10. Advisory groups to the Director selected from membership in eight scientific and technical societies.

SUMMARY

From the Committee's extensive study of the Bureau's functions, its programs for discharging these functions, the facilities of the Bureau and its professional personnel, as well as from discussions with many scientists and engineers, it has reached some general conclusions. The major ones are listed:

1. The Bureau of Standards is of vital importance to national strength.

2. It is an organization with a splendid record and tradition, internationally recognized and respected.

3. It is, in general, staffed with professional men of competence, integrity and loyalty to the Bureau's functions and objectives.

4. With the increasing range and depth of technology, the need for the services of the Bureau of Standards becomes even more important and its functions more complex. The accurate determination of physical constants, the properties of materials, standards and standards practices and testing and evaluation procedures are all essential services for our industrial society.

5. Since the close of the war the technology of the nation has shot rapidly forward. The Bureau's basic programs expanded until 1950 but at a rate beneath that justified by the needs. Since 1950 the decrease in basic programs must be considered as tragic. The ground lost since 1950 should be regained in the next two fiscal years and the programs then expanded as detailed studies by the Director and his advisory committees find necessary.

6. Scientific and technical services to other agencies of Government are important responsibilities of the Bureau. In general, the Bureau has discharged these responsibilities well.

7. The Department of Defense and the Atomic Energy Commission have made broad and significant use of the Bureau. Their use of the Bureau in areas other than development of weapons is of value to the Bureau in its basic programs and should be encouraged.

8. The volume of weaponry development work has become large in comparison with all other activities of the Bureau. Its relative size and its effects on the other Bureau programs make its transfer from the Bureau desirable.

9. Other agencies of Government do not make as large use of the services of the Bureau as might well be expected. The Committee believes that an increase in the use of the Bureau by other agencies of Government should be encouraged.

10. If the recommendations of the Committee are followed, the Bureau should be in a positon to perform its authorized functions in balance at the minimum level for the nation's needs within a four-year period.

Excitatory Factors in Ventricular Tachycardia Resulting from Myocardial Ischemia. Potassium a Major Excitant[1]

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VENTRICULAR ECTOPIC ACTIVITY or the potentiality of ectopic activity following abrupt high ligation of the anterior descending artery of the dog occurs in three phases related to time elapsed since occlusion (*1, 2*). The first phase has a duration of about 10 min. During this period ectopic activity develops in almost all animals and precipitates ventricular fibrillation in 30–50% of them. In the animals in which ventricular fibrillation does not develop, ectopic activity passes through a maximum and declines to reach a level of only an occasional premature beat or ceases completely within 20 min or less after occlusion. First phase ectopic activity can be prevented by two-stage occlusion.

The second phase in the pattern of ectopic events is a period of little or no ectopic activity following the first phase, or following a two-stage occlusion bypass of the first phase. This period, during which there are only occasional ectopic complexes or none, has a duration as brief as 4.5 hr in some animals and as long as 7 or 8 hr in others, the majority being 5–6 hr.

The beginning of the third phase is indicated by the appearance of ectopic beats or a significant increase in their frequency if there were occasional ectopic complexes during the second phase. After the onset

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of the third phase activity, the ectopic frequency increases rapidly during the next 3 or 4 hr, then more slowly. A high-frequency ventricular tachycardia results and persists 2–4 days. Myocardial necrosis begins about the time of the beginning of the third phase, that is, the delayed ventricular tachycardia.

Experiments that were directed toward discovery and identification of excitatory factors that develop in myocardial ischemia and infarction have eliminated, rendered improbable, or relegated to a position of minor importance, certain hypothetical excitants. They have also provided evidence of activity by others.

Excitation via sympathetic nerve impulses, reflexly or otherwise activated, has been shown by sympathectomy experiments to be of little or no importance to the ectopic events that develop in myocardial ischemia and infarction. The delayed ventricular tachycardia develops in dogs with upper thoracic sympathectomy just as it does in dogs with sympathetic nerves intact, and shows little difference in frequency and time course (*2*).

To test the possibility that histamine, liberated from ischemic tissue, might be an excitatory factor in these ventricular tachycardias, histamine phosphate was injected into coronary arteries of normal dogs in doses varying from those that produced very little effect upon blood pressure to those that produced a profound fall in pressure. No ectopic beats resulted. In other dogs with myocardial infarction ventricular tachycardia, Pyribenzamine was administered intravenously in increasing doses to test its effect upon the tachycardia. No diminution in ectopic frequency resulted although Pyribenzamine administration was continued until convulsions were produced. Histamine has been eliminated, therefore, from the list of hypothetical ectopic excitation factors.

