

ANAPHYLAXIS IN THE ISOLATED HEART

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Evidence is not wanting that the heart is affected in the process of anaphylactic shock. Morphological alterations following the injection of foreign protein into sensitized animals, local areas of degeneration of the myocardial cells with round cell infiltration or, later, scar formation, have been reported by Longcope (11), Klinge (9), and by Seegal, Seegal and Jost (14). Electrocardiograms recorded in the intact animal during anaphylactic shock, demonstrating disturbances of conduction and abnormalities of origin and spread of the excitatory process in the heart, have been described by Auer and Robinson (1), Hecht and Wengraf (8), Koenigsfeld and Oppenheimer (10) and by Crip (5). But the exact nature of these effects, whether intrinsic, or secondary to asphyxia (5), or to the remote elaboration of substances which secondarily react upon the myocardium (3), is not clearly defined.

The proof that any organ is intrinsically affected by the process of anaphylaxis must rest upon certain distinct criteria: (a) It should be shown that the capacity of the tissue to react specifically upon exposure to the appropriate antigen survives its isolation from the remainder of the animal and persists in the organ perfused or immersed in artificial solution, and, (b) the particular reaction should be evoked by doses of antigen which fail to affect an organ isolated from an unsensitized or desensitized animal and should diminish in intensity or disappear with successive exposures thereto.

The essential features of anaphylaxis have, indeed, been demonstrated in this fashion *in vitro* upon isolated segments of intestine (6) from sensitized guinea pigs and upon the isolated uterus (13) from similar animals. Reactions which fulfill the above criteria have been observed to occur in the isolated hearts of warm blooded animals by Caesaris-Demel (4), Mendeleeff, Hannevart and Platounoff

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(12), and by Went and Lissák (18). The latter report that, as recorded by a myographic tracing, the heart beat is depressed, sometimes after preliminary acceleration, following the introduction of small quantities of antigen into the perfusing fluid.

The observations reported herein were undertaken with a view to analyzing the anaphylactic reaction by means of simultaneous myographic and electrocardiographic records, together with measurements of the rate of flow of the perfusate through the isolated heart.

Method

Young guinea pigs were rendered sensitive to horse serum by the intraperitoneal injection of 0.1 to 0.5 cc. 3 to 5 weeks later the hearts of these animals were isolated and perfused with Ringer-Locke solution at 35°C. and a pressure of 75 mm. Hg by a modification of the Langendorff technique. A myographic tracing of the ventricular beat was recorded by means of a thread attached to the right ventricle. Electrocardiographic records were obtained by contact electrodes of worsted wet with salt solution attached to tissue of the superior mediastinum removed with the heart and to the apex of the left ventricle.

One detail of this technique deserves particular reference. In this preparation, the inflow cannula being tied into the aorta, the perfusate may follow one of two courses. By far the major portion thereof enters the coronary arteries in the sinuses of Valsalva, flows through the coronary vessels, and leaves them largely through the coronary sinus into the right auricle or *via* those Thebesian channels which empty into the right heart. In the present experiments this fluid has been collected by means of a siphon cannula thrust into the right ventricle through the pulmonary artery, the venae cavae having been previously ligated, and has been measured by means of an electric drop recorder. This, though not actually the entire coronary flow, but certainly a large aliquot thereof, will be referred to below as C flow. The remainder of the perfusate passing through the coronary circuit escapes through those Thebesian vessels which empty into the left heart. This, plus such fluid as may regurgitate past the aortic and mitral valves, finally escapes through the severed pulmonary veins or through a small hole made into the cavity of the left ventricle. Constituting about one-fourth of the total flow this will hereinafter be called leakage flow. Since, when recorded, this leakage flow has always been found to vary in the same direction as the C flow it has not been registered in all the experiments.

The antigen diluted to 1 cc. with warm Ringer-Locke's solution was introduced by injection through the wall of the rubber tubing into the stream of the perfusing fluid immediately above the cannula.

