exploring electrode than that on the dorsal side of the heart, the electric forces derived from the former perhaps should have been somewhat stronger than those derived from the latter. Without more detailed knowledge than is available, however, it is difficult to estimate what the net effect of combining the opposing forces might be.

It may also be pointed out that the lesions produced in the earlier experiments were not only large; they were also deep. In some places they extended through as much as a third of the thickness of the left ventricular wall. In the following section, the possible consequences of this circumstance on electrocardiograms derived by direct or indirect leads will be considered.

TRANSMURAL LESIONS

Early in the course of our experiments an attempt was made to conceive the sequence of electrocardiographic changes which would occur as a lesion was extended from the endocardium through the ventricular wall toward an electrode on the opposite epicardial surface. The diagram in Fig. 9 represents the concept reached. If the lesion initially involved only region a, and then was extended gradually to the size of region c, the negativity at the exploring electrode should

increase as the boundary of the injured zone advanced toward the surface. If, in the acute stage of lesion c, another lesion was produced on the epicardial side at d, the resulting positivity at the electrode due to the second lesion should cancel the negativity due to the first. The amount of RS-T displacement under these final circumstances should be slight. An attempt was made to perform an experiment in which such an extending lesion was created.
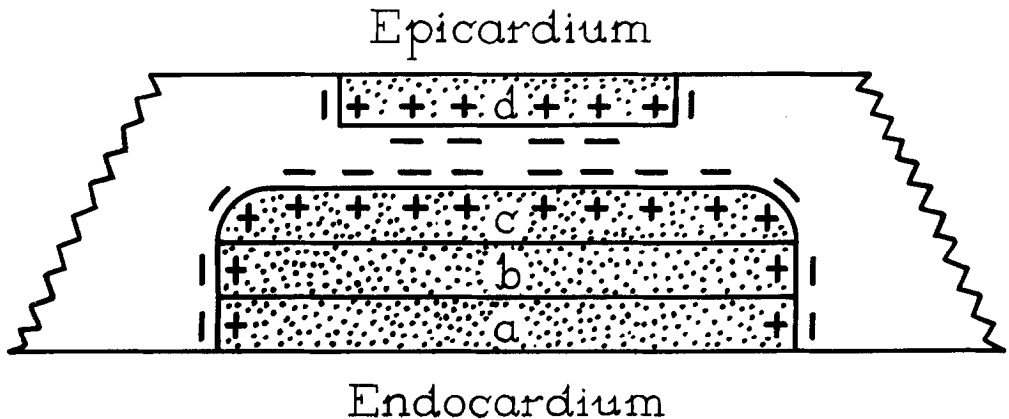
Epicardium

Endocardium

Fig. 9.—Diagrammatic representation of a lesion extending in stages a, b, and c from the endocardial toward the epicardial aspect of the heart wall: d, represents an injury to tissue at the epicardial aspect of the wall. For discussion, see text.

Experiment 6.—A small turtle was prepared in the usual manner. The filiform electrode was introduced into the left ventricular cavity. Electrocardiograms were recorded from the soft-tipped electrode resting on the epicardium of the ventral wall of the heart both before and after introduction of the filiform electrode into the ventricular cavity. Through the filiform electrode the electrocoagulating current was applied to the endocardial aspect of the ventral wall. The strength of the current and the duration of its flow were increased step by step. An electrocardiogram was recorded after each application of the current.

The soft-tipped electrode was then removed from the epicardial wall. With another electrode, a burn was made on the surface of the ventricle. This lesion overlaid but was smaller than the endocardial burn. The soft-tipped electrode was returned to its original position and a final electrocardiogram was recorded.

Post-mortem examination revealed that the endocardial burn was 7 mm. and the epicardial burn 4 mm. in diameter.

The electrocardiograms recorded in Experiment 6 are reproduced in Fig. 10. Only in those recorded immediately after the initial endocardial injury does the sequence of changes follow the anticipated course. Slight downward displacement of the RS-T segment is present in the curve labeled C in Fig. 10. In subsequent records, upward displacement of the RS-T segment is present and steadily increases. In those taken after the production of the epicardial lesion,

the RS-T segment does not become isoelectric but rises still higher to form curves of a monophasic type.

For this discrepancy between the predicted and the recorded results, there is a simple, if initially elusive, explanation. A zone of injured muscle across which a gradient of injury exists and from which a current of injury is derived
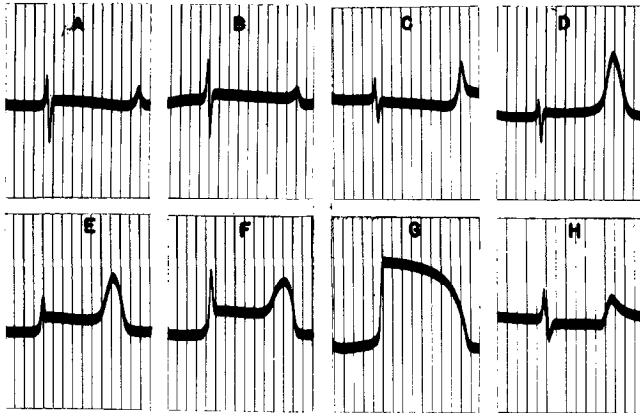

Fig. 10.—All curves except *H* were recorded with the electrode at the same point on the exposed portion of the ventral wall of the heart. *A*, Control; *B*, control after tip of electrode of the electro-coagulation unit had been introduced into the ventricular cavity; *C*, after making initial burn on endo-cardial aspect of ventral wall of heart at a point underlying the epicardial electrode; *D*, after second burn; *E*, after third burn; *F*, after fourth burn; *G*, after making small burn on the epicardial surface at a point overlying the endocardial burn; and *H*, epicardial electrode shifted onto uninjured muscle at right side of ventral wall of heart.

