CHANGES IN MYOCARDIAL REACTIVITY IN WHITE RATS TO REPEATED INJECTIONS OF ADRENALINE

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It has been established that intramuscular injection of 0.5 or 0.8 ml adrenaline produces myocarditis in white rats. Frequent repetition of these doses with intervals no longer than 6 days do not result in repeated acute myocarditis, although there is shock with each injection. Rats sacrificed after many injections show only myocardial scarring similar to that seen in rats after a single injection sacrificed after the same period of time.

When frequent injections are given the animals tolerate doses of adrenaline which even exceed the lethal dose. This is evidently due to "areactivity" of the myocardium to repeated injections, since acute myocarditis is removed from the complex of reactions to adrenaline under these conditions [1].

Changes in myocardial reactivity were discovered morphologically. The effect of repeated injections on cardiac activity remained unclear. This question was studied by means of electrocardiography*.

Initially ECG changes following a single intramuscular injection of 0.5 ml adrenaline (12 rats) were determined. In the majority of the rats changes in the ECG appeared within 5 minutes after injection: displacement of the S-T_{CR4} interval above or below the baseline, diminution or inversion of T_{CR4} and increase or decrease in the voltage of R_{CR4}. These changes became more pronounced after 20-40 minutes, while after 24 hours they were present in all rats, in some cases to a very marked extent and not only in the chest lead IV but also in the three standard leads. Nine rats were sacrificed 24-25 hours after the injection. Microscopic examination of the heart disclosed acute myocarditis of varying intensity. The remaining rats showed the ECG changes described over a period of a week following the adrenaline injection. On the 7th day the S-T_{CR4} displacement was seen to be less marked, the voltage of R was restored and the T wave returned to normal in all leads. By the 12th day after injection the ECG was normal. The rats were sacrificed on the 23rd day after the beginning of the experiment.

Histologic examination of the hearts of these rats revealed only focal cardiosclerosis. The number and size of scars served as indicators of the severity of myocarditis.

These experiments showed that following injection of adrenaline, changes in the ECG often become apparent before the usual histologic methods can demonstrate the presence of inflamatory processes in the myocardium. Thus, 5-40 minutes after adrenaline injection the myocardium only shows hyperemia while the ECG points to disturbances of contraction and metabolic processes (reduction in voltage of the waves, S-T_{CR4} displacement and smoothing out or inversion of T_{CR4}.

Our previous experiments with alternating injections of adrenaline and sympatholitin led to the conclusion that the process underlying myocarditis began almost instantaneously following the injection of adrenaline. Morphologically, however, myocarditis is rarely apparent earlier than 3-6 hours after the injection. ECG also indicates the rapidity with which mechanisms underlying adrenaline-induced myocarditis are called into play – as

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early as 5 minutes after the injection there are consistent changes in the ECG.

Towards the end of the first post-injection day both the histologic manifestations of myocarditis and the ECG changes are fully developed. Acute and subacute myocarditis lasts 6-8 days. During this time the ECG changes also persist. Scarring of the myocardium begins to take place from the 6th day. At the same time a beginning of ECG recovery can also be seen. By the 12th-23rd day, when the myocardial scars are fully developed, the ECG is little different from normal. Apparently focal cardiosclerosis does not always find reflection in the ECG.

Investigations have shown that ECG reflects the development of adrenaline-induced myocarditis, not only when it is morphologically evident but also in its very earliest, insidious period.

It was also found that there was correlation between the extent of ECG changes and the stage of development of myocarditis. In rats with diffuse and predominantly parenchymatous myocarditis the ECG changes were more profound and clear-cut not only in the chest lead IV but also in the three standard leads.