The presence of sympathomimetic substances in heart muscle has been demonstrated by a number of authors (*3–7*). It appeared possible that such substances might be released in ischemia and infarction. The administration of sympathetic blockade or sympatholytic drugs, especially Regitine, has exhibited a significant degree of ectopic impulse suppressor effect in dogs with third phase ventricular tachycardia. The degree of ectopic impulse suppressor effect varies considerably in different animals, and in the same animal on successive days of the tachycardia. These effects of Regitine in the dog with ventricular tachycardia resulting from myocardial infarction can be interpreted, a priori, as meaning that sympathomimetic substances liberated from ischemic myocardium constitute an excitatory factor of varying significance in these animals. If this is true, it appears probable from the same experiments that some other excitatory factor with more constant and predictable effect also exists. Regitine does not fully eliminate ectopic activity in any case, even when infused into the occluded coronary artery distal to the ligation. It must be remembered too that sympathetic blockade agents have other effects than specific antagonism to the action of sympathomimetic compounds, and that the ectopic impulse suppression exhibited might occur via some other mechanism (*8*).

Tissue extracts have been made from infarcted and noninfarcted myocardium from dogs and injected into coronary arteries to test for ectopic excitatory effect. These extracts produced ectopic beats and periods of ventricular tachycardia. In some trials the main ectopic activity resulting from the injection has a long latent period, as long as 10–20 min, and ectopic beats at low frequency may continue much longer. These results indicate clearly that some excitant with properties differing from those of epinephrine was present in the extract. Potassium was considered a possibility.

Potassium chloride solutions in varying concentrations were injected into coronary arteries of dogs without myocardial ischemia. Ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation were produced in different trials; the latency and intensity of the ectopic events depended upon the amount of potassium chloride injected. Analyses of some of the myocardial extracts that had produced ectopic activity demonstrated potassium concentrations equal to the potassium concentrations of some of the active KCl solutions. The experimental data to be presented are concerned with the problem of excitation by potassium: potassium that is liberated from the ischemic and autolyzing myocardium and potassium that is injected into coronary arteries.

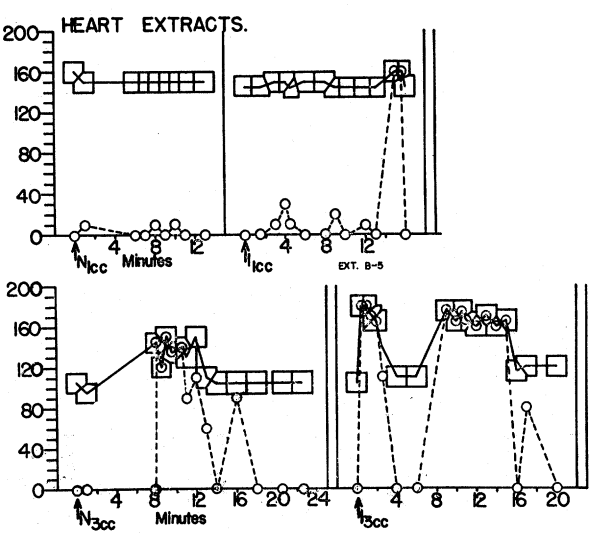

FIG. 1. Ectopic excitatory effects of injections of myocardial extracts. Arrows, times of injections; N, extract of normal tissue; I, extract of 24-hr infarct tissue; ordinates, beats/min; circles, ventricular ectopic rate; squares, total heart rate.

Figure 1 shows some of the results of injections of myocardial extracts prepared according to a method of von Euler (*9*). In the experiment illustrated in the upper chart, injection of 1 cc of extract from normal myocardium (each cubic centimeter prepared from 2 g tissue) produced a scattering of ectopic beats lasting about 10 min. In the second trial illustrated, 1 cc of

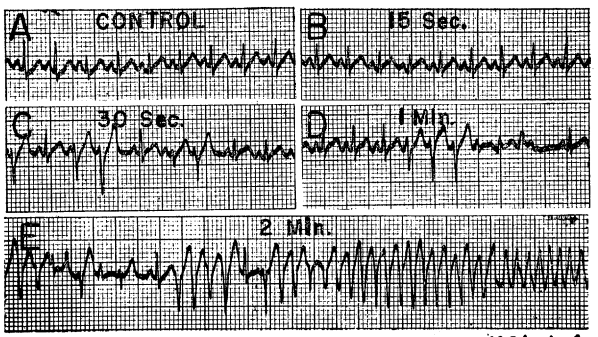

FIG. 2. Electrocardiograms: effect of injection of KCl, 2.8 mg/kg into the anterior descending artery.