Ordinate scale uncertain, but approximately 3 millivolts per centimeter.
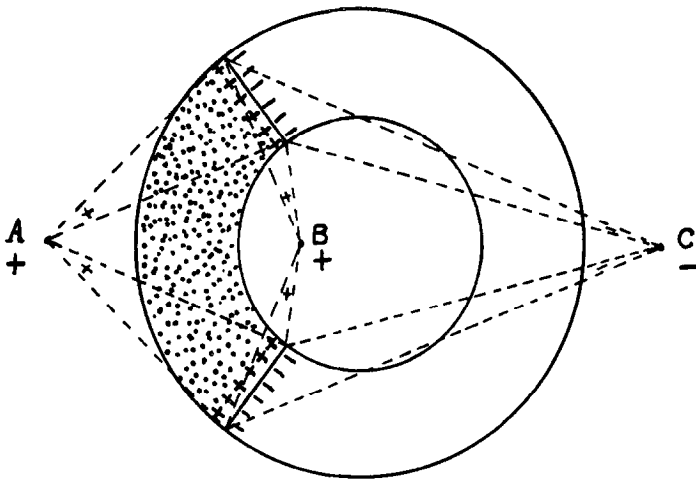
Fig. 11.—Diagrammatic representation of the electric field produced by an injury extending through the heart wall. This field is similar to one which would be produced if the injured muscle were polarized in the sense indicated. An electrode placed at a point adjacent to either the epicardial or endocardial aspect of the lesion would lie in a portion of the field where the potential was positive. An electrode placed at a point remote from the endocardial aspect of the lesion might lie in a portion of the field where the potential was negative.

lies just within the boundary between injured and uninjured muscle. In order to promote simplicity of description in the discussion which follows, the origin of the electric forces derived from an acutely injured muscle will be considered as located at this boundary. When an endocardial lesion is produced, a boundary of this kind is created, part of which is nearly parallel to the epicardial and endocardial surfaces, but there is another part which is more or less nearly perpendicular to these surfaces (Fig. 9). This latter part lies at the periphery of the lesion. Its breadth increases as the lesion is made deeper. During the inscription of the RS-T segment, the electric forces generated at this peripherally located boundary give rise to positivity at an exploring electrode placed on the epicardium at a point adjacent to the center of the lesion. These forces are opposed to those associated with the remaining parts of the boundary, which are parallel to the epicardial and endocardial surfaces. When the electrocardiograms reproduced in Fig. 10, D were recorded, the opposing forces apparently were of equal magnitude and the downward displacement of the RS-T segment present in the preceding electrocardiogram had disappeared. In the subsequent curves, the forces derived from the lateral aspects of the lesion apparently had a greater effect on the potential at the exploring electrode than those originating in the part of the boundary that was roughly parallel to the ventricular wall involved. With the production of the burn on the epicardium, another boundary parallel to the ventricular wall was created. Its orientation was such that the resulting forces opposed those associated with that portion of the boundary of the endocardial lesion which lay in a parallel plane. As a result, the forces produced at the peripheral portion of the boundary of the endocardial lesion gained the ascendancy and made the potential at the exploring electrode strongly positive. The RS-T segment was displaced upward and monophasic curves were recorded. A diagrammatic representation of this final stage is presented in Fig. 11.

Suppose that the distribution of boundaries defined in this diagram is an accurate representation of the situation which exists when an acute injury extends through the heart wall. Then an electrode placed on the endocardial surface of this transmural lesion should lie in a portion of its electric field where the potential is almost identical with that existing at an electrode placed on its epicardial surface. An experiment was designed to test this conclusion.

Experiment 7.—A large turtle was prepared in the usual manner. A lesion involving the endocardium on the left side of the ventricular cavity had been produced earlier in the experiment, but the electrocardiographic changes which had developed in the acute stage of that lesion had disappeared. The endocardial electrode was moved to the right side of the ventricular cavity and a set of electrocardiograms was recorded from the epicardial and endocardial electrodes. Through the endocardial electrode, the electrocoagulating current was applied in great strength for approximately five seconds. The white face of the burned tissue extended to the epicardium over an area 4 mm. in diameter. A series of electrocardiograms was recorded under circumstances described in the legend of Fig. 12.