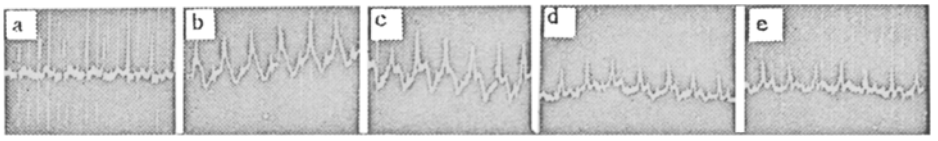

Fig. Rat No. 1029. Daily injections of 0.5 ml adrenaline. Rat sacrificed on the 9th day. Microscopic evidence of diffuse cardiosclerosis. Electrocardiograms – chest lead IV. a) 5/9/1955 ECG before the experiment. R = 0.7 mv; b) 5/10/1955. ECG 24 hours after first injection. R = 0.8 mv. S-T displacement above baseline; T negative; c) 5/12/1955 ECG 24 hours after third injection. R = 0.5-0.7 mv. T negative; d) 5/16/1955. ECG 24 hours after seventh injection. R = 0.5-0.8 mv. T weakly negative; e) 5/17/1955. ECG 24 hours after eighth injection. R = 0.5 mv. T positive.

In the next group of experiments (16 rats) injections of "myocarditic" doses of adrenaline (0.5 ml) were given daily. ECG records were taken before each injection and 40 minutes after it. The rats were sacrificed on the 9th day, 24 hours after the eight injection.

Forty minutes after the first adrenaline injection there was lowering or increase in the R_{CR_4} voltage and sometimes notching of this wave, displacement of the $S\text{-}T_{CR_4}$ interval above or below the baseline and lowering and sometimes inversion of T_{CR_4}. 24 hours after the first injection the same changes were seen, but more marked; in some rats they were seen in all four leads.

During the next 5-6 days no new changes were observed in the ECG.

Neither the first nor the subsequent injections were usually accompanied by disturbances of the cardiac rhythm.

Signs of recovery appeared in the electrocardiagram 6-8 days after the first injection: increased height or appearance of a positive T wave in all leads and restoration of the R wave voltage. On the 9th day the ECG of these rats differed little or not at all from normal (see Fig.).

Correlation of ECG changes with histologic data showed that the extent of ECG changes in this group of experiments corresponded to the severity of myocarditis associated with the first injection.

These investigations thus established that with daily injections of "myocarditic" doses of adrenaline only the first injection is significant with respect to the myocarditis. Further "areactivity" of the myocardium consists not only of the absence of new bursts of acute myocarditis following repeated injections, but also of the absence of repeated characteristic changes in the ECG.

There is no doubt that electrocardiographic changes reflect the appearance of acute myocarditis. They either remain on the same level or become somewhat more pronounced during the acute and subacute periods of myocarditis. As myocarditis changes to cardiosclerosis the ECG becomes more normal despite the daily

administration of "myocarditic" doses of adrenaline. Since it is taken that ECG reflects biochemical processes in the myocardium it would appear that the complex of reactions characteristic for adrenaline undergoes qualitative changes on repeated injections of large doses of this substance. There are references in the literature [2] to adaptation of the organism to adrenaline.

The data obtained point to adaptation to an "extraordinary" stimulus as being at the basis of the changed reactivity of myocardium to repeated large doses of adrenaline. This is more especially interesting since adrenaline under the particular experimental conditions is an "extraordinary" stimulus in the quantitative sense only, being a constant agent in the physiology of the organism. Such rapidly developing adaptation can be referred to the category of tachyphylaxis. This phenomenon, known to occur with respect to adrenaline as evidenced by functional indicators, can apparently also occur in such organic lesions as adrenaline-induced myocarditis.

SUMMARY

Frequent injections of large doses of adrenaline in rats, resulted in myocarditis with characteristic changes of ECG only after the first injection. As the myocarditis developed into cardiosclerosis, the ECG became normal in spite of daily injections of "myocarditic" doses of adrenaline.

The changed adrenaline response following the first injection may be regarded as an adaptive phenomenon.

LITERATURE CITED

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