RESULTS

The injection of 0.01 to 0.1 cc. of horse serum into the perfusate about to enter the heart removed from a normal guinea pig, so isolated,

is without significant effect. In a small proportion of instances the larger doses may provoke a slight evanescent change in the amplitude of contraction or an occasional extrasystole. It is noteworthy that such effects, when observed, are completed within 8 to 20 seconds after the injection and are unaccompanied by demonstrable changes in C or leakage flow. Identically negative results are obtained when horse serum in such amounts is brought into contact with a heart removed from an animal after fatal anaphylactic shock evoked *in vivo* by the same antigen, or with a heart previously sensitive *in vitro* but desensitized by one or more exposures to small amounts of antigen in the perfusate.

When, on the other hand, 0.002 to 0.005 cc. of serum is introduced into the heart removed from a guinea pig previously sensitized with the same, there ensues an entirely different series of events. There is no noticeable effect for about 1 minute. Then occur a striking acceleration of the heart rate and alteration in the amplitude of contraction. Electrocardiograms taken at intervals before and after the onset of this reaction disclose prolongation of the P-R interval, changes in form of the QRS and T complexes, and ectopic rhythms. In a number of instances the ventricular rate has exceeded the auricular, producing auriculoventricular dissociation with ventricular tachycardia. All these phenomena pass off within 5 to 15 minutes and the myographic and electrocardiographic records reassume the form present before the injection of serum. Subsequent injections of even larger amounts of serum produce less pronounced reactions or none.

The magnitude of the cardiac acceleration observed in eight such experiments with the chief alterations in the electrocardiographic records in each instance are summarized in Table I. Portions of representative electrocardiograms are illustrated in Text-fig. 1.

But in the present study an additional effect, which is presumably of primary importance, has been observed invariably to accompany the phenomena of cardiac anaphylaxis just described. In every instance the reaction has involved a striking reduction in the rate of coronary (C) flow. This is illustrated in Text-fig. 2, in which are depicted cardiac rate and coronary (C) flow in a characteristic experiment, and in Table II*a*. In many instances the sudden drop in

coronary flow has been observed to precede, by a perceptible interval, the typical myographic and electrocardiographic changes. That these variations in the rate of C flow represent actual changes in caliber of the coronary vascular system, and are not due simply to increase in heart rate or tonus, is demonstrated by such experiments as those illustrated by Text-fig. 3 and Table III, wherein the heart was driven at a constant rapid rate by means of induction shocks. The characteristic reduction of C flow following the administration of antigen still takes place when the cardiac rate is controlled. Moreover, the coronary flow is not slowed by the introduction of antigen in such