Post-mortem examination revealed that the burn involved an area 8 mm. in diameter on the endocardial aspect of the wall of that portion of the ventricular cavity lying farthest to the right.
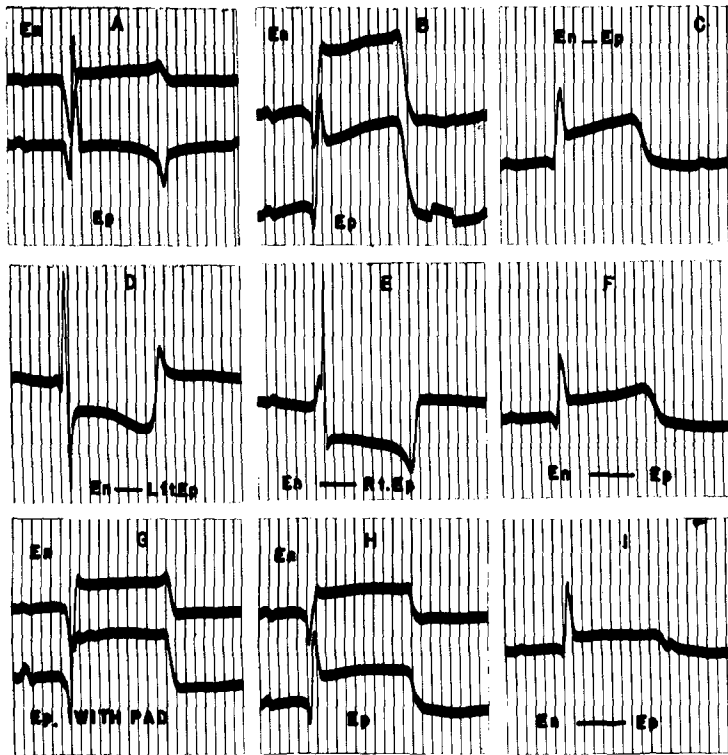

Fig. 12.—In all records where there are two curves, the upper one was derived from an electrode in the ventricular cavity (En) and the lower one from an electrode on the epicardial aspect of the right wide of the ventral wall of the heart (Ep). A, Control (ordinate scale: upper curve, 5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); B, immediately after production of a burn extending from the endocardial to the epicardial aspect of the ventral wall of the heart on the right side, electrodes were in contact with the epicardial and endocardial aspects of the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); C, epicardial electrode attached to left arm terminal of galvanometer and endocardial electrode to right arm terminal, lead selector set on Lead I (ordinate scale: 3.5 millivolts per centimeter); D, connections as in C, epicardial electrode moved onto uninjured muscle 8 mm. to left of lesion; E, connections as in C, epicardial electrode 3 mm. to right of lesion; F, epicardial electrode returned to site of lesion; G, pad soaked in Ringer's solution laid over ventral surface of heart, endocardial electrode on lesion and epicardial electrode on surface of pad at a point overlying the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 1 millivolt per centimeter); H, pad removed from heart, endocardial and epicardial electrodes on respective surfaces of lesion (ordinate scale: both curves, 3.5 millivolts per centimeter); and I, connections, disposition of electrodes, and ordinate scales as in C.

The electrocardiograms recorded in Experiment 7 are reproduced in Fig. 12.   They afford evidence that during inscription of the RS-T segment the potential was positive both at the epicardial and at the endocardial surface of the transmural lesion relative to the potential at a point remote from the heart. Covering the air-exposed portion of the ventral surface of the heart with a pad soaked in Ringer's solution produced certain changes in the electrocardiograms.

A reduction occurred in the amplitude of deflections recorded from the electrode placed on the surface of the pad at a point overlying the lesion. However, when the sensitivity was increased in that circuit in which the epicardial electrode was included, the curves recorded were quite similar to those obtained when the wick of the electrode rested on the surface of the lesion (Fig. 12, G and H).

The electrode on the epicardial surface of the lesion was attached to the left arm terminal and the electrode on the endocardial surface was attached to the right arm terminal of the same circuit. The lead selector switch was set on Lead I. The electrocardiograms reproduced in Fig. 12, C were then taken. With the connections described, the upward displacement of the RS-T segment indicates that the potential at the epicardial surface was positive relative to that at the endocardial surface. When the same connections were maintained and the epicardial electrode was moved off the surface of the lesion and onto uninjured muscle lying either to the right or to the left of the lesion, the potential at the epicardial electrode became negative relative to that at the endocardial electrode (Fig. 12, D and E).

These findings are compatible with those which would be anticipated if the significant electrical boundaries of the transmural lesion were disposed as is represented in Fig. 11. The fact that the potential of the epicardial surface of the lesion was positive to that of the endocardial surface rather than isopotential with it does not create a problem of significant proportions. In another experiment comparable to the one reported here, a lesion was produced which was less intense at the epicardial surface. The potential at the endocardial surface was then positive relative to that of the epicardium. The less pronounced positivity of the potential at the endocardial surface of the lesion in Experiment 7 was not the expression of a lesser intensity of injury on that aspect of the lesion. It may have been related to the complete desiccation of the tissues adjacent to the electrode with resultant alteration of the nature of the contact between the electrode and the cardiac surface.

A lesion extending through the ventricular wall from the epicardial to the endocardial surface has certain features in common with an infarct. In an attempt to define this relation more clearly, additional experiments were undertaken in which acute myocardial infarction was produced in dogs.