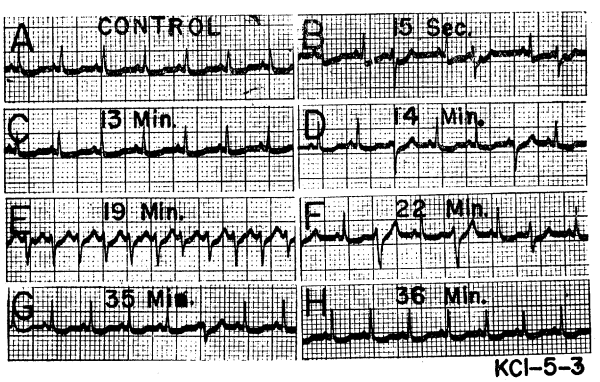

FIG. 3. Electrocardiograms: effect of injection of KCl, 1.15 mg/kg into the anterior descending artery.

extract from the infarcted region also produced a scattering of ectopic beats up to about 13 min, when a brief period of ventricular tachycardia with a frequency of 160/min was recorded. In the experiment 3 cc of extract from normal tissue produced no ectopic activity for the first 8 min. After a latency of 8 min, ventricular tachycardia with a maximal frequency of 150/min developed. Ectopic activity with varying frequency continued up to the 16th min. The injection of 3 cc of infarct extract to this dog produced an immediate ventricular tachycardia with a frequency of 180/min, which subsided after 3 or 4 min and then reappeared again at the 8th min and continued until about 17 min after injection. The immediate ectopic effects could have been due to sympathomimetic substance but the delayed tachycardia could not. Following some intracoronary injections of heart extracts, the ectopic activity continued in the form of occasional ectopic beats until approximately 40 min after injection. The differences in effects shown are random variations. No consistent difference was found between extracts from normal myocardium and those from 24-hr infarcts.

Results of injections of potassium chloride into the anterior descending artery are shown (Figs. 2 and 3). In Fig. 2, following the control electrocardiogram, KCl, 2.8 mg/kg in 5 cc of the dog's own blood was injected. This was a large dose. No ectopic activity is seen in the 15-sec record, but abnormal complexes are present in the 30-sec and 1-min segments. The 2-min record shows ventricular tachycardia accelerating into ventricular fibrillation. In Fig. 3, the control record was followed by intracoronary KCl, 1.15 mg/kg in 5 cc of blood, a much smaller dose. Little ectopic activity is shown until the 19th min when paroxysmal ventricular tachycardia with a frequency of 280 supervened. After the paroxysm, low frequency ectopic beats were recorded until the 35th min. The chart (Fig. 4) shows

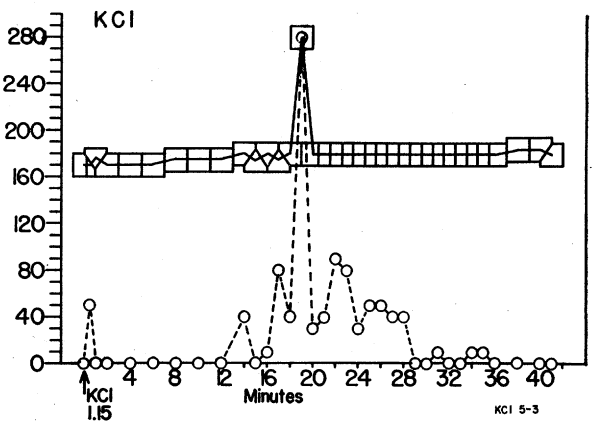

FIG. 4. Chart: experiment from which Fig. 3 was taken.