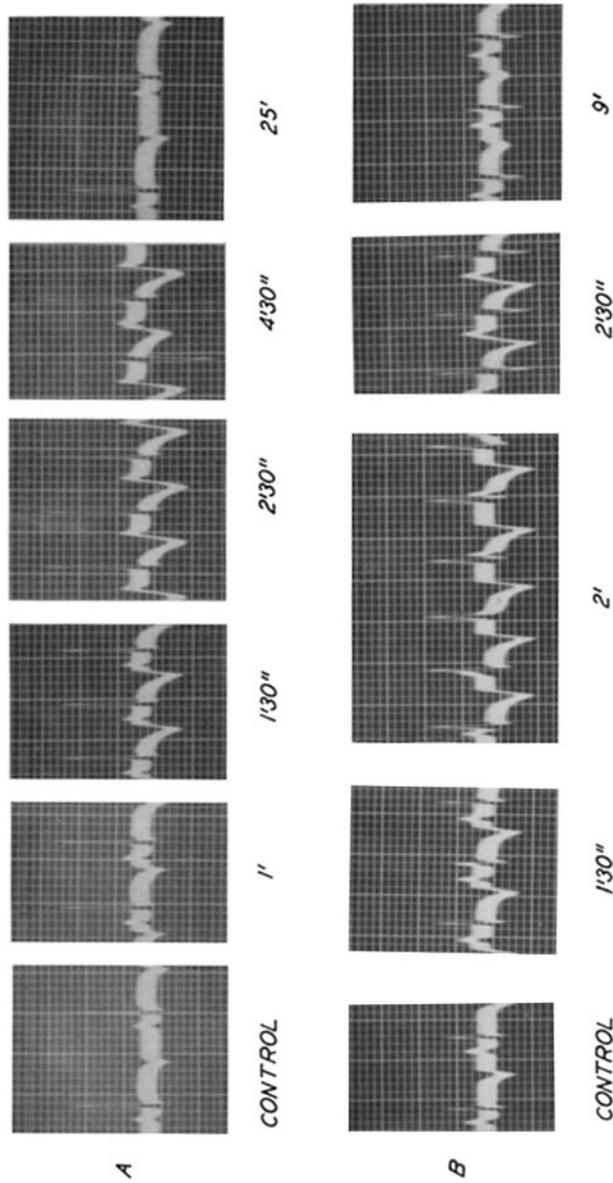
TABLE I

Date	Initial rate (beats per min.)	Maximum rate after serum (beats per min.)	Interval between injection of serum and maximum effect <i>min. : sec.</i>	Electrocardiographic alterations
Nov. 16	144	215	1	A-V dissociation with nodal tachycardia
" 30	125	200	1 : 40	Ventricular extrasystoles. Ventricular tachycardia
Dec. 2	135	220	1 : 30	Sinus tachycardia. Prolonged P-R interval
" 3	210	250	1 : 10	Sinus tachycardia
" 14	178	210	1 :	" "
" 17	155	220	1 : 30	" "
" 21	180	260	1 : 30	A-V dissociation. Ventricular tachycardia
Jan. 6	170	220	2	" " " "

These are samples of 32 similar reactions observed.

an amount into the driven normal heart or following desensitization of a previously sensitive organ. The magnitude of this effect and the regularity with which it is produced suggests that it is fundamental to the anaphylactic reaction of the heart in this species. Similar results have been observed in a small number of experiments with the hearts of sensitized rabbits. In both species the electrocardiographic changes are strikingly similar to those recorded after mechanical constriction of the coronary arteries.

The effect of the interaction of antigen and antibody upon the cardiac tissue devoid of coronary circulation is not, of course, to be discerned in the results of such experiments, but Baker (2) has demon-



TEXT-Fig. 1A. Sample electrocardiograms show progressive increase in the P-R interval from 0.07 seconds, reaching a maximum of 0.12 at 4½ minutes after introduction of antigen, where an extrasystole of supraventricular origin also appears, returning to the initial value at 25 minutes. Transient increase in rate and in the depth of the T waves is also illustrated, together with depression of the S-T segment.

TEXT-Fig. 1B. Electrocardiograms of another experiment showing similar changes in T waves and S-T segments; and, at 1½ minutes, alternate excitations arising in two separate supraventricular foci, one with a P-R interval of 0.07 seconds and the other 0.09 seconds; at 2 minutes auriculoventricular dissociation with the ventricular rate slightly more rapid than the auricular.

TABLE IIa

Date	Cardiac rate (beats per min.)			C flow (drops per min.)			Perfusate
	Before serum	After serum	Increase <i>per cent</i>	Before serum	After serum	De- crease <i>per cent</i>	
Feb. 1(1)	150	225	50	97	30	69	Ringer-Locke
“ 1(2)	160	240	50	100	30	70	“ “
“ 4	211	250	19	100	32	68	“ “
Mar. 12	160	210	31	110	40	63	“ “
“ 29	120	180	50	110	14	87	“ “
July 13	162	198	22	96	42	56	“ “
“ 14	150	216	44	114	54	53	“ “
June 2*	180	202	12	186	66	66	“ “
Average.....			34.7			66	