MYOCARDIAL INFARCTS

The chief characteristics of the electrocardiographic changes which commonly follow acute myocardial infarction either in man or in animals are well established. The explanation of these changes in terms of the dipole theory has been, on the whole, satisfactory and fruitful, but some perplexing problems presented by them are still unsolved. The facts indicate that a transmural infarct produces upward RS-T displacement in leads in which the exploring electrode faces the epicardial aspect of the involved wall. Changes of an inverse type are recorded in leads from an exploring electrode which faces the epicardial aspect of the uninvolved ventricular wall opposite the infarcted region. Thus, in infarction of the anterior apical portion of the left ventricle, upward RS-T dis-

placement occurs in electrocardiograms derived from an exploring electrode on a part of the thoracic wall which overlies the affected muscle. Such infarcts also commonly produce changes in the left arm potential, which result in upward RS-T displacement in leads from this extremity and in Lead I and downward displacement in Lead III. A unipolar lead from the left leg may show downward RS-T displacement. These changes which occur in anterior apical infarction are the inverse of those which develop during the acute stage of a posterior basal lesion.

The dilemma created by these findings has been defined by Bayley.[2] An acute subepicardial injury produces upward RS-T displacement in a lead from an exploring electrode which faces the affected portion of the ventricular wall. It is assumed that in this same lead an acute subendocardial injury would produce downward RS-T displacement. If the infarct is transmural and involves both the subepicardial and the subendocardial muscle, how then can the RS-T displacement so constantly associated with acute myocardial infarction develop? The problem becomes more perplexing if it is demonstrated that an infarct usually presents a more extensive surface on its endocardial than on its epicardial aspect. In the presence of such a lesion, the sum of the forces produced at the endocardial boundary would be greater than the sum of those produced at the epicardial boundary. Hence, downward RS-T displacement would be anticipated in a lead from an exploring electrode facing the epicardial surface of the infarct.

In his attempt to solve this problem, Bayley reviewed the studies of Mallory, White, and Salcedo-Salgar[14] and of Karsner and Dwyer[12] which concern the pathologic changes of myocardial infarction. Mallory and associates reported that a layer of subendocardial muscle 0.3 to 0.5 mm. in thickness is preserved in the infarcted region. Bayley reasoned that if, during the acute stage of myocardial infarction, the muscle fibers in this subendocardial layer retained the physiologic properties of uninjured cells, then a boundary between uninjured and injured muscle would persist in the subendocardial zone of the ventricular wall. Consequently, the forces contributed to the electric field by the infarct would have the same orientation as those produced by a lesion confined to the subepicardial myocardium. If a subendocardial muscle layer is invariably preserved over all the infarcted portion of the ventricular wall, the kind of RS-T displacement usually observed in cases of coronary occlusion is satisfactorily explained.

In our discussion of lesions extending outward from the endocardial to the epicardial surface of the heart of the turtle, an account was given of a discrepancy which arose between the electrocardiographic phenomena anticipated and those recorded when a transmural lesion was produced. In our experiments the subendocardial tissues were injured. Such trauma as occurred within the subepicardial zone was transmitted through the underlying layers of the myocardium. Upward RS-T displacement was recorded not only in unipolar leads from the endocardial surface but also in unipolar leads from the epicardial surface of transmural lesions. We have suggested that the site of origin of the electric forces which produced these electrocardiographic effects was the boundary between injured and uninjured tissue at the periphery of the lesion. Irre-

spective of the validity of this hypothesis, the fact remains that an electrode placed on the epicardial aspect of an acutely injured region extending completely through the heart wall lies at a point in the electric field of that lesion where the potential is positive during the inscription of the RS-T segment. Preservation of a subendocardial muscle layer is not essential to the production of this particular feature of the usual electrocardiographic changes associated with acute myocardial infarction.

Our observations do not prove that a boundary between injured and uninjured muscle does not persist in the subendocardial zone of a myocardial infarct. Experiments designed to record the potential variations at the endocardial surface of an acutely infarcted region offer an approach to this problem likely to contribute relevant and significant data. If, at this stage of infarction, a layer of subendocardial muscle is preserved in a functional as well as in an anatomic sense, an electrode placed on the endocardial surface of the infarct would be at a negative potential with respect to an indifferent reference point during the RS-T period. If the subendocardial cells are injured so severely that no significant gradient of injury exists in this region, then at the endocardial surface as at the epicardial surface a relatively positive potential would develop at the end of the QRS interval (Fig. 11).

An experiment designed to record the potential variations at a point on or near the endocardial surface of an infarct is readily conceived. Its execution is attended by certain difficulties. The usual procedure for recording the potential within the ventricular cavity entails the introduction of a sharp-tipped electrode through the ventricular wall. The position of the tip of such an electrode can be estimated by simple measures with reasonable accuracy. However, production of an injury with the electrode itself must be avoided if a significant record of the potential changes in the cavity is to be obtained. For this reason, the tip of the electrode must not be pressed firmly against the endocardial surface of the infarcted region, but should be placed in proximity to that surface. The distance of the electrode from the endocardial surface determines its position in the electric field of the injured muscle. If this distance is not too great, the electrocardiographic changes recorded should be similar to, though of lesser magnitude than, those which would occur if the exploring electrode were in contact with the inner surface of the lesion.

