STUDIES
on
CARDIAC TONUS

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I.-DEFINITION OF TONUS..

Tonus is "that state of constant muscular tension which underlies and makes possible all orderly motion"(36), or the degree of resistance of a muscle to extension or deformation (36), or the energy of contraction (7), or the physiological fitness of the muscle fiber to contract (36), or "a sustained partial diastolic contraction independent of the systolic contractions (in the case of heart muscle) by virtue of which the muscle fibers resist distention during diastole more than they would because of their mere physical properties" (36). Cardiac tonus according to the last and best definition does not include such diverse things as elastic properties of muscle, physiological fitness of its fibers, sustained contractile activity, contraction remainders, and contractures. Cardiac muscle, like skeletal, goes into a state of long sustained contraction, when exposed to extremes of pH, excess Ca, CCl_3H, caffein, alcohol, digitalis, etc. These contractures are not examples of tonus, according to Meek (36), for they are disturbances in the normal rythmical contractions, are really exaggerated contraction remainders and are not directly related to sustained diastolic contraction. Furthermore, the theories of contracture do not refer to tonus in the above specific sense; they attribute contracture to lactic acid formation in the muscle by the action of the contracture-producing substances, which later prevent relaxation by their direct physicochemical action on the muscle (Meyerhof (36),), or according to the other views (Bethe (36),) contracture is the direct result of the action of

these substances on the muscle tissue. Riesser and Heinzan (36) agree to both views for they have demonstrated the absence of lactic acid in acetyl choline contracture and its presence in other contractures.

II.-TESTS FOR THE EXISTENCE OF CARDIAC TONUS.

First, spontaneous changes in the extent of diastolic relaxation. Second, alterations in these spontaneous changes brought about by any of the following physical, chemical, and physiological factors, O_2, CO_2, temperature, nerves, distending pressures and chemical composition of the nutrient media. Such alterations should not, according to tonus in the specified sense, effect the rate or the contour of the rythmical contractions in any way that may secondarily alter the so-called general diastolic level.

III.-TECHNICAL METHODS OF STUDY OF CARDIAC TONUS.

First, suspension methods, second, plethysmographic volume curve method, third, manometer intra-auricular and intraventricular pressure curve method.

IV.-DOES TONUS EXIST IN THE AURICLES?

a.- Application of the first test.

Fano (36) in 1887 described spontaneous tonus waves in the auricles of Emys europea. Action current determinations by the capillary electrometer showed oscillations similar to these waves, and segments from the tip of the auricles showed them also. Bottazzi (36) reported similar waves and studied various factors controlling them. Gaskell (36) observed no tonus oscillations in the land tortoise. Gruber (19, 20, 21, 22, 23), Porter (44) report such oscillations in the tortoise auricles. Gesell (18) used these oscillations by

recording isotonic and isometric auricular contractions to study the effect on cardiac function of varying initial length of fiber with initial tension constant or initial tension with initial fiber constant. The weight of the evidence, therefore, meets the requirements of the first test for the existence of tonus in the auricles of cold-blooded animals. There is only one reference (32) on auricular tonus in the hearts of warm-blooded animals which shall be discussed later but which does not, in any way, clarify the conception of tonus.

b.- Application of the second test.

The requirements of the second test have also been satisfied by the investigations of the workers just mentioned.

(1).- Evidence from the effect of temperature.

Fano (36) found that a rise in temperature abolishes tonus waves and augments the fundamental contractions. Periera (43) reported that a rise in temperature applied to the auricles of the heart perfused with Phosphate Ringer solution not only augments the tonus waves but also makes them appear in hearts that do not show them spontaneously, or in hearts that are tonically depressed by atropine. .75% NaCl, as was also reported by Fano, reversed the effect of temperature.

(2).- Evidence from the effect of nervous stimulation.

Fano (36) found that vagal stimulation either did not effect the tonus waves or increased them and provoked the corresponding electrical oscillations in the action current. Bottazzi (36) was careful not to consider as tonus oscillations changes in the diastolic level that are secondary to changes in rate or contour of the fundamental contractions, and because Gaskell (36) had suspected that these

tonus waves were under nervous control, Bottazzi, by grading the stimuli studied the effect of nervous excitation and could produce thru vagal stimulation a postive tonotropic effect, before any negative inotropic or chronotropic effect appeared and thru sympathetic stimulation a negative tonotropic effect before the appearance of any positive inotropic or chronotropic effects. Oinuma (36) confirmed these findings of Fano and Bottazzi on the nervous control of auricular tonus in the hearts of cold-blooded animals.

(3).- Evidence from the effect of various drugs and chemical solutions.

Fano and his associates (36) found that muscarine stimulates while atropine, nicotine, veratrine, depress the tonus waves; digitalis abolishes them together with the regular contractions at the same time that it raises the general tonus level. Gruber in his previous references reported thatadrenaline decreases tonus waves while KCl, nicotine, digitalis, $BaCl_2$ increase them and raise the general diastolic level; that the effects of atropine and pilocarpine are not definite; that adrenaline and KCl are antagonistic while KCl and $CaCl_2$ are synergisic; and that adrenaline is effective even after atropine. Snyder and Andrus (48) elicited tonus changes thru appropriate pH's in the perfusates and abolished them or prevented their appearance by application of papaverine and benzadehyde; they found, for instance, that pH 7.3-7.4 abolishes tonus while pH 7.6 reestablishes it in the terapin's heart; that morphine alkaloids stimulate while papaverine alkaloids depress tonus in the terrapin's heart inspite of the presence of the adequate pH. Since atropine does not alter these effects the tonotropic fibres are probably not parasympathetic and because adrenaline stimulates tonus when pH is

also tonus-stimulating unless the tonus is already maximum and depresses it when the pH is tonus-depressing the tonotropic fibres, both positive and negative, must probably be sympathetic with the activity of either being ~~therefore~~ dependent on the pH. Gemmill (16) found that the concentration of lactic acid in the terrapin's auricles is .036% (by weight), and that vagal stimulation does not alter it which ~~thereby~~ suggests a possible relation between lactic acid concentration and tonus maintenance. Clark (11) reports that the sympathetics contain vaso-dilators which secrete Sympathine I and vaso-constrictors which Sympathine E and that the threshold of the former to adrenaline is lower than that of the latter and hence the arterioler vaso-dilating effect of small doses of adrenaline. Salant and Johnston (45) found that an acid Ringer solution has a negative inotropic effect on the frog's heart while an alkaline Ringer solution has a positive inotropic effect; and that small doses of adrenaline produce a positive chronotropic and inotropic effect in alkaline Ringer and a negative chronotropic and inotropic effect in acid Ringer while bigger doses produce positive effects in both. It is, therefore, not at all surprising to find such controversial results of the effects of drugs, pH, ions, and nervous stimulation on tonus since there are so many factors to control like the concentration of the drug, the concentration of the ion, pH, and the species of animals used, all of which were not given their due consideration by the earlier investigators. Blood, for instance, was found by Bain (4) to be antagonistic to acetyle choline and adrenaline in their action on the smooth muscle of the gut while Ort (41) discovered that the lack of erythrocytes in the perfusate increases cardiac permeability, both examples ~~all~~ of which goes to show the delicacy of this type of research and the relative ease of

finding conflicting data and arriving at unwarranted conclusions. Nevertheless, inspite of all this controversy, the weight of the evidence so far presented is in favor of the existence of auricular tonus in the hearts of cold-blooded animals which is capable of alteration in response to various physical, chemical, and physiological factors.