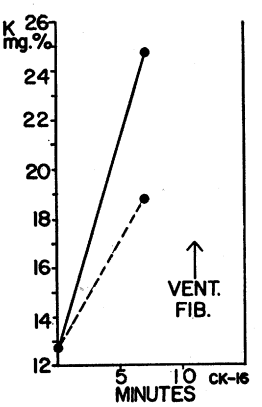

FIG. 5. Large increase in potassium concentration in blood plasma from coronary veins draining ischemic muscle and lesser increase in blood from vein in normal area during ventricular tachycardia preceding ventricular fibrillation.

the entire course of ectopic events recorded in the experiment from which the electrocardiograms in Fig. 3 were taken. The paroxysm was not sudden in onset and offset but showed a crescendo-decrescendo pattern lasting about 16 min.

Evidence of release of potassium in ischemic myocardium was obtained by determination of potassium concentration in plasma of venous blood drawn from the coronary veins draining the ischemic area following coronary occlusion. Figure 5 (solid line) shows a large increase in potassium content of venous blood from the ischemic area following abrupt occlusion of

the anterior descending artery. This blood sample was taken 7 min after occlusion, while ventricular tachycardia existed. The concentration rose from the control level of 12.75 mg% to 24.5. The ectopic activity continued and grew faster, culminating in ventricular fibrillation 4 min after the sample was drawn, or 11 min after occlusion. Determination of potassium in venous blood from a vein from the posterior surface of the ventricle (dotted line) shows a rise in potassium concentration about one-half as great as that in the vein in contact with the area of ischemia. This indicates that the venous drainage is mixed and that the liberation of potassium in ischemic heart muscle is greater than the quantities that are shown by analysis of blood from veins from the ischemic area alone, although these veins receive the greater concentration of excess potassium.

Figure 6 shows potassium concentrations in plasma from the ischemic region in an experiment with long duration. A pattern of variations that is characteristic of all 6 occlusion experiments of long duration with coronary venous plasma determinations is illustrated. The potassium concentration rose during the first few minutes of occlusion, fell off again, and then began a greater rise which reached its maximum on the first postocclusion day (22 hr determination). After passing through this maximum, the concentration declined again. In some experiments the potassium concentration has returned to the control level on the second or third postocclusion day. In the experiment shown, some elevation remained at the time of the last observation, 117 hr after occlusion. In other experiments, with determinations at different intervals than those in the experiment illustrated, the increase in potassium has shown a marked acceleration at about 4–5 hr after occlusion. The potassium concentrations show an encouraging positive correlation with the phases of ectopic activity. The first postocclusion day has always been the period of fastest ectopic ventricular complexes and the time when the tachycardia was most difficult to control with drugs.

Determination of potassium concentration in tissue, from the infarct and from normal myocardium on the fifth postoperative day in the dog from which the data (Fig. 6) were obtained, showed a loss of four-fifths of the potassium from the infarct.

It appears that sympathomimetic substances in necrotizing heart tissue may be an excitatory factor of some importance, but this conclusion is supported only by experiments with sympathetic blockade drugs.

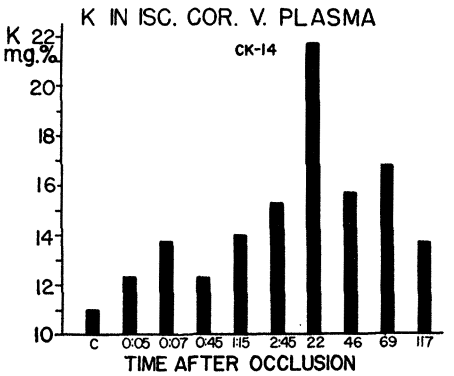

FIG. 6. Changes in potassium concentration in blood plasma from coronary veins draining ischemic (infarcted) area at selected times during 5 days of coronary occlusion.

Therefore, the participation of sympathomimetic substance in excitation during ischemia and infarction is regarded as probable, but not demonstrated.

Potassium, liberated in the ischemic muscle, however, is the factor upon which definite evidences from a variety of experiments converge in an unequivocal manner. Potassium injected into a coronary artery of a dog with continuing circulation produces ectopic activity. Ischemia of ventricular myocardium liberates potassium in sufficient quantities to significantly elevate potassium concentration in coronary venous blood from the ischemic area. A positive correlation exists between the periods of major elevation of potassium concentration in these samples and periods of most intense ectopic ventricular activity. The potassium concentration in these samples reapproaches control levels at times that correspond approximately to the times of disappearance of ectopic activity in infarction. Potassium content of infarcted muscle is greatly reduced at that time. The evidence for locally liberated potassium as an excitatory agent is very strong.

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