Method.—Dogs weighing between 10 and 12 kilograms were used in these experiments. Anesthesia was induced with morphine and urethane. The pericardium was exposed either by splitting the sternum or by resecting the fourth, fifth, and sometimes the sixth rib on the left side. The pericardial sac was incised and its margins were sutured to the thoracic wall. A major branch of the left coronary artery was ligated by passing a suture under the artery and its vena comitans. When only temporary occlusion of the artery was desired, a wire was included in the ligature and only a single knot was tied. Removal of the wire and release of traction on the thread restored the flow of blood.

In the initial experiments, records were taken with the Sanborn Tribeam electrocardiograph. In later experiments the Einthoven galvanometer was used.

Because of technical difficulties, satisfactory electrocardiograms were secured in only the last five of the nine experiments. The electrode used for obtaining records from the epicardium was the relatively nonpolarizable soft-tipped device already described. A similar electrode was placed in contact with the subcutaneous tissues of the left hind leg and this served as the reference point for this lead when the Einthoven galvanometer was used. The electrode introduced into the ventricular cavity was of the filiform type described in the account of the experiments on turtles. The tip of this electrode was thrust through the ventricular wall in a region supplied by the artery to be ligated. Its shaft was sutured firmly to some portion of the adjacent thoracic wall. This electrode was highly polarizable. Hence it was essential that the resistance of the circuit in which it was included should be high. For this reason, the cavity electrode was connected to the grid terminal of a vacuum tube amplifier and thus indirectly to the galvanometer. The indifferent electrode for cavity leads was a copper disk 2 cm. in diameter, which was placed in contact with the subcutaneous tissues of the left hind leg. When leads from the electrode on the epicardial surface to the electrode in the ventricular cavity were used, the former electrode was attached to the left arm terminal and the latter to the right arm terminal of the galvanometer. The lead selector switch was then set on Lead I.

Results.   The electrocardiograms reproduced in Figs. 13, 14, and 15 were taken with the Einthoven galvanometer. They were obtained in the course of an experiment which was not wholly satisfactory in certain respects. In the first place, ligation of the anterior descending branch of the left coronary artery at a point 2 cm. below the tip of the left auricular appendage did not produce pronounced displacement of the RS-T segment either in the lead from the epicardial or in that from the endocardial side of a part of the ventral ventricular wall apparently supplied .by this vessel. Only after ligation of the terminal branches of the circumflex division of the left coronary artery (Fig. 16) did more striking displacement of the RS-T segment develop. Secondly, because the region of infarction included only a limited portion of the myocardium at the apex of the left ventricle, the first electrode introduced into the left ventricular cavity did not lie opposite the center of the injured region. A second electrode, therefore, was introduced into this cavity at a point more centrally located relative to the infarct, but this was done only after the coronary vessels had been ligated and the resulting electrocardiographic changes had already developed.

In other respects the experiment was satisfactory. At the end of it, the heart was opened and the tips of both electrodes that had been introduced through the ventricular wall were observed to lie within the cavity of the left ventricle. The first electrode extended into this cavity a distance of 8 mm. and the second, a distance of 4 millimeters. A small thrombus 3 mm. in diameter had formed around that portion of each electrode which projected beyond the inner surface of the ventricular wall. Except at the points of entrance, no gross endocardial injury produced by the electrodes could be identified.
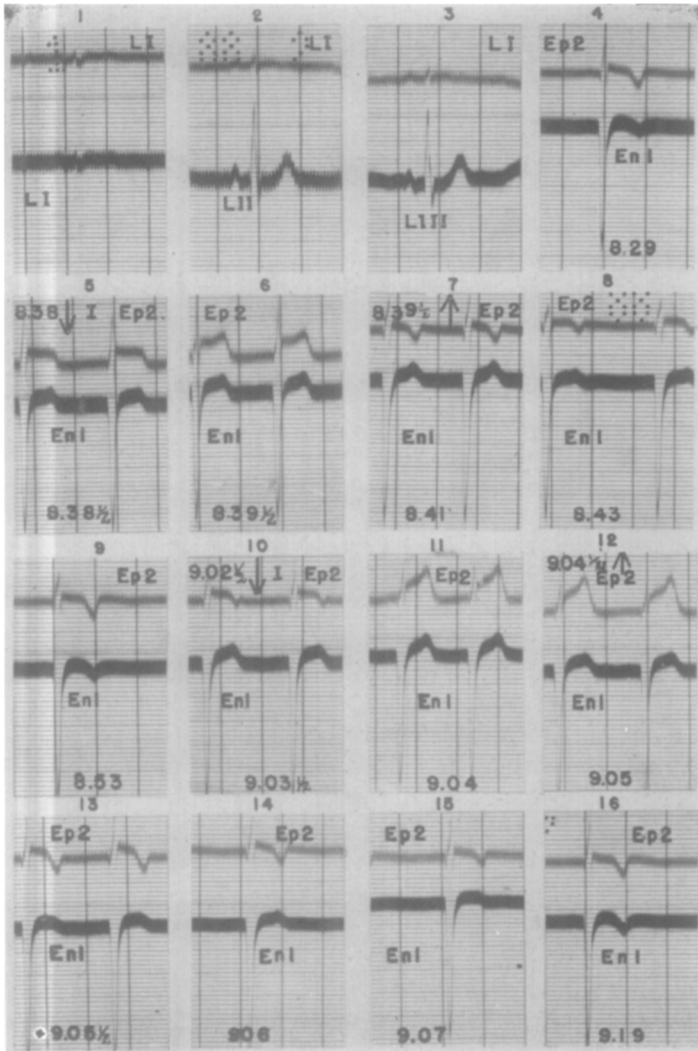
Fig. 13.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity, 20 millivolts per centimeter.