V.-NATURE OF AURICULAR TONUS.

a.- Tonus oscillation is of myogenic rather than neurogenic origin. This is suggested by the finding of Fano (36) that non-ganglionated segments from the tips of auricles show spontaneous tonus waves. The findings of Fano, Bottazzi, and Gaskell (36), however, indicate that the latter are under the control of nervous regulating influences.

b.- Tonus oscillation is dependent on the contractile rather than on the elastic properties of muscles. This is suggested by Fano's experiment on digitalis (36) where the tonus waves were abolished together with the fundamental contractions, and by Bottazzi's finding that the former are inhibited by KOH, CCl_3H which are muscle tissue poisons.

c.- Increase in tonus is an anabolic rather than a catabolic phenomenon. This agrees with the fact that vagal stimulation which is accompanied by positive electrical variation raises the general tonus level.

d.- Tonus oscillation is the rythmical automatic contraction and relaxation of sarcoplasm. The sluggish character of the tonus waves reminded Bottazzi (6), the promulgator of this theory, of pseudopodial movement. But as Cobb (36) remarks there is no direct anatomical or physiological proof that sarcoplasm is contractile.

In addition, Gaskell (36) reports, as was already mentioned, that the heart of the land tortoise, though rich in sarcoplasm, shows no tonus oscillations. These findings would have weakened Bottazzi's sarcoplasmic theory of the nature of tonus if it were not for the work of Bottazzi and Grunbaum (36) who showed that smooth muscle which is rich in sarcoplasm has contractions similar to auricular tonus waves in their response to temperature and drugs.

e.- Tonus oscillation depends on some structure other than the sarcomeres which are concerned with the fundamental contractions. This is suggested by Bottazzi's experiments (36) on nervous stimulation and on KCl which he found to be inhibitory to these fundamental contractions before being depressant to the tonus oscillations and by Fano's (36) and Pereira's (42) experiments on the effects of temperature. This theory is also supported by Porter's finding (44) that tonus waves in the tortoise auricles could be superimposed and built into a tetanus, which made him believe that tetanus in all muscle tissue is a fusion of tonic contractions and not of the fundamental contractions.

f.- Smooth muscle theory. Bottazzi's theory (6) emphasized that cytoplasm is the structure responsible for tonus oscillation but was intended to mean that smooth muscle which is rich in sarcoplasm is the really responsible structure. Rosenzweig (36) discovered "a sheath of smooth muscle cells under the endocardium of Emys europea". Schaner (46) described the same thing in Emys blandingii. Bottazzi (36) confirmed Rosenzweig's discovery and found that smooth muscle is more abundant in the auricles than in the ventricle. Laurens (30) found no tonus waves in the heart of the lizard Lacerta viridis,

which also showed no smooth muscle. Snyder and Andrus (48) gave a chemical proof of this smooth muscle theory in their work on papaverine and benzaldehyde which are smooth muscle poisons, and on morphine and papaverine which have a similar action on smooth muscle as on terrapin's cardiac muscle. McSwiney and Newton (35) threw some doubt on this chemical proof by their work on gastric musculature. They found that an increase in pH produced a fall and a fall in pH a rise in the base line of rythmical smooth muscle contractions. This is of course contrary to the findings of Snyder and Andrus just referred to. They furthermore (34) showed that the fundic musculature of the stomach which is a tonus musculature has a curve of response to pH changes very similar to that of the gelatine, and that this response is myogenic because it is not effected by pilocarpine, atropine, nicotine, and nerve generation. Thus the effect of pH on smooth muscle may not agree fully with its effect on the tonus of cardiac muscle. But Macht (31) gave a pharmacological evidence in support of the smooth muscle theory which may be said to have outbalanced the evidence against it given by the work of McSwiney and Newton just mentioned. He found that members of the pyridine phenanthrene group like morphine, for example, stimulate by their pyridine radical the contraction and raise the tonus of smooth muscle, while members of the benzyl isoquinoline group like papaverine exercise thru their benzyl radical the opposite effect. The smooth muscle theory is, therefore, the most acceptable because it is supported not only by the anatomical but also by the physiological, chemical, and pharmacological data as well.

VI.- DOES TONUS EXIST IN THE VENTRICLE?

a.- Evaluation of the evidence from the study of the effect of cardiac nerves.

(1)- Vagal effects. Altho spontaneous tonus changes have been rarely described in the ventricle, it does not follow that the latter has no degree of sustained contraction during diastole. Dilatation from vagal stimulation was considered as loss of tonus. The relation of tonus to dilatation will be described later. To find out whether the vagus has any effect on ventricular tonus or not Frank's work and Hoffman's work (36) must be reviewed. Frank, by working on frog's heart under isotonic and isometric conditions, varied the degree of cardiac filling by varying the perfusing pressure, and plotted the effect on systolic and diastolic pressures against volume. He got isometric and isotonic maxima (systolic) and minima (diastolic) curves, and found that isometric minima curves ran lower than the isotonic minima curves showing that the relaxation in both types of contraction was not of the same nature or rapidity. Vagal stimulation did not alter the isometric minima curve (relaxation in the resting heart being quick and complete), but lowered the isotonic minima curves only in those points which were above the horizontal (indicating that the ventrical was still relaxing) but never to a point below the isometric minima. The suggestion, may, therefore, be made that vagal stimulation has no effect on the degree or rate of relaxation of a resting heart and hence no effect on tonus [redacted]. Hofmann, using the suspension method on frogs' hearts

cautioned against two indirect effects of vagal stimulation on the diastolic level that may be wrongly ascribed to tonic changes. The first of these, which was also noticed by Gaskell (36), is the effect of a change in rate on the diastolic level. Since the ventricle,ordinarily, relaxes slowly, the diastolic level will be higher the quicker the rate and lower the slower the rate. Therefore, the vagus should not be credited with an effect on tonus which is really secondary to its influence on the heart rate. The second indirect effect is a change in diastolic level due to a change in the course of the fundamental contractions brought about by vagal stimulation. Gaskell (36) in the volume curves from the frogs' ventricles attributed any change in diastolic level in the absence of any alteration in rate to a vagal influence on tonus. Vagal stimulation, however, brings about the following effects in order: a shortening of systole and an earlier diastole; a negative inotropic effect (that usually accompanies the previous one); and a negative chronotropic effect. It is thus seen that the diastolic level may be lower even before any change in rate has occurred; this lowering is due to the first vagal effect on the contour of the fundamental contractions and not to a change in tonus. Hofmann in further defense of this point reportsthat the diastolic level can be lowered by vagal stimulation more when the heart rate is artificailly maintained at one beat per three seconds than at one beat per ten seconds. Similarly the softening effect of vagal stimulation on cardiac

musculature reported by Francois-Frank, (36) cannot ~~also~~ be taken as evidence for the existence of tonus, for the method of its study is too rough to lead to any accurate findings on this delicate phase of the problem. Gemmill (16) more recently supplied a chemical "proof" of this lack of vagal influence on tonus in the ventricle by his finding that vagal stimulation does not alter the lactic acid concentration in the terrapin's heart (.026% by weight in the ventricle); it remains to be proved, however, that the concentration of this lactic acid is a chemical index of the state of tonus.