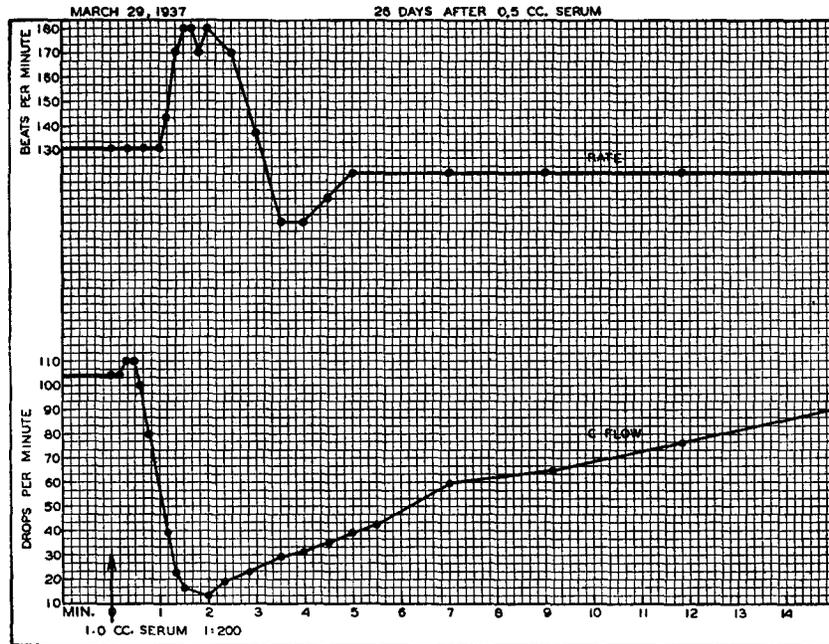
TABLE IIb

Date	Cardiac rate (beats per min.)			C flow (drops per min.)			Perfusate
	Before serum	After serum	Increase <i>per cent</i>	Before serum	After serum	Decrease <i>per cent</i>	
July 7(1)	168	228	36	168	144	14	Atropine 1/100,000 in Ringer-Locke
“ 7(2)	204	228	12	198	186	6	“ “ “ “ “
“ 1*	162	204	25	120	120	0	“ “ “ “ “
May 10	170	220	29	180	120	33	“ “ “ “ “
“ 27	198	252	27	102	66	35	“ “ “ “ “
“ 26	180	240	33	54	33	39	“ “ “ “ “
July 8(1)	204	246	21	108	108	0	“ 1/75,000 “ “ “
“ 8(2)	150	222	48	156	102	35	“ “ “ “ “
“ 12	156	198	26	162	162	0	“ 1/50,000 “ “ “
“ 13	168	210	25	102	72	30	“ “ “ “ “
Average.....			27.5			21.6	

* Passive sensitization.

strated depression of the activity of the auricles of sensitized rabbits upon exposure to minute amounts of antigen and Sherwood (15) has described anaphylactic effects in the hearts of chick embryos

2 to 7 days old, before any extensive coronary circulation has developed. On the other hand, Wachstein (17) has reported that heart muscle strips from normal and from sensitized rabbits and guinea pigs react similarly to horse serum in dilutions of 1/200 to 1/2000.

