LETHAL CARDIAC ANAPHYLAXIS IN THE RABBIT.*

FOURTH COMMUNICATION.

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PLATES 44–47.

INTRODUCTION.

The general meaning of the term anaphylaxis is now fairly well understood by everybody and it is probably not necessary to go into many details. The term was coined by Richet in order to show that this symptom complex, or rather symptom complexes, was the opposite of immunity. Thus, for example, a guinea pig tolerates an intraperitoneal or intravenous injection of horse serum as if it were salt solution. If the injection, however, be repeated any time after two or three weeks, the animal responds with powerful toxic symptoms, and with proper dosage it usually succumbs. The first injection instead of causing immunity[1] has produced hypersensitiveness or anaphylaxis.

But this remarkable reaction to a second injection of a soluble proteid is limited not only to the guinea pig. The list of animal species which may be sensitized is steadily growing larger, and without hesitation the opinion may be advanced that anaphylaxis represents a fundamental biological phenomenon.

To the scientific interest of this reaction is added the practical moment that anaphylactic phenomena are by no means uncommon in man. Nor are these manifestations always limited to non-fatal complications as in von Pirquet and Schick's[2] serum disease. Gil-

* A preliminary note was published in the *Zentralbl. f. Physiol.*, 1910–11, xxiv, 957. Received for publication, September 5, 1911.

[1] The word is used in its older meaning of protection.

[2] von Pirquet and Schick, Die Serum Krankheit, Leipzig, 1905.

lette[3] has compiled a series of cases from the literature where the injection of antitoxin caused alarming collapse and even death, and similar isolated case records may be found scattered through the medical journals. It is therefore desirable that the functional disturbances which characterize anaphylaxis be investigated, for it is being recognized that the great step forward in therapeutics represented by the employment of sera is accompanied occasionally by some drawbacks. As matters now stand, the practical physician who injects a therapeutic serum sometimes finds that he has brought not life but death to his patient.

This undesirable adventitious action of sera must therefore be neutralized in some way or another, and this obviously can only be done intelligently when the nature of the vital functional disturbance is known. For the very acute anaphylaxis of guinea pigs, where the second injection of serum causes death within a few minutes, the cause of death has been established[4] and one kind of treatment indicated.[5] It might now be assumed that acute anaphylactic death in other species of animals was caused by the same factor as in guinea pigs. It is interesting and instructive that this is not true. A guinea pig, for example, in acute anaphylaxis, dies of strangulation, due to a stenosis in the finer pulmonary air passages. A rabbit, however, which dies of acute anaphylaxis shows practically no sign of pulmonary stenosis and yet its exitus in typical cases is just as rapid as in the guinea pig. In the following pages, it will be shown that acute anaphylactic death in rabbits is due primarily to a failure of the heart muscle to perform its work.

EARLIER WORK ON ANAPHYLAXIS IN THE RABBIT.

Most of the earlier work on anaphylaxis in rabbits deals only incidentally with the acute form of death, and it may be legitimately neglected in this place. The more recent investigators

[3] Gillette, *Therap. Gaz.*, 1909, xxxiii, 159; *New York State Jour. Med.*, 1909, ix, 373.

[4] Auer and Lewis, *Jour. Am. Med. Assn.*, 1909, liii, 458; *Jour. Exper. Med.*, 1910, xii, 169.

[5] Auer, *Am. Jour. Physiol.*, 1910, xxvi, 439. See also preceding articles.

whose work demands attention are Arthus,[6] Wolff-Eisner,[7] Scott,[8] Cesaris-Demel,[9] and Friedberger associated with Hartoch[10] and Gröber.[11]

The earliest as well as one of the best experimental descriptions of serum anaphylaxis in the rabbit we owe to Arthus. He described objectively the most important symptoms of acute anaphylactic death, as well as the more ordinary type which ends in recovery. Among the symptoms which characterize non-fatal anaphylaxis in the rabbit, he described the respiratory disturbance, general prostration, drop in blood pressure, and increased peristalsis associated usually with the expulsion of feces. In cases of acute anaphylactic death in the rabbit, he noted the main characteristics of the blood pressure curve: rapid fall associated with a marked decrease of the amplitude of the beat and abolition of respiratory waves. The only objection to Arthus' work is that his analysis did not go far enough, in short that there is a lack of interpretation of the physiological disturbances which he so clearly describes.