Concerning the effect of vagal stimulation on mammalian ventricular tonus, there is very scanty literature. The vagus has a negative inotropic effect on the auricles (12) but no definite ~~decisive~~ effect on the ventricle. Its influence on the latter is an old physiological controversy which was abandoned after Cullis and Tribe (12) found that pilocarpine and muscarine are ineffective on the ventricles of the cats' or rabbits' hearts after sectioning of the A-V bundle, altho their auricular effects persisted. Mammalian ventricle, therefore, receives no vagal fibres and any vagal influence on it must be only ~~indirect thru its~~ secondary to the effect on the auricle; it is however rich in sympathetic fibres that come to it not solely thru the A-V bundle, but thru other channels as well. This is similar to Snyder and Andrus deduction from their work on the terrapin's heart (48) that the tonotropic fibres have no relation to the cardiac parasympathetic supply. Fredericq (15) described in turtles a positive bathmotropic effect of vagal stimulation due to direct vagal action on the myocardium and not to the

vagal influence on the heart rate, but he made no reference to tonus. It also is true that ventricular volume curves (36) show a lengthening of systole on vagal stimulation, but again, this effect is not due to a changing tonus; it is rather due to the direct effect of the vagus in increasing the diastolic filling thereby leading to an increase in initial volume and tension.

(2).- Frank found (36) that stimulation of these nerves did not alter the isotonic and isometric minima curves. Boknenkamp (36) reports that sympathetic stimulation lengthens the systole of the frog's ventricle and therefore raises the diastolic level or decreases the extent of relaxation when all other factors are kept constant. No experiments were however described.

Sympathetic stimulation in the mammalian heart also showed no direct effects on tonus. The shortening of systole reported by earlier workers may not be due to direct sympathetic action on the ventricle. Changes in intraventricular pressures were also secondary. Henderson and Barringer (36) maintained that sympathetic stimulation would not bring about any augmentor effects unless the arterial blood pressure was low and the cardiac musculature in a state of decreased vigor. Wiggers and Katz (36) and Katz (36) investigated this point and found by avoiding the effect of rate thru use of systole-cycle ratios that the contraction period was reduced by stimulation of the cardiac accelerators; this finding, however, throws no light on the tonus problem.

The conclusion seems therefore warranted that there is no sustained partial diastolic contraction in the ventricles of cold-blooded and mammalian animals under vagal or accelerater control.

b.- Evaluation of the evidence from a study of the effect of possible supraventricular tone centers.

Failure to show any ventricular tonus under extrinsic nervous control directed attention to the possibility of existence of tonus under the control of supraventricular centers. This possibility was suggested by the following experimental findings which were later, however, criticised and the conclusion ~~then~~ arrived at that there is no ventricular tonus under the control of such centers.

(1).- Pietrkowski (36) inflated the frog's auricle with air and the ventricle became tonically contracted as if the frog had been digitalized. This auricular stretching sensitized the ventricle to digitalis, $BaCl_2$, $CaCl_2$, and methylviolet. He, therefore, concluded that ventricular tonus is controlled by a tone center in the auricle which is muscularly connected with the ventricle. But since the stretching of the ventricle brings about according to Galtz (36), some maintained shortening or even a systolic standstill and since blowing up the auricles with air probably results in a simultaneous stretching of the ventricle due to valvular incompetence, the data of Pietrkowski offer no real evidence for the existence of a tonus center in the auricle. Furthermore, Koch (36) repeated Pietrkowski's experiments after tying the A-V orifices and obtained no effect on the ventricle.

(2).- Lowe (36) two years later found that the ventricular "tonus" increased on distending the auricles with saline solution as well as with air. He noted that the ventricular strips were normal in all respects even after oxygen deprivation for several hours, except in that they showed no "tonus" changes and did

not respond to members of the digitalis group, while auricular strips would go into a standstill if subjected to the action of the latter, and if then stretched, would go into a long maximal tonic contraction. Ventricular strips, on the other hand, would not behave similarly unless they retained their connection with the auricles. This stretch response could then be provoked by stretching the auricle or the ventricle after digitalis sensitization or salline distension and cocain would abolish it. Lowe therefore concluded that there is an intracardiac tonus reflex nervous mechanism the center of which is in the auricles around their ganglionated region receiving afferents from both auricles and ventricles and sending out afferents to both. Wickels (36) came to the same conclusion from similar experiments where he found that cocain would abolish the stretch reflex but would not interfere with automaticity and that this reflex could be provoked in the ventricle only if it remained attached to the ganglionated portion of the auricles and after digitalis treatment. But Machiela (36) repeated the experiments of Lowe and Wickels, and obtained exactly opposite results. The stretch reflex could be provoked on any segment of the heart if oxygen supply was sufficient and the load was not heavy; similarly, strophantine contractures would occur in any strip under these conditions also. Thus the existence of supraventricular tone centers was also disputed.

(3).- Frohlich and Pick (36) believed that there are nervous centers for contracture and tonus in the auricular

septum; that chloral could hardly raise diastolic level of the ventricle unless the latter's connection with the auricle and sinus was left intact; and that ventricular contracture produced by $BaCl_2$ would spontaneously increase and decrease in intensity suggesting an underlying nervous mechanism. But Amsler and Frohlich found (36) that chloral would produce ventricular contracture when the rate is fast enough irrespective of whether the ventricular attachment to the auricles is intact or not. If the rate is slow, artificial stimuli at a faster rate may be applied and contracture would quickly be precipitated. Again, therefore, the evidence for the control of ventricular tonus by supraventricular centers is proved nonconclusive.

(4).- Amsler and Pick (36), bathing ventricular strips in s strophantine, found that those that were completely detached from the auricles went into contracture while those that were attached did not; this was the case inspite of the resulting chronotropic depression of the vagal node. They, therefore, inferred the possible existence of a contracture-inhibiting center in the auricles. But such findings are not in agreement with those of Lowe or of Machiela. None, however, tried to prove or disprove them; but Rossler (36) found that the contraction curves of isolated ventricular portions were higher than those still attached to the auricles due, not to a fuller diastole but to a stronger systole. This means that the contour of the fundamental contractions has been altered by the separation and therefore any further change in this contour as by strophantine, for example, can not be taken as an evidence for the sudden appearance of tonus or for its previous inhibition by a higher center.

(5).- Szent-Gyorgi (36) discovered that tying off the sinus in a frog's heart resulted in the following three changes in the suspension curves of the ventricular beats, a greater diastolic filling, a steeper or quicker diastolic ddescent, and "a short series of after vibrations similar to those described by Emanuel for atonic muscle" (36). These changes were ascribed to the loss of tonic impulses from the sinus. Regelsberger (36) avoided injury to the A-V groove and artificially stimulated the ventricle at a constant rate and then mildly removed the sinus influence either by cooling or by applying urethane; in one group of hearts he obtained a fall but in another group there was no change in the diastolic level. But Szent-Gyorgi's findings could be reproduced by alterations in the rate as Koch actually found out by further adjustment of the lever-masses or could be ascribed to inaccuracies in the recording system. The fall in diastolic level after the removal of the sinus was due to the resultant slowness in the rate of the ventricle, while the steeper diastolic descent and the after oscillations were due to the lever mass which could express itself more markedly at the slowed rate. Altho Szent-Gyorgi tried to remove the effect of rate changes, thru gradual depression of the sinus rythm by CO_2-deficient perfusates to the point at which the ventricle became automatic and found a fall in the diastolic level as the sinus ceased to function, yet he presented no curves to demonstrate this effect. Koch (36) similarly disproved Regelsberger's evidences on a basis of changes in rate and in loading. Artificial stimulation of the ventricle at a constant rate did not in his hands, contrary to the findings of Regelsberger,

produce any lowering of the diastolic level after removal of the sinus. Regelsberger, however, found a fall in the diastolic level under these conditions but the contour of the curves was changed. Also the normal slow rate, after the sinus removal, would allow more diastolic descent with light levers than with heavier ones which would have fully distended the ventricle before the removal of the sinus. The finding of Laurens (30) in lizards and tortoises that the A-V bundle is rich in ganglions and nerves may offer a recent evidence for the existence of supraventricular or possibly ventricular tone center, but no experimental proof has as yet been presented. Again, therefore, and this time disproof has been of the strongest evidence for the existence of supraventricular tone centers no proof is as yet available to demonstrate the existence of ventricular tonus under the control of a higher intracardiac center.

c.- Evaluation of evidence from the study of action currents.

