# PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

## REFLEX MECHANISMS IN THE PATHOGENESIS OF ADRENALIN MYOCARDITIS

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We have shown previously [1] that a single injection of a pharmacological solution of adrenalin into rats, at certain dosage levels (0.5-0.8 ml), causes a myocarditis, usually in an acute form. The response of the animals to adrenalin changes after the first, myocarditis-provoking injection, and subsequent injections no longer give rise to myocarditis. Experiments making use of adrenalin antagonists showed that the process leading to development of myocarditis begins almost immediately after the injection of adrenalin, and precedes considerably the appearance of morphological signs of myocarditis.

We hence concluded that the nervous system is basically involved in the development of adrenalin myocarditis.

In order to elucidate the role of nervous factors in the initiation and development of adrenalin myocarditis we instituted experiments in which myocarditisdoses of adrenalin were administered to anesthetized animals (ether, amytal) and to animals which had been subjected to decortication, to bilateral vagotomy, and to intramuscular injections of procaine.

Adrenalin was injected in doses of 0.9 ml into 6 rats given ether anesthesia, immediately after disappearance of corneal reflexes. Ether was discontinued immediately after completion of the injections, so as to avoid overdosage with ether. One rat died 2 hours after injection, with symptoms of adrenalin shock, with pulmonary edema and hemorrhagic infarction of the lungs. The remaining rats survived the adrenalin shock, and were killed by administration ofether 24 hours after the injection. Histological examination of the heart showed that all five were suffering from acute myocarditis, which was severe in 3, and mild in 2 animals.

Amytal was injected subcutaneously into 10 rats in doses of 1.5 to 2.3 ml of 2.5% solution, and adrenalin (0.8 ml) was injected immediately after disappearance of corneal reflexes. Two rats died soon after, with symptoms of adrenalin shock, and the surviving 8 rats were killed 48 hours after the adrenalin injection; they were all suffering from severe acute myocarditis.

One ml of 2% procaine was injected into the right femoral muscles of each of 12 rats, followed after 30 minutes by 0.8 ml of adrenalin into the left thigh. All the animals went into adrenal shock; ten of them died within a few hours of the injections. The 2 survivors were killed 48 hours after injection of adrenalin and were found to be suffering from acute myocarditis.

Bilateral vagotomy was performed under amytal anesthesia, in a one-stage operation on the cervical section of the vagus nerves. One rat of the group of 10 operated died an hour later, and 6 rats after a few hours; autopsy revealed focal and confluent pneumonia in these animals. Injections of 1 ml of adrenalin were given to the three survivors, 1 hour after operation to one, and 24 hours after to the other two; of the latter, one died an hour after injection. The two surviving rats were killed with ether 24 hours after the injection, and both were found to have acute myocarditis.

A group of 10 rats was decorticated under profound amytal anesthesia (1-1.2 ml of 2.5% amytal subcutaneously); the cortex of both frontal lobes was removed with a sharp curette, as well as the convex surface of both cerebral hemispheres. Four rats died within a few hours or days of the operation, 9 days after which the surviving rats were given an intramuscular injection of adrenalin (0.8 ml). One rat died in adrenalin shock soon after the injection, and the remaining rats were killed 24 hours later. All of them had severe diffuse acute myocarditis.

Thus none of the measures taken by us prevented the onset and development of adrenalin myocarditis, which was particularly severe in decorticate animals.

We next proceeded to investigate experimental conditions such as would permit of a closer approach to the elucidation of the reflex mechanisms involved in development of adrenalin myocarditis. With this object we studied the effect of transecting the spinal cord at $C_7$-$D_1$ level.

This experimental procedure was based on experimental morphological data on the afferent innervation of the heart.

According to the work of A. E. Smirnov [5, 6], B. I. Lavrentyev [3], and E. K. Plechkova [4], the afferent fibers of the heart proceed partly with the vagus nerves, and largely through the posterior roots of the upper thoracic segments of the spinal cord, passing through the stellate ganglion. E. K. Plechkova's experimental morphological studies [4] showed degeneration of myocardial receptors following excision of the upper thoracic intervertebral ganglia, in confirmation of Langley's physiological studies, from which it appeared that the first five and partly the sixth thoracic ganglia receive afferent fibers from the heart.