It may not be out of place to call attention to the fact that Arthus' work in anaphylaxis of the rabbit[12] and the dog[13] has not received the attention which it merits. I regret to state that I was not fully familiar with his work on anaphylaxis in the rabbit when my preliminary note on acute anaphylactic death in the rabbit was published,[14] and thus I failed to mention the earliest accurate work on this subject.

In 1904, Wolff-Eisner[15] described briefly acute death in rabbits after the animals had previously received two to four intravenous injections. After a short period of incubation, the animals show a very marked dyspnea, then tonic and clonic convulsions set in, which are followed by death after a few minutes or after hours. Wolff-Eisner rules out the possibility of air embolism, for he obtained the same symptoms after intraperitoneal injections, but he gives no other explanation.

Scott observes after the intravenous injection of serum in properly sensitized rabbits that a certain percentage of the animals die within five to ten minutes after the injection. The main symptoms which he notes are an initial hyperemia of the ears followed swiftly by a marked anemia. Associated with this anemia is marked panting respiration and a rapid, feeble heart beat. Within two or three minutes, the animal lies with legs extended and its head on the floor;

[6] Arthus, *Compt. rend. Soc. d. biol.*, 1903, lv, 817; also more complete in *Arch. internat. de physiol.*, 1908–09, vii, 472.

[7] Wolff-Eisner, *Centralbl. f. Bakteriol., Orig.*, 1904, xxxvii, 576.

[8] Scott, *Jour. Path. and Bacteriol.*, 1910, xv, 33.

[9] Cesaris-Demel, *Gior. d. r. Accad. di med. di Torino*, 1910, lxxiii, 69.

[10] Friedberger and Hartoch, *Ztschr. f. Immunitätsforsch., Orig.*, 1909, iii, 581.

[11] Friedberger and Gröber, *ibid.*, 1911, ix, 216.

[12] Arthus, *loc. cit.*

[13] Arthus, *Arch. internat. de physiol.*, 1910, ix, 179–203.

[14] Auer, *Zentralbl. f. Physiol., loc. cit.*

[15] Wolff-Eisner, *loc. cit.*

the respiration is labored, and the abdomen large and full. There is discharge of fecal matter. In five to ten minutes, convulsions and rapid death may occur. Respiration ceases first, and the heart usually continues to beat for several minutes, and then slows and stops. When the blood pressure was recorded, Scott noted that a fall to 30 mm. of mercury may occur within three or four minutes in the fatal or severe cases. When the respiration stops, there is a slight rise, and then the blood pressure falls to the base level within three or four minutes.[16]

Scott accounts for the prostration and paresis by the profound drop in blood pressure. The fall in blood pressure itself he thinks is due to a rapid and intense capillary dilatation of the portal area, so that the systemic circulation is rapidly depleted into the portal system of blood-vessels. Scott explains this loss of capillary tonus by assuming a sympathetic nerve action or a direct injury of the endothelial cells.[17]

The heart as a possible factor in the production of death is not mentioned.