If there is a condition of sustained diastolic contraction, then, a monophasic curve from a string galvanometer applied to theheart would show a displacement from the position of rest. No such records, are, however, available. Evans (36) found that the electrical changes ceased on CO_2 induction of tonic contraction in the snail's heart. Schaffer (36) found a slow return of the string to the isoelectric position after a contraction or a series of contractions in the frog's ventricle. He thus "argues that the heart during a series of beats is in a constant state of tonic excitation", as evidenced by the string deflection, and that the gradual return of the latter to the isoelectric position accompanies relaxation rather than contraction. As yet, no argument exists as to whether tonus is associated with electrical variations or not, or even with contracture altho Schaffer and Licht reported (36) a long monophasic variation accompanying acetyl choline cont-

racture. Evans' finding, on the other hand, that no electrical variation accompanies contracture, agrees with Schaffer's first finding but the latter may be taken especially in the light of his later discovery to mean that sustained diastolic contraction is accompanied by a slow electrical variation which ultimately dies off. Such ~~indeterminate~~ indefinite findings plus the technical difficulties involved in this type of research (36) make this mode of approach to the problem of cardiac tonus not very condusive to much illuminating information.

d.- Evaluation of evidence from the study of "Special Contributions That Have Touched On Tonus" (36).

(1).- Bruns (36) observed spontaneous variations in diastolic and systolic volumes independent of changes in rate or in distending pressure after overexerting the ventricles of frogs' hearts by a long rapid series of contractions. Such variations were less marked in fresh hearts. Fatigued hearts were also more extensible by increase in distending pressures than fresh ones. The spontaneous variations seemed to be tonic oscillations and increased extensibility, a change in diastolic elasticity due to fatigue which according to Harrison (24) is the result of a decrease in the buffering cardiac ability and in the concentration of potassium (brought about perhaps by the lack of erythrocytes in the perfusate (41),), which occur in cases of congestive heart failure. Scott (47), however, found that the concentration of potassium in the heart is 0.23% by weight in edematous as well as in non-edematous cases. This change in the diastolic elasticity is a factor in the production of cardiac dilatation. Socin (36) working on cats' heart-lung preparations

produced acute cardiac weakness by CCl_3H; dilatation occurred but was secondary to weakened contractility (which left some blood in the ventricle after each systole) and not to a change in elasticity or in tonus. Cardiac dilatation, therefore, is not always equivalent to theloss of cardiac tonus. Few of Socin's experiments showed dilatation before any fall in the plethysmograms was noticed suggesting that either elasticity or tonus has been decreased. But, Straub (36), by his work diagrams on mammalian hearts found that "even toward the end of diastole the diagram is convex to the abscissa, which means that a certain degree of contraction remainder has persisted throughout nearly all of the filling time". This shows that the curve of the extension minima of the mammalian heart does not lie on the curve of the extension minima of the resting heart; just as was found by Frank to apply also to cold-blooded hearts (36). As in the latter, so in the former, an increased diastolic relaxation reported by both Bruns and Socin, just mentioned, does not indicate tonus. Furthermore, Straub found that fatigue does not alter the position of the extension minima but of the extension maxima meaning that the dilatation that was produced was due to decreased contractility and not to any changing in tonus. Of course, most of Socin's results agree with this deduction, but those of Bruns do not, probably because the latter subjected the hearts to extremely exhausting conditions not likely to be found even in pathological cases.

(2).- Henderson (36) defines tonus as "the degree of resistance to deformation". This diastolic resistance to distention must be uniform if all plethysmograms of the mammalian heart

are to be superimposable (Henderson's law of uniform cardiac behavior). Rate, the only factor that alters tonus, which according to him varies but little with every heart and is really therefore a contraction remainder. Venous pressure does not alter this diastolic resistance because the latter is larger than the former. His laws of cardio-dynamics are all based on this conception of tonus which does not, however, illuminate the problem. In acapnia he says the heart goes into extreme tonus, but this is really a contracture either of a fatigued or of a poisoned heart. Any of those influences that act on the tonus of the resting skeletal muscle are inconsistent with his law of uniform cardiac behavior; therefore, he can not conceive of tonus as a diastolic contraction sustained independently of the fundamental contractions.

(3).- Starling (36) also disbelieves in the existence of any sustained diastolic contraction independent of the fundamental contractions. Diastolic size according to him depends on the length of the diastolic phase and on the speed with which blood enters the heart. The contracted heart of shock is the result of decreased inflow resulting from capillary stasis; the distended heart of increased peripheral resistance or of myocardial weakness is the result of an increased amount of blood in the heart leading to dilatation until compensation supersedes. Both of these results, he adds, need not be ascribed to changes in tonus. His disbelief in tonus in the specific sense is based on his findings that no change in intraventricular pressure occurred during diastole; that the curve fell to zero and "the fall in pressure at the end of systole occurred just as rapidly as the systolic rise". The distending pressure over a wide range of inflow

can therefore be negligible. Sustained diastolic tone, if present, would not allow such a fall in diastolic pressure, and altho other workers (36) reported slightly higher figures yet the evidence from this angle of approach is not convincing enough to warrant a belief in tonus. Furthermore, the lack of fluctuations in pressure and volume curves in experiments under normal conditions speaks against the presence of a sustained diastolic contraction that can be modified to meet various physiological needs. Starling (36) together with Bordet (7) therefore consider tonus as the contractile fitness of a muscle; but such a nomenclature does not, in any way, clarify our conception of the problem and is rather misleading.

(4).- Tonus and dilatation. Reference has already been made, more than once, to dilatation. Morittz (36) classifies the latter into two types: tonogenic (resulting from an increased tension in the muscle fiber and is characterized by an increased initial and maximal intraventricular pressure and a maintenance or an increase of the stroke volume; the heart is passive and the process is physiological and compensating), and myogenic (due to cardiac weakness or injury). These two types can be distinguished according to Straub (36) by determining the peripheral resistance. Hering (36) subdivided the myogenic dilatations into two types, hypinogenic (due to decreased contractility) and hypotonogenic (due to decreased muscular tonus). The latter is related to tonus as such, but it is not clear whether it applies to tonus in the already specified sense or not. Wiggers (36) in his work on the volume-elasticity coefficient of the relaxed heart plotted the volume increase against equal increments of the

distending pressure and obtained what may be called a tonus curve. A similar curve, plotted after vagal stimulation, would show the change in tonus (for a given pressure would then cause a greater volume change if the tonus is lowered). In dilatation, however, this tonus curve would not change or be abnormal; if it were, it would indicate a change in tonus.

e.- Evaluation of evidence from the study of the effect of the chemical composition of the nutriant media.