A second indication for our experiment was to be found in present-day concepts of spinal shock. It is known that spinal shock following partial or total transection of the spinal cord is manifested by transient disappearance of reflex reactions in which the parts of the spinal cord distal to the section are involved. The duration of this condition varies for different animal species, from hours for poikilotherms to weeks for homeotherms, in particular for the higher forms (dogs, monkeys [2]. The duration of spinal shock in rats has not, to our knowledge, been established. It is supposed that the suppression of reflex activities caudal to the traumatized point of the spinal cord is due basically to development of inhibitory processes. Active inhibition is ascribed to disturbance of interneuronal (synaptic) transmission in the spinal cord distal to the point of section [2].

On the strength of these data we transected the spinal cord immediately above the zone of spinal innervation of the heart (at the $C_7$-$D_1$ level). It was hoped that this would be followed by temporary suppression of the reflex activity of the parts of the spinal cord distal to the section, including its upper thoracic segments, which are directly concerned in the innervation of the heart.

Additionally, transection of the spinal cord at this level should to some extent eliminate central nervous system effects on the spinal innervation of the heart, and should, in particular, interrupt impulses from the carotid sinus zone.

Altogether 146 rats were operated, in deep amytal or ether anesthesia (disappearance of corneal reflex), the spinal cord being cut immediately below the spinal process of the 7th cervical vertebra. Of the operated rats 56 died before injection of adrenalin (action of the anesthetic, during section, or post-operational). Intramuscular injections of adrenalin were given to 90 rats at various times after the operation, from 10 minutes to 48 hours; 54 rats received 0.5 ml, and 36, 0.8 ml of adrenalin.

The clinical manifestations of adrenalin shock in operated rats were atypical. Asthmatic symptoms were not always seen, labored, infrequent respirations being observed in a number of cases. Exophthalmos was not seen, as would be expected, in view of the trauma to the spinal center of the ocular reaction, and of the possibility of suppression of synaptic transmissivity in the thoracic segments of the spinal cord in spinal shock. Only 21 of the rats survived longer than a day after the injection (these were killed by decapitation or ether). Of the others, 2 survived for 15 and 16 hours, 6 for 9 hours, 4 for 6 hours, 14 for 3-4 hours, and the remainder died within 3 hours of the injection, in adrenalin shock.

Before proceeding to describe the results of these experiments we would like to consider our earlier results, on adrenalin myocarditis in normal animals following a single injection of adrenalin, at the same dosage levels (0.5 and 0.8 ml) as fo the spinal animals. We found that at dosage levels of 0.5 ml 8.7% of the rats did not

develop myocarditis within 24 hours of the injection, as compared with 1.3% with doses of 0.8 ml. Various degrees of intensity of myocarditis were encountered at one and the same dosage levels, and there were wide variations in the relative intensities of the vasomotor and exudative components of the inflammatory reaction.

The histological data on the control animals allows of its classification according to severity of myocarditic changes – mild, moderate, and severe. A mild degree of inflammatory change was observed in only 6% of rats receiving doses of 0.8 ml, and in 8.7% of those receiving 0.5 ml of adrenalin.

As for the controls, histological studies were made of transverse sections of the heart of adrenalin injected spinal animals. Two or three fragments 2-3 mm thick were taken from the region of the papillary muscles, as compared with one piece from the same level of the heart of control animals. We did not take longitudinal sections through the whole length of the heart, in view of the topography of the inflammatory changes, which are most often encountered in the papillary muscles and in the wall of the left ventricle. The fragments were sectioned on a freezing microtome, and were stained with Sudan III and hemotoxylin.

Signs of myocarditis were found in only 9 of the 21 operated rats which survived 24 hours or more after adrenalin injection, and the condition was of mild intensity. No evidence whatsoever of myocarditis could be found in the remaining 12 rats; the myocardial changes were confined to hyperemia and more or less marked protein dystrophy of the muscle fibers. The control rats, injected at the same time as the spinal ones, with identical doses, and killed 24 hours later, gave histological evidence of severe myocarditis (20 rats).

A comparison of the incidence of myocarditis in the control groups of this and of our earlier experiments (196 rats) with that found for spinal rats shows clearly that absence of myocarditis in 12 of 21 animals could not be fortuitous, the more so as it was of only very mild degree in the remaining 9 rats. Our control material shows that such mild reactions are only very seldom encountered.