After my experimental work was completed, an article by Cesaris-Demel[18] was found, in which this author demonstrated unequivocally that the heart of a sensitized rabbit reacts powerfully in anaphylaxis. Cesaris-Demel perfused the excised hearts of sensitized animals with a Ringer-Locke solution to which he added horse serum in concentrations varying from 1.3 to 5.5 per thousand. The solution exerted a distinctly toxic effect upon the normal heart, but the effect on sensitized hearts was considerably more marked. The sensitized hearts responded by a rapid diminution of the amplitude of the beat and by a strong increase in tone so that practically no beats were visible. On perfusing again with Ringer-Locke's solution, the heart resumed its pulsations. The same reaction could be obtained several times, but finally the organ no longer responded but behaved like a normal heart.[19]

Cesaris-Demel obtained similar reactions when the animals were sensitized with bovine serum, egg albumen, and milk. The corresponding antigen was then added to the perfusion liquid. His experiments were carried out in rabbits and guinea pigs.

According to his original article, it does not seem that Cesaris-Demel attempted to find out whether the heart of the intact animal behaved as did the excised one, nor does he give any closer description of the heart during the temporary anaphylactic stoppage.

The work of Friedberger and his co-laborers, Hartoch and Gröber, does not demand much consideration, as far as their experimental interpretation of the functional disturbances of acute anaphylaxis are concerned. The curves and protocols illustrating Friedberger and Hartoch's article[20] do not deal with the acute fatal type of rabbit anaphylaxis, and therefore need no discussion here. In another article by Friedberger,[21] a tracing of blood pressure and respiration

[16] Scott, *loc. cit.*, pp. 33–34.
[17] Scott, *loc. cit.*, pp. 35–36.
[18] Cesaris-Demel, *Gior. d. r. Accad. di med. di Torino,* 1910, lxxiii, 69–80.
[19] Cesaris-Demel, *ibid.*, p. 76.
[20] Friedberger and Hartoch, *loc. cit.*, pp. 630–632.
[21] Friedberger, *Ztschr. f. Immunitätsforsch.*, 1909, iii, 692.

in a passively anaphylactic rabbit is given where the reinjection led to acute death apparently within a few minutes after the injection. This result, however, is utilized by Friedberger only to show that there is a passive anaphylaxis in rabbits.

The third article by Friedberger and Gröber is illustrated by a number of tracings and protocols which show that sensitized rabbits may die acutely after the toxic injection of goat serum. A study of the protocols gives us no information whatsoever regarding the nature of the vital changes involved, and this opinion is expressed by the authors themselves.[22] In fact, this paper may be considered largely as an amplification of work done by Arthus a number of years ago.[23] It must be added, however, that this work of Arthus has escaped the notice of Friedberger and Gröber.

EXPERIMENTS.

Sensitization.—Young rabbits were used which weighed originally less than one kilo. These were sensitized with normal unheated horse serum in a variety of ways: by repeated subcutaneous, peritoneal, or intravenous injections; usually a combination of these routes of injection was used. The dose injected each time varied between 3 and 5 c.c., and the time interval was from five to six days. The number of injections varied between four and eight.

The animals usually showed a well marked loss of appetite and consequent emaciation during the process of sensitization.

Toxic Dose.—The toxic dose of warm horse serum varied between 5 and 20 c.c., and was injected usually into the jugular vein. The time interval between the last sensitizing dose and the toxic dose varied between four and six weeks, though excellent results were also occasionally obtained after six months.

Certainty of Sensitization.—Rabbits are by no means as easily sensitized to a high degree as guinea pigs. While there is no difficulty in so sensitizing rabbits that the toxic injection causes a drop in blood pressure, increased heart rate, and active cecal peristalsis associated usually with fecal discharges, as Arthus[24] accurately described for the first time, there is considerable uncertainty in obtaining an acute lethal exitus. In the various series of rabbits I used, a certain number merely showed the signs described by Arthus and ultimately recovered, while the others died, either within a few minutes or within some hours. If the animals which did not die acutely received another injection of horse serum, this injection, as a rule, produced no effect on the blood pressure or respiration, and the animals behaved as if salt solution had been infused. This state of anti-anaphylaxis has been thought not to exist in rabbits, but the possibility of its production is undoubted and has been observed before this by Scott,[25] Friedberger and Gröber,[26] and others.

The total number of rabbits used was about thirty-five.