Gaskell (15) noted that an alkaline perfusate (with NaOH) produced a systolic standstill while an acid perfusate (with lactic) produced a diastolic standstill; he could not say whether the pH effected the elasticity or the tonicity of the muscle or whether the contractility was changed thru combination of the muscle tissue with the ions added or an idiomuscular contraction brought about. Mines (40) reported that an alkaline Ringer solution raises diastolic level and increases the systolic level, while an acid Ringer lowers the former alone or the latter together with the former; antiarin digitalin and atropine behave like alkalis, while muscarine and pilocarpine, like acids. Alkalinity, he adds, favors oxidation and makes possible the tonic state of the vascular system which shows that the cardiac musculature reacts to pH changes as the smooth musculature of the vessels. Andrus (1) later showed that a pH change from 7.4-7.6 augments the tonus waves of the turtle's heart and decreases the amplitude of the fundamental contractions while a pH change from 7.4-7.3 decreases the tonus waves. He also reported that the auricular tonus waves are more sensitive to pH changes than the occasional ventricular ones. Applying

this finding to cardiodynamics he deduced that pH regulates ventricular output either thru its direct effect on the ventricular tonus (as in cases of reversed cardiac beat when the auricular output does not influence the ventricular output) or, as is usually the case, thru its effect on the more sensitive auricular tonus and amplitude. Andrus (2) explains this effect of PH on auricular tonus on the rabbit as follows: the intracellular pH is lower than the extracellular pH; auricular excitability for rythm and susceptibility to excitation or inhibition of any kind depend on this difference in pH and decrease with its diminution. H_2CO_3, for instance, does not alter the auricular rythm but Na_2HPO_4 does, for the latter decreases the extracellular pH and being unable to endosmose reduces this pH difference between the inside and the outside of the cell, and thereby diminishes the rythm while H_2CO_3 to which the plasmahaut is permeable effects both pH's almost equally and hence does not influence rythm. For this same reason, sympathetic stimulation and sympathomimetic drugs are more effective on the heart at pH 8 than pH 7 while vagal stimulation and vagomimetic drugs at pH 7 than at pH 8. Mines (39) gives a different explanation: the hearts of frogs, pectens, and elasmobranchs would go into a diastolic standstill on addition to the perfusate of magnesium or of a smaller amount of a simple trivalent kation, or of an alkaline rare earth metal; they are more sensitive to simple than tocomplex kations and are revived by making the perfusate more alkaline, but their readiness to respond in this manner is of course variable. From all these findings he conc-

luded that the heart muscle contains an emulsoid which is negatively charged and that decreasing this negative charge by acids or kations would produce a diastolic standstill thru impairment of the rythm mechanism because excitability and contractility depend on plasmahaut differential ionic permeability which in turn depends on plasmahaut surface charge, the latter being determined by the nature of the plasmahaut and by the ionic composition of the cell medium. Kations by adsorption render the emulsoid much less negative or even positive, while alkalis bring about the opposite effect and thus lead to revival due to the amphoteric nature of the proteins. The emulsoid constituent of the hearts of frogs, pectens, and elasmobranchs differ in their isoelectric points owing to differences in their chemical structure. The excess negative charge on the plasmahaut or on the emulsoid surface as would entail a lack of magnesium, for instance, produces such aheightened excitability as to lead to a systolic standstill which can, however, be prevented or removed by the addition of an acid. Because the isoelectric point of the cardiac emulsoid of pectens is higher than that of elasmobranchs or frogs, the lack of magnesium in a neutral perfusate which produces a systolic arrest in the pecten's heart results only in an acceleration of frogs' or elasmobranchs' hearts. Mines [illegible] similarly tried the effect of alkaline rare earths on frogs' hearts and found that they resemble H^+ in producing a diastolic arrest but are much more potent and their effect is neutralized or prevented by OH^- (37,38). He finally classifies the ions that alter surface charge in the following way: nomadic

ions (like Na,K,Li,Rb,Cs,H,Cl,NO_3,OH) combining ions (like Ca,Sr, Ba) and polarizing ions(like H,Mg,Ce, and other simple trivalent kations, OH,citrate,phosphate, and complex trivalent kations). Iawi (36) found that a change of pH from 7.4-7.5 increased the diastolic tone in the isolated cat's heart while a change to pH 7.2 caused diastolic relaxation. Not only does a low pH produce a greater ventricular relaxation but a faster one too; thus in exercise as the pH changes from 7.3-7.1 (Barr and Himwick (36),) the heart may still be able to put out the normal amount of blood per beat inspite of the acceleration in rate. Henderson's superimposable plethysmograms of the heart would then not be always reproducible. In any case, such an effect of the pH is not considered as an evidence for the existence of tonus since the character of the contraction and relaxation has been altered.

Potassium brings about a smaller systole and more rapid diastole without any inotropic effect necessarily accompanying it, and thus lowers the diastolic level; while calcium hastens systole and delays diastole and so inhibits relaxation and raises the diastolic level. These changes are,furthermore, independent of any changes in rate or of any variation in the sustained diastolic contraction. Holzlohner and Otto Frank (36) as well as Gasser and Hill (36) discuss the action of these kations and ascribe their effects to physicochemical reactions of some kind that modify the normal course of contraction. Howell (2#) found that NaCl decreases the tone of the terrapin's ventricle, while $CaCl_2$ increases it and that both together produce a relaxation and contraction respectively. KCl antagonizes $CaCl_2$ but the antagonism is less in the presence of NaCl. Burridge (9) found that

lactic acid produces in the frog's skeletal muscle a quick surface shortening due to an increase in the osmotic pressure of the sarcomeres brought about by the exosmosis of potassium salts which are adsorbed on the colloids, followed by a slower shortening due to the exosmosis of potassium salts present in a suspensoid state in the colloidal system of the sarcomere. Potassium salts produce a tonic state in the frog's intestine; in small doses they produce a diastolic standstill, in bigger doses they have initially a similar effect followed later, however, by a maintained contraction. This action of potassium does not depend on a change in the osmotic pressure for an isosmotic NaCl solution in any dose always produces a diastolic standstill. Changes in surface tension may be the underlying mechanism of such effects of potassium and lactic acid. In any case, as far as potassium or sodium is concerned, neither of them varies sufficiently in concentration in the blood to be able to alter by their relaxing and contracting effects the physiological response of the heart muscle. Anyway, this study of the chemical composition of the heart's media does not, according to Meek (36) throw much light on the existence and nature of tonus for the followingtwo reasons:first, the alteration in the chemical composition of these nutrient media that produces a change in the diastolic level usually effects the contour of the fundamental contractions also; second, it would bring about such a physicochemical change in the diastolic phase that would allow a different type of relaxation or that would modify the elastic properties of the muscle or that would possibly alter the degree of sustained diastolic contraction (tonus) even tho it would

not lead to any alteration in the course of the fundamental contraction. To attribute, therefore, the results of the action of ions on the heart only to changes in tonus would probably be incorrect or at least not sufficiently substantiated by the experimental findings.

f.- Application of the two tests for the existence of cardiac tonus to the more recent experimental investigations.

So far, no positive proof has been given of the existence of tonus in the ventricle of cold-blooded or warm blooded animals. The absence of the spontaneous oscillations in the diastolic level (first test) plus the lack of proof of the influence on this level, ~~of the sustained diastolic contraction~~ of nervous stimulation, temperature, pH changes and ionic alterations (second test) warrant such a conclusion. But the requirements of these two tests have, however, been met since 1927 by the investigations of the following workers, and the evidence for the existence of ventricular tonus has, therefore, since, been found conclusive.

