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Article 10580, by Steele, 1939, **41**, 86: Reference 4 should read, 1938, **38**, 10; Reference 8 should read, Hamilton, W. F., Brewer, G., and Brotman, I., *Am. J. Physiol.*, 1934, **107**, 427.

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Alterations of the Cardiac Cycle and of Polygrams Produced by Artificial Fever.

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According to Neymann[1] "the heart or its functioning is not harmed by artificial fever produced by physical means." The observations of Bazett and coworkers[2,3,4] on the effects of prolonged exposure to heat clearly indicate that a warm, humid external environment gives

[1] Neymann, C. A., *Artificial Fever*, Charles C. Thomas, Baltimore, Md., 1938, 251.

[2] Bazett, H. C., *Med. Rec.*, 1938, **147**, 301.

[3] Bazett, H. C., *J. Am. Med. Assn.*, 1938, **111**, 1841.

[4] Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D., *Am. J. Physiol.*, 1937, **119**, 93.

rise to changes which cause cardiovascular strain and subjects the patient to 'incipient cardiovascular failure'. Their observations show that factors leading to the development of a severe reduction in the venous return of blood to the heart overbalance the compensatory mechanisms of the cardiovascular system and eventually bring about the development of cardiovascular inefficiency. Furthermore, their findings are in agreement with the view that dehydration and diminished blood volume explain quite satisfactorily the prostration and discomfort of patients exposed to high external temperatures of long duration (8 to 10 hours) but it seems unlikely that these factors are responsible for the development of the undesirable subjective and objective symptoms frequently encountered during the induction stage of artificial hyperpyrexia. Since this phase of the problem has not been exhaustively investigated we elected to make a study of it by means of pulse tracings.

Studies on the cardiac cycle during fever therapy were made on human subjects. Optically recorded polygrams utilizing Frank capsules were combined with electrocardiograms. Central sphygmograms recorded from the subclavian or lower carotid artery were employed to determine the ejection phase of the cardiac cycle and phlebograms recorded from the subclavian or jugular vein were used to measure the various components of the filling phase. Artificial fever therapy was induced by means of an air-conditioned fever cabinet. The general procedure employed in our experiments was as follows: (a) control electrocardiograms of leads I, II and III were made; (b) control polygrams of the subclavian or jugular vein, subclavian artery, lower carotid, upper carotid, radial artery and apex beat were recorded simultaneously in groups of two on an electrocardiogram; (c) after finishing the control records, the subject was placed in the fever cabinet and the artificial fever started; (d) polygrams consisting of a central sphygmogram, a phlebogram and a lead II electrocardiogram were recorded at approximately each degree Fahrenheit during the elevation of body temperature up to and including 106°F.

Such observations were made on a series of 7 normal subjects and upon 4 patients who were receiving artificial fever therapy treatments. Our results may be briefly presented by citing some of the data obtained from the analysis of the polygrams thus recorded from a typical individual in the group. The pulse tracings of Subject No. 13 showed the following results: (1) The heart rate increased from 57 per minute to 140 per minute and the duration of the total cardiac cycle decreased from 1.05 seconds to 0.43 second. (2) The emptying time of the ventricles was progressively shortened from a normal duration of 0.34 to 0.18 second (53% of the normal emptying time). The reduced ejection phase was slightly more shortened than the maximal ejection phase. (3) The total filling time of the ventricles was rapidly reduced to 40% of the normal duration by the time the temperature was elevated to 100.5°F, and at this temperature level the filling time was less than the emptying time. Within a few minutes the filling time slightly increased in duration so that it again became greater than that of the emptying time, the body temperature in the meantime continuing to rise. (4) The constituent phases of ventricular filling were rapidly and more or less progressively diminished in duration as the body temperature was elevated, reaching their lowest respective levels at 102.5° to 103.5°F. The duration of the filling phases except for the phase of diastasis increased again as the temperature level was increased. (5) The phase of diastasis was often completely abolished at temperatures higher than 103.0°F. (6) Graphs constructed from the data showed that the duration of atrial systole and diastole practically parallel the ventricular isometric relaxation curve. These curves suggested the presence of similar functional changes in the behavior of the atrial musculature to those which presumably occurred in the ventricles during isometric relaxation. (7) The rapid filling and slow filling phases of the ventricles showed a marked reduction in the duration of the filling time at temperatures ranging between 102.5° and 103.5°F. Both the rapid and slow filling phase increased and remained somewhat prolonged though considerably less than the control filling time values. (8) The sphygmograms showed considerable alteration in size, shape and composition. They became more irregular in shape and were often definitely 'spiked'. The dicrotic notch became lower on the catacrotic limb, descending considerably below the base line. The dicrotic wave was frequently enlarged and prolonged. Additional anacrotic waves appeared and there were frequently several extra predicrotic and postdicrotic waves of frequencies ranging from 20 to 40 cycles per second. (9) The phlebograms showed considerable variation in size, shape and contour. The 'C' wave became accentuated, often converting an atrial type of phlebogram into an intact type. The vibratory waves of the second heart sound became exaggerated, the 'V' waves frequently became quite inconspicuous. Quite often there appeared to be no line of demarcation between the slow and rapid filling phases. The 'A' waves showed alterations in size. During the induction stage the 'A' wave frequently became relatively decreased in size but beyond 103 or 104°F, the 'A' waves again became relatively increased. These observations on the alterations of the 'A' wave of the phlebogram suggest that an increase in atrial activity may be a factor in cardiac compensation during the induction stage of artificial hyperpyrexia.

Conclusions. Analysis of the polygrams recorded during artificial fever suggest that the distressing symptoms one observes and the subjective discomfort experienced by patients during the induction of artificial hyperpyrexia are caused by an inadequate filling of the heart. The inadequate filling of the heart may be accounted for, in part at least, by an insufficient duration of the filling time. These observations further support the belief that the undesirable symptoms which occur during artificial fever therapy are caused by a temporary cardiac decompensation resulting from inadequate filling. Reduced cardiac filling probably results from (1) a reduced venous return resulting from uncompensated peripheral vasodilatation, (2) a shortening of the filling time, and (3) reduced blood volume.

Compensation may be accounted for not only by an increase in the efficiency of the emptying of the ventricles but also by a more adequate filling brought about by an increase in the venous return, an increase in the duration of the filling time and possibly by increased atrial activity.

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A Histological Problem Concerning the Conditions at the Nerve Endings in Skeletal Muscle.

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Until the recent appearance of the chemical transmission hypothesis[1] it was generally assumed that the excitation of skeletal muscle was effected electrically by the action current of the nerve ending. At present neither the chemical nor the electrical hypothesis can be considered to be well established. It seems likely from the nature of the problem that much of the decisive evidence must come from a demonstration that the structures and arrangements at the neuromuscular junction are more suited to the one type of transmission than to the other. In any case, the point of view must be consistent with respect to the structure of the junction and its function. It is our purpose to discuss a serious inconsistency which exists at present

1 Dale, H. H., Feldberg, W., and Vogt, M., *J. Physiol.*, 1936, 86, 353.