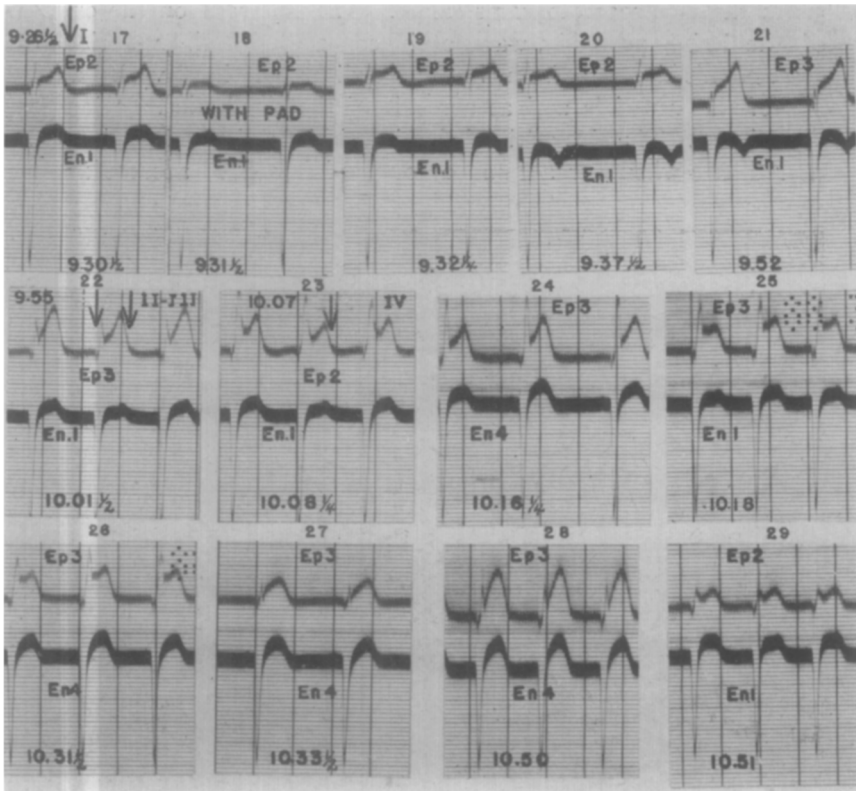| Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
1	8:00	Lead I	Lead I
2	8:02	Lead I	Lead II
3	8:04	Lead I	Lead III
4	8:29	Point 2 (see Fig. 16)	Point 1
	8:38 Occlusion at I (see Fig. 16) for 90 seconds		
5	8:38½	Point 2	Point 1
6	8:39½	Point 2	Point 1
7	8:41	Point 2	Point 1
8	8:43	Point 2	Point 1
9	8:53	Point 2	Point 1
	9:02½ Occlusion at I for 105 seconds		
10	9:03½	Point 2	Point 1
11	9:04	Point 2	Point 1
12	9:05	Point 2	Point 1
13	9:05½	Point 2	Point 1
14	9:06	Point 2	Point 1
15	9:07	Point 2	Point 1
16	9:19	Point 2	Point 1

Fig. 14.— Ordinate scale: 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
	9:26½	Occlusion at I (see Fig. 16) permanently	
17	9:30½	Point 2 (see Fig. 16)	Point 1
18	9:31½	Point 2 with pad	Point 1
19	9:32¼	Point 2	Point 1
20	9:37½	Point 2	Point 1
21	9:52	Point 3	Point 1
	9:55	Occlusion at II and III permanently	
22	10:01½	Point 3	Point 1
	10:07	Occlusion at IV permanently	
23	10:08¼	Point 2	Point 1
24	10:16½	Point 3	Point 4
25	10:18	Point 3	Point 1
26	10:31½	Point 3	Point 4
27	10:33½	Point 3 with pad	Point 4
28	10:50	Point 3	Point 4
29	10:51	Point 2	Point 1

Analysis of the electrocardiograms in Figs. 13, 14, and 15 should not be extended to exact quantitative determinations. After the first of the standard limb leads had been taken, the sensitivity of the galvanometer was readjusted and it was not altered again throughout the remainder of the experiment. It should be recognized, however, that other factors affected the magnitude of the