Appelrot (3) working on the isolated ventricles of Emys blandingii found very definite and spontaneous tonus waves that could be reproduced from the ventricle alone or from the aortic ring alone but much more markedly from both together. These aortic tonus waves in themselves offer a physiological proof of the smooth muscle theory of tonus oscillations. A rise of temperature augmented the ventriculo-aortic waves in intensity and frequency (as Pereira (4) found in the auricles of the cold-blooded animals) and had a similar effect on the fundamental contractions with this exception that the effect on the tonus waves outlasted the effect on the

beats while a fall in temperature had exactly the opposite effect. Vagal stimulation was without any influence or perhaps was slightly stimulating to these waves, at the same time, that it resulted in complete cardiac arrest. Furuta K. (14), however, reported that vagal stimulation in the turtle is depressant to the ventricular tonus waves altho his curves, according to Appelrot (in a personal communication to him) show that in those cases where apparent tonic inhibition occurred during vagal stimulation no cardiac arrest was simultaneously produced indicating that the stimulation was ineffective; on cessation of the latter there followed a period of definitely augmented tonic oscillations. In a later paper Furuta ( ) confirmed Appelrot's findings in this connection. Appelrot, in the same paper, reports that adrenaline in 1:1,000,000,000 and 1:20,000 concentrations depressed the tonus waves while ergotamine, in the same concentrations, had no effect. In the light of the work of Snyder and Andrus (48), previously mentioned, this finding may be explained on the basis of a lack of the adequate pH or of the paralysis by argotamine of both kinds of tonotropic fibers in the sympathetic. Hou and Chia's (25) finding that stimulation of the pure sympathetics in the toad raises the diastolic level of the suspension curves from an isolated sympathetic-vagus-heart preparation is contrary to this finding of Appelrot and adrenaline, but the discord may be ascribed to a difference in degree of concentration or stimulation applied. This sympathetic effect on the diastolic level is probably due to a tonic change because it was different in the auricular from the ventricular tracings indicating that it was not second-

ary to changes in the rate of the fundamental contractions. Appelrot further reports that carbon dioxide in high concentrations increased the tonus waves while oxygen had no effect. This effect is either due to CO_3 anion or to its effect on pH. Since it does not alter the difference between extracellular and intracellular pH (2), its effect on tonus must be rather ascribed to its ionic nature. But, ~~Furthermore~~ the attribution of its effect on tonus to a change in pH does not agree with Gaskell's finding (15) already referred to. Ketgham (29) had previously reported that carbon dioxide depresses the tonus level in the hearts of cold and warm-blooded animals. Marmorstein (32) working on dog's heart found that the auricular tone activity is not exclusive of ordinary contractile activity, but at the same time has no influence on it, and that a rise in the intraventricular pressure is secondary to a rise in the auricular tone which may be taken as an evidence against one of Andrus' (1) suggestions, already described, of the possible mode of action of pH on ventricular discharge. He also found that stimulation of the intraventricular septum below the pulmonary semilunar valves produces ventricular tonic contraction; whether this was secondary to any change in rate or contour of the fundamental contractions or not there is as yet no sufficient experimental data to decide. But this finding plus the finding of Laurens, (30) already referred to, may be taken as an evidence for the possible existence of a ventricular tone center in the hearts of mammalian and cold-blooded animals.

Thus, the appearance of spontaneous oscillations in the diastolic level of the fundamental contractions of the cold-blooded

ventricles (first test) plus their being subject to variation by temperature, nerves, drugs, pH, and ions (2nd test), definitely prove, beyond any doubt, the existence of tonus in these ventricles. The evidence for the existence of ventricular as well as of auricular tonus in the hearts of warm-blooded animals is still not as convincing, although smooth muscle, the anatomical basis of tonus has been reported in some of them by Maximow (33). The success of previous workers in proving definitely the existence of auricular tonus in the hearts of cold-blooded animals and their failure to discover in them ventricular tonus as well as auricular and ventricualar tonus in the hearts of warm-blooded animals may be attributed to a difference in the genera and species of animals used or to a difference in the amount of smooth muscle present even within different members of the same species or to differences in the experimental conditions (pH, temperature, drafts, handling, ions, etc.) which have, as was already mentioned, a definite regulatory influence on tonus waves and on the degree of sustained diastolic contraction

VII.-NATURE OF VENTRICULAR TONUS.

In the light of the more recent experimental findings just described the following conclusions about the nature of ventricular tonus seem warranted:

a.- Tonus oscillations depend on some structure in the muscle other than the sarcomeres which are responsible for the production of the fundamental contractions.

b.- Tonus oscillations are probably the rythmical automatic contractions and relaxations of smooth muscle.

c.- Elevation in the tonus level is probably an anabolic while its depression a catabolic process.

VIII.- FUNCTIONS OF CARDIAC TONUS.

a.- Prevention of valvular incompetence .

b.- Regulation of the systolic discharge (which is related to initial tension (1,17),).

c.- Prevention of mural dilatation.

d.- Direction of the greater and lesser circulations in the hearts of cold-blooded animals from the auricles to the ventricle.

I.- PROCEDURE.

Ventriculo-aortic and auricular tonus in 73 river turtles of the genus Testudo from Damascus was studied by the suspension method. The technique of Appelrot and Carlson (3) was followed with this modification that the hearts were not perfused but subjected to the action of various solutions by the drop method. The experiments were performed in autumn, winter and early spring and unless otherwise stated the temperature applied was that of the room. The effects of pH and ions were studied and ordinary solutions as well as buffers for pH control were used. Attempts at perfusing the ventriculoaortic preparations thru the aortic cannula were not successful on account of clotting which was impossible to remove or prevent without introducing a variable pH or ion factor. Heart preparations in situ were not studied because the turtles, even after decapitation, exhibit sluggish bodily movements which would interfere with the tracings. Such movements when they occurred in the limbs seemed purposive and aimed at position maintenance or correction; they continued usually for an hour after the excision of the heart and Papilian (42) who could produce them in whole animals after death by chemical injections, attributed them to chemical factors. The conditions reported in the literature as being inhibitory to the spontaneous tonus waves were carefully avoided; no air drafts were allowed (3); solutions of various ions (5) and at various pH's (48) and temperatures (43) were used;

the turtles were kept in water to cool (19) and the preparations were left standing for sometime to recover from the shock of handling (6).

II.-RESULTS.

No spontaneous oscillations in the diastolic level were noted in all the preparations used in this work. Only one, out of the 73 preparations showed oscillations similar to the spontaneous tonus waves of Emys described by Appelrot and Carlson (3) and by Furuta (14). Histological sections (8) of the six hearts examined showed the complete absence of smooth muscle from both auricles and ventricle.

A characteristic rise in diastolic and usually in systolic level followed by a corresponding fall, with no alteration in heart rate was produced in four heart preparations by lactic acid at pH 2.35 and by H_3PO_4 at pH 2.27. The fall began after the withdrawal of the solution and subsequent applications after H_3PO_4 of either lactic acid at pH 2.35 or H_3PO_4 at pH 2.27 reproduced the same wave in a more abrupt and intense way (see on page 38,39, tracings No. 1,2,3,4,5).

No significant changes in the diastolic level were noted when each of the following solutions at the different pH's mentioned was added to fresh hearts; neither was the heart rate changed but alterations in the amplitude were usually incurred:- Na-K-PO_4 buffer in 15 preparations, K-PO_4 and Na-PO_4 buffers in 7 preparations (10) (28) at pH 5.6, 5.8, 6.5, 6.8, 7, 7.2, 7.4, 7.6, 7.8, 8, 8.2; .11M NaCl in 16 preparations, .11M KCl in 10 preparations, and .11M $CaCl_2$ in 7 preparations at pH 5.5, 5.8, 6, 6.3, 6.5, 6.9 . The $CaCl_2$

solution, however, usually produced a transient marked wavy descent in the diastolic level.