Considerable differences were also found between controls and animals which survived only 16, 15, and 9 hours after injection; myocarditis was either absent from the latter group, or was of very mild degree, whereas it was usually fairly well developed in the control animals. No clear-cut differences were observed between control and spinal animals in the groups surviving injection of 0.8 ml of adrenalin for 6 and 3 hours, the only changes being marked hyperemia, with extravasation, found in both the control and the spinal animals, although myocarditis did not as a rule develop in the latter. This is evidence that the myocarditic process cannot be considered to be a result of a reaction to neuroparalytic hyperemia, which is more likely to be only a component of the inflammatory reaction, rather than its cause. We therefore think that we are justified in considering the changes found in the myocardium after injection of large doses of adrenalin as myocarditic ones, the more so as they possess all the morphological features of inflammation, varying only in intensity from one case to another.

Our experiments show that injections of myocarditic doses of adrenalin into rats after section of the spinal cord at the $C_7$ - $D_1$ level either do not result in myocarditis, or are followed by only a very mild form of the disease. This may be taken as evidence that interference with the reflex activity of the spinal cord in the zone responsible for innervation of the heart modifies the response of the myocardium to dosage levels of adrenalin which regularly cause an inflammatory reaction in intact rats. It hence follows that the process leading to development of myocarditis is connected with a reflex mechanism. Our earlier experiments with Sympatholytin* provide indirect confirmation of this view. The exceptionally severe form of adrenalin myocarditis encountered in decorticate animals is also undestandable from this viewpoint. It may be related to the heightening of stimulability, and hence of reflex activity, of the lower levels of the central nervous system, as well as of the medulla oblongata and the spinal cord, after elimination of the inhibitory action of the cortex. Disturbances of compensatory nervous mechanisms due to ablation of considerable parts of the cerebral cortex may also enter into the picture.

There are two elements which may be of significance in the mechanism of development of adrenalin myocarditis in spinal animals. These are depression of reflex activity of the parts of the spinal cord caudal to the section (spinal shock), and interruption of centrifugal and centripetal impulses passing through the spinal cord. In the acute experiments here described the former element is given more prominence, viz.. the significance of suppression of reflex activity of the spinal cord in spinal shock. It will in the future be necessary to study the effect of injecting adrenalin at later stages, after the disappearance of the symptoms of spinal shock.

*An adrenalin antagonist [1].

Such studies should contribute to the elucidation of the relative importance in the pathogenesis of adrenalin myocarditis of spinal shock, on the one hand, and of interruption of conducting systems of the spinal cord on the other.

Section of the spinal cord is admittedly a serious trauma of the nervous system, evoking a complex series of changes in nerve tissue relations. However, our experiments with decorticate rats show that the results observed are not merely a consequence of traumatization of the central nervous system, and the same is shown by experiments on animals in which the spinal cord had been transected at the $L_1$ level (11 animals). In both of these groups the animals had suffered equally severe trauma of the central nervous system, but adrenalin myocarditis developed in both groups, and was particularly severe in the decorticate rats.

There are a number of possible explanations of the development of mild forms of myocarditis in spinal rats after adrenalin injection. Firstly, the localization of the spinal centers of cardiac innervation may vary from one individual to another, so that transection at the $C_7$ - $D_1$ level does not interrupt impulses from centers situated more distal than ordinarily. Secondly, under our experimental conditions the vagus innervation of the heart remained intact. B. I. Lavrentyev [3] has shown that in some cases the greater part of the cardiac receptors may be connected with nerves of the vagus system, instead of with the thoracic intervertebral ganglia. According to him, this may be the reason for the variable results obtained in treatment of angina pectoris by procaine block of the stellate ganglion. A third possible explanation of the development of myocarditic symptoms in some of our experimental rats is that the experiment was designed for conditions of spinal shock, i. e., of functional changes in spinal reflex arcs connected with the heart; different degrees of depression of reflex activity are hence possible, as well as differences in duration of the condition of spinal shock.

We would like, in conclusion, to mention that adrenalin myocarditis can be regarded as an experimental model of myocarditis, very frequently used in physiology and pharmacology for the study of various physiological phenomena and of the action of drugs used for its treatment. The results of our study of the pathogenesis of adrenalin myocarditis may be taken into account in deciding whether to use this model, and how to apply it to other experimental studies. Our basic object in undertaking the present research was to find an approach to the problems of the pathogenesis of myocarditis encountered in the clinic.

## LITERATURE CITED


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