deflections in the electrocardiograms taken. The electrode on the endocardial aspect of the lesion probably was not in contact with the ventricular wall. The distance of this electrode from the endocardium may have varied during the contraction of the ventricle and as a result of the rhythmic inflation and deflation of the lungs. The size of the deflections in leads from the epicardial electrode was reduced whenever a small amount of free fluid accumulated about
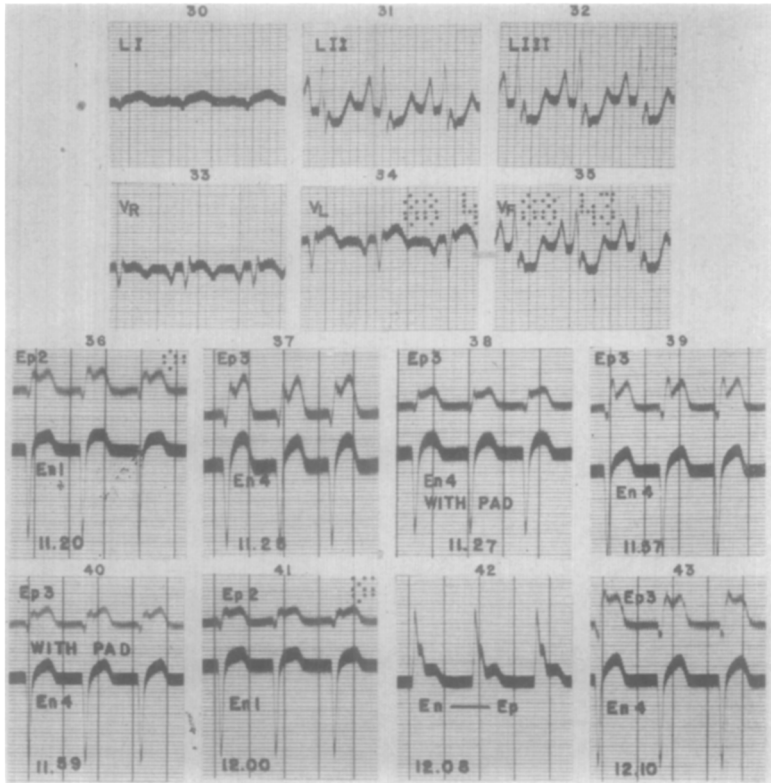

Fig. 15.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity. 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
30		} Lead I	
31	10:55	} Lead II	
32		} Lead III	
33		(Unipolar lead, right foreleg	
34	11:05	{ Unipolar lead, left foreleg	
35		(Unipolar lead, left hindleg	
36	11:20	Point 2 (see Fig. 16)	Point 1
37	11:25	Point 3	Point 4
38	11:27	Point 3 with pad	Point 4
39	11:57	Point 3	Point 4
40	11:59	Point 3 with pad	Point 4
41	12:00	Point 2	Point 1
42	12:08	L. A. terminal at epicardial point 3; R. A. at endocardial point 4	
43	12:10	Point 3	Point 4

the tip of this electrode. Therefore, while the magnitude of the RS-T displacement in the electrocardiograms of this series is of some interest, we shall emphasize only its direction, which is of greater significance.

Fig. 16. –Diagram of heart indicating points to which reference is made in legends of Figs. 13, 14, and 15.

In Fig. 13, curves 5 to 9, are represented the electrocardiographic changes associated with, and sequential to, temporary occlusion of the anterior descending branch of the left coronary artery. During this initial procedure the occlusion was maintained for ninety seconds. Upward displacement of the RS-T segment developed in leads from the electrode placed on the epicardium. The magnitude of this displacement was not great. In leads from the endocardial electrode, the inverted T wave became upright and this change was accompanied by a slight upward shift in the RS-T level. These phenomena appeared within thirty seconds after occlusion of the artery and regressed with almost equal speed.

Twenty-four minutes after the first occlusion of the artery, traction was again placed on the ligature and was maintained on this occasion for 105 seconds (Fig. 13, curves 10 to 16). The changes during this period of ischemia were slightly more pronounced in leads from both the epicardial and the endocardial electrodes. In other respects, the developments were like those which followed the initial occlusion.

Twenty-four minutes later the ligature was tied permanently (Fig. 14, curve 17). The electrocardiographic changes which appeared during the first few minutes after this occlusion simulated those occurring in the preliminary periods of ischemia. However, after five minutes there was some decrease of the upward displacement of the RS-T segment in leads from both the epicardial and endocardial electrodes, particularly in the latter (Fig. 14, curve 19). In the

records made twenty-six minutes after the permanent occlusion (Fig. 14, curve 21), the epicardial electrode was shifted to a point nearer the center of the injured region; the position of the endocardial electrode was not changed.

Twenty-nine minutes after the final ligature had been placed on the anterior descending branch of the left coronary artery, the first of the terminal branches of the left circumflex artery was occluded (Fig. 14, curve 22). Twelve minutes later, the third and last ligature was placed around one of these branches (Fig. 14, curve 23). Fifty minutes after the first permanent occlusion, an electrode was introduced into the left ventricular cavity at a point near the center of the injured myocardium and an electrocardiogram was recorded from this lead (Fig. 14, curve 24). Between ninety and 120 minutes after the first permanent occlusion, the degree of elevation of the RS-T segment was maximal in both the epicardial and the cavity leads. It was at this time when the potential at two points on the endocardial aspect of the injured muscle was positive during inscription of the RS-T segment that the standard limb leads and the unipolar extremity leads were recorded. The presence of downward displacement of the RS-T segment in the unipolar lead from the left hind leg at a time when cavity leads displayed upward RS-T displacement is of particular interest.