A rise in diastolic and usually in systolic level succeeded by a fall was noted in 11 preparations after the application of either .00073M lactic acid or .00071M H_3PO_4 followed immediately by .0023M $NaHCO_3$ at pH 7.47 or .2M NaOH or .13M NaCl at acid pH or .6M KCl at acid pH or .5M $CaCl_2$ at acid pH (see on page 39, tracings No. 6,7,8).

III.-DISCUSSION.

The lack of smooth muscle in the hearts of the turtles used in this work probably explains the absence of spontaneous cardiac tonus ascillations since Schaner (46) and Laurens (30) and others have ascribed the latter to the rythmical contractions of the smooth musculature. The single preparation that showed them may have been of a different species of the same genus or may have had some smooth muscle. ~~in its heart.~~

The artificial single waves produced by lactic acid at pH 2.35 and by H_3PO_4 at pH 2.27 may be considered as tonic waves because they did not incur any alteration in the rate or contour of the fundamental cardiac contractions.

The fact that .11M NaCl or KCl or $CaCl_2$ and the phosphate buffers of either Na or K or both produced no change in diastolic level in spite of the variations made in their pH suggests that pH in itself, independent of the nature of ions, has no effect on general tonus. The work of Mines (39) already discussed shows the relative ineffectiveness of pH as compared with ions in producing a certain effect on the diastolic level.

In addition the conclusion of Haskell (15) and of Andrus (1) that a rise in pH raises diastolic level and a fall in pH lowers it, may not necessarily follow from their findings, because they perfused the heart preparations with several ions without running control experiments to isolate the effect of the pH from the effect of the ion. Gaskell, for instance, used as a perfusate defibrinated blood mixed with saline and regulated the pH with additions of lactic acid and NaOH, while Andrus used Ringer solution containing NaCl, KCl, $CaCl_2$, $NaHCO_3$, NaH_2PO_4 and regulated the pH with additions of HCl and $NaHCO_3$. In the light of this present work, no such conclusion as to the possible effect of pH on tonus can be warranted until the effects of these various ions at various pH's have been studied.

The artificial waves produced by the application of either .00073M lactic acid or .00071M H_3PO_4 followed immediately by .0023M $NaHCO_3$ (at pH 7.47) or .2M NaOH or .13M NaCl at acid pH or .6M KCl at acid pH or .5M $CaCl_2$ at acid pH are also tonic waves for the following three reasons. In the first place, they could not be produced until a certain level of the general tonus has been attained; this shows that they are dependent on a certain degree of sustained diastolic contraction which according to our definition of tonus is a definite prerequisite thereof (36). In the second place, they are independent of any alteration in heart rate since they persisted even when the heart rate became slow. In the third place, they are independent of the regular contractions and of any possible

changes in their contour as can be deducted from the fact that they continued to appear even after these fundamental contractions had almost disappeared.

The fact that the artificial fall in these waves was produced by $NaHCO_3$ or NaOH on the alkaline side of pH as well as by NaCl, KCl, $CaCl_2$ on the acid side at once removes the possibility of their being due to changes in pH; they must, therefore, be caused by changes in the character of ions. Our finding that H_3PO_4 produced a rise while the phosphate buffers of Na or K or of both when applied at different pH's brought about no change in tonus suggests that the PO_4 anion is a tonus stimulant and Na^+, K^+ kations are tonus depressants or are antagonistic to the PO_4 effect on tonus. On the other hand our finding that the descent in these artificial tonus waves was produced by NaCl or $NaHCO_3$ or NaOH while the attempt to produce them by varying the pH of NaCl or KCl or $CaCl_2$ obtained negative results, suggests that Ca^{++} as well as Na^+ and K^+ kations are probably tonus depressants while Cl^- anion is their antagonist.

These findings and deductions that the tonus level can be raised by PO_4^{---} or lactate or possibly Cl^- anions and lowered by Na^+ or K^+ or Ca^{++} kations support Mines' theory (39) of the mode of action of pH and ions, in general, on tonus and Burridge's conception (9) of the mode of action of lactate anion in particular. Again, the finding that the chloride of the divalent kation Ca^{++} had a transient wavy depressant effect on tonus, while the chlorides of the monovalent Na^+ or K^+ kations, as well as the phosphate buffers of Na or K

or both had none, also supports this theory of Mines on the relation between tonus level variation and the alteration in the surface charge of the cardiac emulsoid. The finding however, that NaCl, KCl, $CaCl_2$ lowered the tonus level after it had been raised by lactate or PO_4^{---} anions, is probably to be explained on the basis of a possible increase in the adsorptive power of the cardiac emulsoid subsequent to its subjection to the action of either of these two anions.

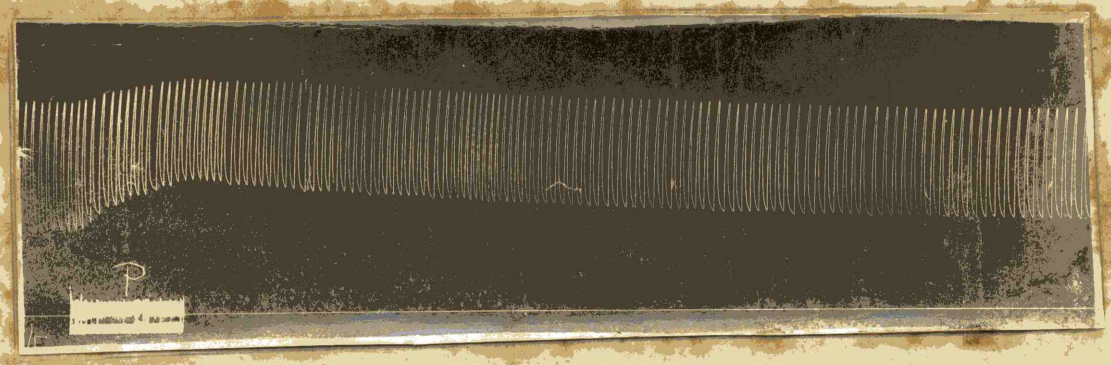
IV.- CONCLUSIONS ON CARDIAC TONUS IN THE RIVER TURTLE TESTUDO IBERIA:-

A.- No spontaneous auricular or ventriculo-aortic tonus waves could be recorded in the heart preparations of the turtles used which may probably be ascribed to the lack of smooth muscle.

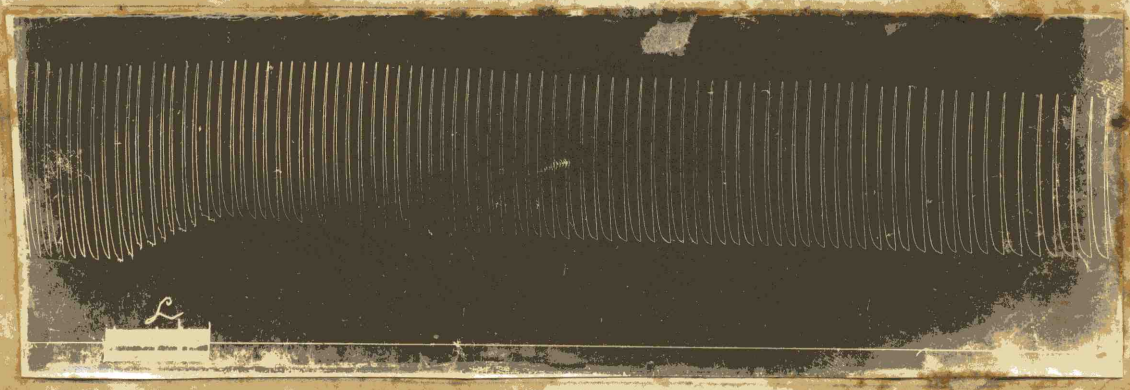
B.- The tonus level is uninfluenced by variations in pH that are independent of changes in ~~H~~ ions.