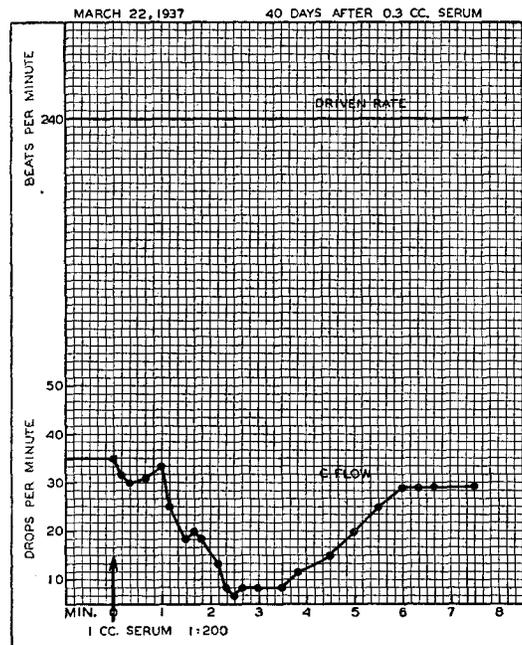


TEXT-FIG. 2. Cardiac rate and coronary (C) flow during anaphylaxis in the isolated heart. Beginning at 30 seconds following the introduction of antigen there is a transient reduction in coronary (C) flow which slightly precedes the acceleration in the rate of contraction.

In this and other charts each vertical division represents an interval of 10 seconds.

In view of the current hypothesis (7) that the manifestations of anaphylaxis are consequent upon the elaboration of histamine or an histamine-like substance, the effects of histamine have been tested upon this same preparation. Text-fig. 4 illustrates that certain transient changes identical with those observed in cardiac anaphylaxis are produced when a small amount of histamine is introduced

into the perfusate about to enter the heart: increase in rate of beat, transient auriculoventricular dissociation and a striking reduction



TEXT-FIG. 3. Anaphylactic reaction with ventricular rate controlled.

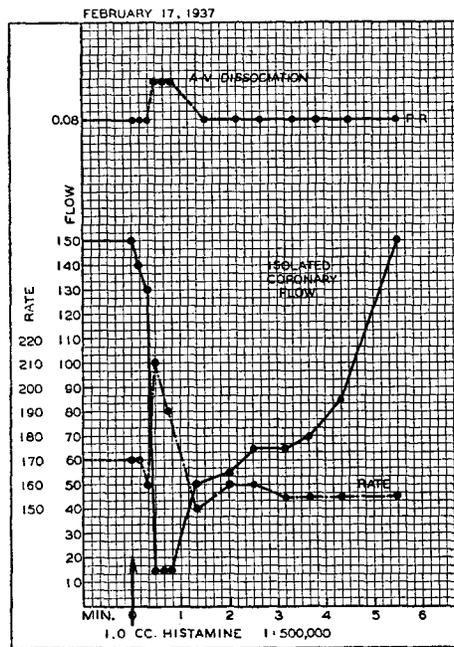
TABLE III

Date	Driven rate (beats per min.)	C flow (drops per min.)		
		Before serum	After serum	Change <i>per cent</i>
May 22	240	35	7	80
Mar. 24	210	85	50	41
" 25	320	78	21	73
" 30	350	45	20	55

Note that different driven rates were employed. 4 such experiments done.

in C flow. This latter is demonstrable though the ventricular rate be controlled by driving. Several experiments are summarized in Table IV *a*. In contrast, however, with the effect of serum, the

action of histamine upon the isolated preparation is the same whether the heart be that of a normal or a sensitized animal, or one which has been desensitized by previous exposure to antigen. Moreover, the reaction to histamine itself invokes no demonstrable degree of desensitization; subsequent exposure to the same dose of histamine, or, in the case of sensitive hearts, to a small amount of antigen, is followed by a typical reaction undiminished in intensity.



TEXT-FIG. 4. Cardiac rate and coronary (C) flow as influenced by histamine.

Finally, a series of observations was made to study the effect of atropine upon the phenomena of anaphylaxis in the heart and to compare this with the influence of atropine upon the reaction to histamine. The results are summarized in Tables II and IV.