One of the last electrocardiograms in the series (Fig. 15, curve 42) records the potential difference between the electrode placed near the center of the epicardial aspect of the infarcted tissue and an electrode in the ventricular cavity 3 or 4 mm. from the inner surface of the same part of the infarct. The upward displacement of the RS-T segment in this lead indicates relative positivity of the epicardial electrode at the end of the QRS interval. However, the degree of positivity of the epicardial relative to the endocardial electrode was less than the degree of positivity of the epicardial electrode relative to an electrode placed at a point remote from the heart (Fig. 15, curve 43).

Finally, attention may be directed to one other observation which concerns the magnitude rather than the kind of electrocardiographic alterations which developed. In many of the curves reproduced in Figs. 13, 14, and 15, electrical alternans is present. This phenomenon is most obvious in curve 23 of Fig. 14. Examination of these curves reveals that when upward displacement of the RS-T segment was greater in the epicardial electrocardiogram, it was likewise greater in the lead from the endocardial electrode. If the electric forces responsible for this displacement arose at a boundary which lay between the epicardial and endocardial surfaces, greater positivity on one side of the ventricular wall should have been accompanied by greater negativity on the other. If, on the other hand, the electric forces in question originated at the periphery of the lesion, an increase in their magnitude would have a similar effect on the potential of both surfaces of the ventricular wall and, therefore, on that of both electrodes.

The observations presented here illustrate a series of experiments which was incomplete. In particular, studies should have been made of the changes of potential within the left ventricular cavity following ligation of the circumflex branch of the left coronary artery. One attempt to do this was made but the results of this experiment could not be interpreted precisely because of inadequate information regarding the position of the endocardial electrode.

In summary of the available data on the electrocardiographic effects of experimental myocardial infarction, the following statements may be made.   In experiments on dogs, the artery or arteries supplying the anterior apical portion of the left ventricle were ligated and the potential changes within the left ventricular cavity were recorded.   The tip of the exploring electrode was placed in this cavity at a point near the center of the injured region of the adjacent myocardial wall.   During the RS-T interval, the potential at the tip of the cavity electrode was positive relative to the potential at an electrode placed at a point remote from the heart.   This positivity at the endocardial aspect of the lesion existed in the presence of changes typical of anterior apical infarction in leads from the epicardial surface of the lesion, in the standard limb leads, and in the unipolar extremity leads.

The results of our experiments do not justify the conclusion that the electric forces responsible for RS-T displacement in acute myocardial infarction always arise at boundaries which define the peripheral limits of the lesion.   We may add that the application of concepts derived from experiments in which the blood supply of some part of the healthy canine myocardium was suddenly cut off to the interpretation of what takes place when the nutrition of the human heart is disturbed by thrombosis of one of its sclerotic arteries must always be accomplished with due regard for the possibility of error.   To assume that the results of our experiments can be applied to all cases of myocardial infarction in man would be premature.

Having accorded these considerations the recognition which they merit, we may make the following statements without elaboration of their implications. A boundary between injured and uninjured muscle must define all or part of the peripheral limits of every myocardial infarct.   Since the left ventricle is conical and since extension of a zone of infarction to its basal border would not produce a junction between injured and uninjured muscle in this region, the combined areas of the apical and basal boundaries of the infarct may be small in comparison with the areas of its other boundaries.   In a heart which is not dilated, the area of the boundaries at the periphery of the infarct may approach the area of the endocardial aspect of the injured tissue.   This would be most likely to happen during ventricular systole.   At this time, the size of the ventricular cavity is decreased and the thickness of the ventricular walls is increased.   It is during systole that the RS-T segment is inscribed.

<center>SUMMARY AND CONCLUSIONS</center>

The modifications of the RS-T segment of the ventricular complex produced by acute lesions of various types were recorded in a series of experiments on turtles and dogs.

In experiments on turtles, it was found that when the ventral surface of the heart was exposed to air an acute injury involving only the outer layers of the exposed ventricular wall produced upward RS-T displacement in unipolar leads from the epicardial surface of the affected region but, as a rule, did not produce downward RS-T displacement in leads from an adjacent portion of the ven-

tricular cavity.   Downward RS-T displacement did occur in such cavity leads when the ventral epicardial surface was in contact with a conducting medium.

When a lesion involved the same part of the ventricular wall but was confined to the subendocardial muscle layers, the RS-T displacement was upward in leads recorded from an adjacent part of the ventricular cavity and in leads from the epicardial aspect of the ventricular wall opposite the damaged portion of the myocardium.   RS-T displacement was downward when the exploring electrode was placed on the epicardial aspect of the affected ventricular wall.

When, in experiments on turtles, a lesion involving both the inner and outer layers of the ventricular wall was produced by electrocoagulation, upward RS-T displacement was recorded in leads from either the epicardial or the endocardial aspect of the region of injury.   Similarly, when acute myocardial infarction was produced in the anterior apical portion of the canine heart by coronary ligation, the RS-T displacement was upward in leads from a portion of the ventricular cavity adjacent to the injured muscle and in curves recorded with the electrode on the epicardial surface of the region of infarction.   The electric forces responsible for upward RS-T displacement on both aspects of these transmural lesions were attributed to the boundaries between injured and uninjured muscle at the peripheral margins of the lesion.

Muscle juice, probably because of its high potassium content, produces maximal RS-T displacement when it is placed on the ventricular surface.

An attempt has been made to interpret these observations in terms of the dipole theory as it applies to the electrocardiographic consequences of acute myocardial injuries.

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