C.- The tonus level can be raised by the anions lactate, phosphate and possibly chloride and lowered by the kations sodium, potassium, and calcium.

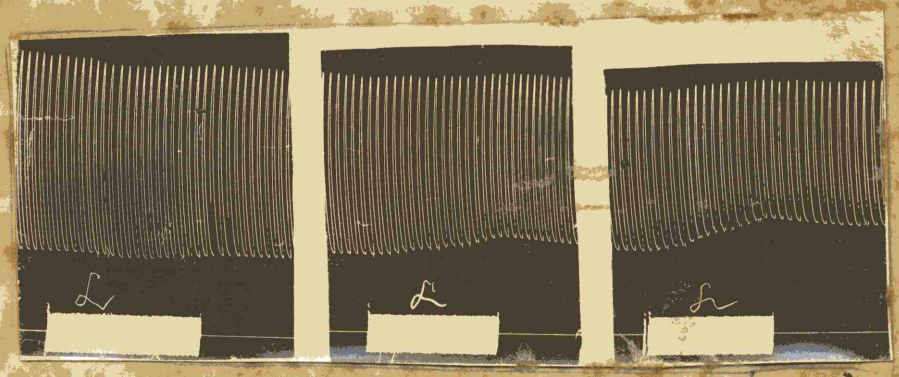
D.- Artificial tonus waves can be produced either by the separate application of lactate and phosphate anions, or, by their application quickly to be followed by the kation sodium, or potassium, or calcium.



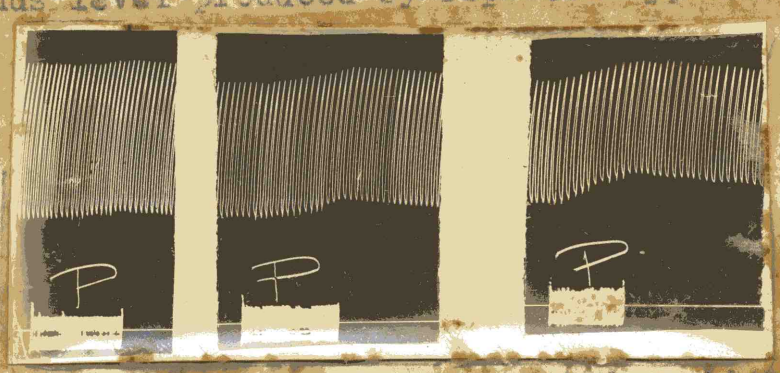
Tracing No.1
Showing tonus wave produced by application of H_3PO_4 alone.



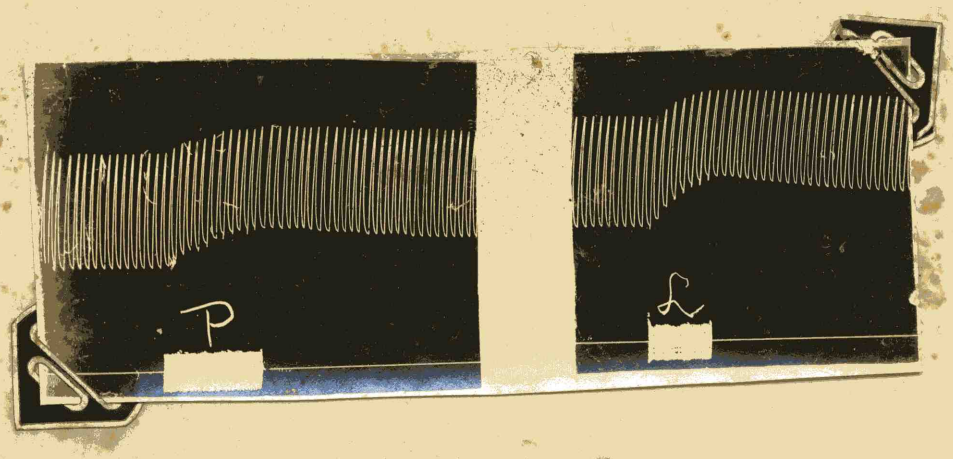
Tracing No.2
Showing tonus wave produced by application of lactic acid alone.



Tracing No.3
Showing effect on tonus level produced by repeated applications of lactic.

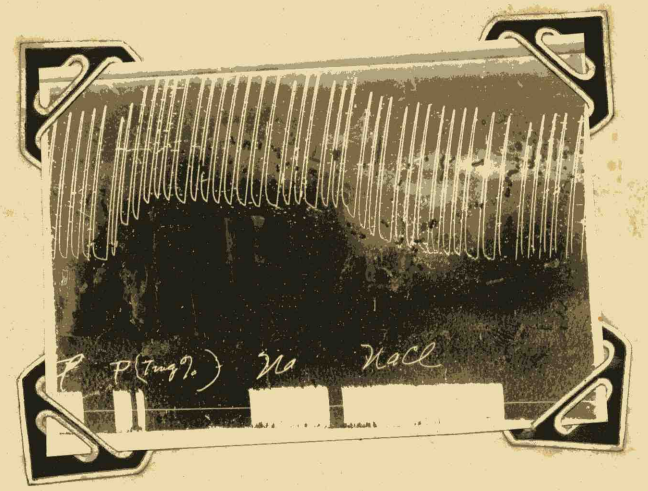


Showing effect on tonus level produced by repeated applications of H_3PO_4
Tracing No.4

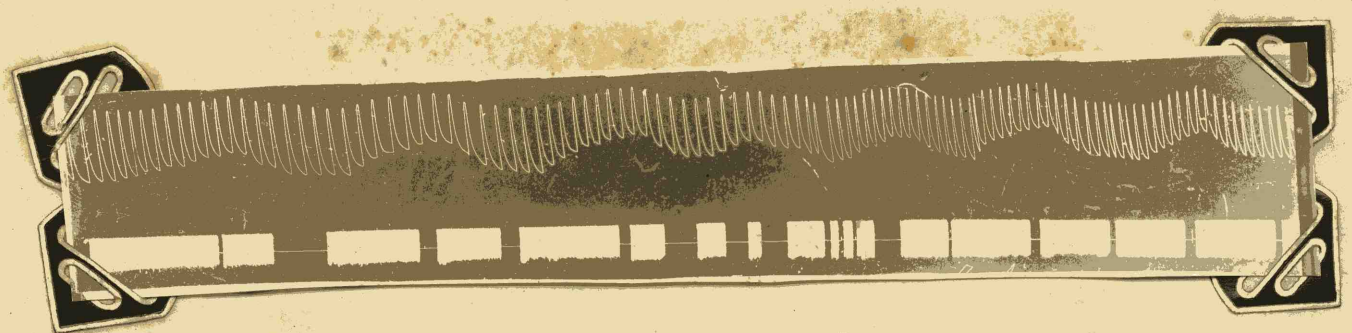


Tracing No. 5
Showing the tonus wave produced by lactic acid following H_3PO_4 Wave.

Tracing No. 6
Showing tonus level raised by lactic acid followed by a fall due to NaOH, rate of heart being slow.



Tracing No. 7
Showing tonus level raised by H_3PO_4 followed by a fall due to $NaHCO_3$ and then to NaCl, rate of heart being almost normal.



Tracing No. 8
Showing artificial tonus waves produced by alternating lactic withNaCl.

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