With hearts which are demonstrably sensitive to horse serum the presence of atropine in concentrations of 1/100,000 to 1/50,000 in the perfusate has little or no effect in preventing the acceleration of cardiac rate typical of the anaphylactic reaction. Upon the changes in coronary (C) flow the effect of atropine is distinct; in all of the ten

experiments recorded in Table II *b* the reduction of coronary flow is considerably less than in those of Table II *a* in which the perfusate

TABLE IV *a*
Ringer-Locke Perfusate

Date	Dose of histamine	Cardiac rate (beats per min.)			C flow (drops per min.)			Remarks
		Before	After	Change <i>per cent</i>	Before	After	Change <i>per cent</i>	
Feb. 17	0.5 cc. 1/500,000	150	210	40	150	30	80	Normal pig
" 18	" " "	180	190	5.5	170	80	53	" "
" 24	" " "	130	220	69	80	25	62	Desensitized <i>in vivo</i>
Mar. 30*	" " "	300	300		45	16	64	Desensitized <i>in vitro</i>
Apr. 22	" " "	160	180	12.5	95	38	60	" " "

These are samples from a group comprising 15 animals and 26 injections; in 4 such observations the contraction rate was controlled by driving.

TABLE IV *b*
Atropine 1/100,000 in Ringer-Locke Perfusate

Date	Dose of histamine	Cardiac rate (beats per min.)			C flow (drops per min.)			Remarks
		Before	After	Change <i>per cent</i>	Before	After	Change <i>per cent</i>	
Feb. 17	1 cc. 1/500,000	130	150	15	102	102	0	Normal
Apr. 19	0.5 " "	170	230	35	100	100	0	"
May 12	" " "	144	216	50	150	144	<1	"
July 7	" " "	180	210	16	108	108	0	Desensitized <i>in vitro</i>
Mar. 17	" " "	170	190	12	85	85	0	Normal
Apr. 22	" " "	150	165	10	120	120	0	Desensitized <i>in vivo</i>

These are samples from 17 injections on 12 animals.

* Driven.

contained no atropine. Indeed, in three instances, although the cardiac rate increased during "shock" by 20 to 25 per cent, the coronary flow changed not at all.

The effect of histamine in constricting the coronary arteries in this species is almost completely suppressed by atropine in the above concentrations though its cardio-accelerator action is little influenced thereby (see Table IV*b*). This effect is in confirmation of that reported by Viotti (16). Here again identical results are obtained whether the effect is produced in the hearts of normal animals or in those desensitized *in vivo* or *in vitro*.

In the sense that the effect of atropine upon the reactions of the guinea pig's heart to both anaphylaxis and to histamine are *qualitatively* similar, these observations lend support to the view that the manifestations of anaphylaxis are due to the elaboration of histamine or an histamine-like substance. In that the phenomena characteristic of anaphylaxis are here *quantitatively* less susceptible of inhibition by atropine than are the effects of histamine, it may be urged that, in the anaphylactic reaction, additional substances may be involved.

Went and Lissák (19) have suggested that the active material elaborated during anaphylactic shock may be choline rather than histamine; in their experiments anaphylaxis was characterized by depression rather than stimulation of the heart beat. The results reported herewith indicate that, if substances other than histamine are produced in this reaction, such substances are atropine resistant. In either case it seems plain that the heart of a sensitized animal may be profoundly influenced by the reaction of antigen and antibody taking place in its own tissue aside from any secondary effect of substances elaborated elsewhere in the body, and that one fundamental characteristic of this anaphylactic reaction in the guinea pig is a conspicuous constriction of the coronary arteries.

SUMMARY

The isolated hearts of guinea pigs sensitized to horse serum have been shown to react characteristically upon exposure to small amounts of antigen. The cardiac rate is temporarily accelerated and transient alterations in amplitude of contraction are to be observed. Electrocardiographic abnormalities, previously recorded by remote leads during anaphylactic shock in the intact animal, have been recorded by direct leads from the isolated perfused hearts of sensitized animals during this reaction.

An additional effect of anaphylaxis in the isolated heart of the guinea pig is reported: a striking reduction in the rate of flow through the coronary vessels.

The anaphylactic reaction of the isolated heart of the guinea pig has been compared with the action of histamine upon the same preparation and the effect of atropine upon each has been observed. The implications of certain quantitative differences in the influence of atropine upon these reactions are discussed.

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