[22] Friedberger and Gröber, *loc. cit.*, p. 237.
[23] Arthus, *Arch. internat. de physiol.*, 1908–1909, vii, 487–489.
[24] Arthus, *loc. cit.*
[25] Scott, *loc. cit.*, p. 32.
[26] Friedberger and Gröber, *loc. cit.*, p. 235.

Operative Technique.—The animals were usually anesthetized by ether; only rarely was morphin employed.

For preliminary tests the toxic dose was always injected into an ear vein; during graphic experiments, through a jugular cannula.

The blood pressure was always recorded from the carotid artery by means of a Hürthle spring or membrane manometer. The connecting tubing was filled with 10 per cent. sodium citrate. The mercury manometer was not employed in order to avoid the entrance of fair quantities of anti-coagulant fluid into the circulation during a drop in blood pressure.

When the vagi were cut, tracheotomy was always performed.

Respiration was recorded by a Meltzer pleural cannula[27] connected with a Marey tambour.

When the heart and lungs were merely inspected, the chest was split transversely and held apart by weights. Artificial respiration was given through a tracheal cannula.

When the central nervous system was to be excluded, the medulla was first thoroughly destroyed; then the cord was pithed, through an opening in the lower lumbar region, by a strong wire which was passed upwards into the cranial cavity and allowed to remain *in situ*. Artificial respiration was started after destruction of the medulla.

When the aorta and vena cava were clamped to exclude the splanchnic circulation, laparotomy was performed and these blood-vessels were clamped just below or just above the diaphragm. When done above, the thorax was entered through the tendinous centre of the diaphragm.

In order to prevent loss of heat during the operative procedures, the animals were stretched out on an electric pad.

Controls.—Numbers of normal rabbits received 5 to 40 c.c. of horse serum intravenously without showing any symptoms even remotely resembling anaphylaxis.

RESULTS.

Before giving the results, it should be stated again that this investigation deals practically only with the acute fatal type of anaphylaxis in the rabbit, a type similar in its rapidity to that which may be observed in the guinea pig when the toxic injection is given intravenously.

Symptoms.—In a highly sensitized rabbit, the symptoms of anaphylaxis are as follows: After such a rabbit receives about five cubic centimeters of normal horse serum through the lateral ear vein, very little is to be noticed except perhaps a transitory quickening of the respiration. The animal squats quietly in its box. Within a few minutes, however, the respiration slows and the animal suddenly falls over on its side with a short clonic convulsion.

[27] Meltzer, *Centralbl. f. Physiol.*, 1896, x, 536.

The head is retracted, the pupils are wide, the iris (in white rabbits), tongue, and gums pale, and in some instances, a few feeble cries are heard. There is no respiration. Palpation of the chest shows the heart beat to be very weak or absent. After a little time, a short group of respirations appear, which swiftly grow weaker and finally disappear. The animal is dead. (See figure 1 for a graphic record.)

Autopsy.—Immediate examination shows the animal to be perfectly limp. The abdominal muscles are pale and relaxed; they contract on stroking the peritoneal surface. The peritoneal cavity contains no excess fluid. The gut is usually pale, though the larger veins are visible. There is slight or no peristalsis. The mesenteric veins are very full and the arteries are seen as thin red threads. No hemorrhages are visible in the gut or stomach. The liver and kidneys are dark and full of blood.

On opening the chest, the lungs collapse well, but not fully. The heart is fairly dilated, especially the right auricle and right ventricle. The auricles usually beat swiftly and regularly, but feebly. The ventricles either do not contract at all or only feebly, and at a much slower rate than the auricles; at times hemorrhages may be seen on the ventricular surface. Stimulation of the heart ventricles by stroking, pricking, or faradic current causes only slight or no contraction. On excising the heart, the blood is fluid, and there are no clots or fibrinous masses in the heart chambers, the pulmonary artery, or the aorta. The endocardial surfaces of the ventricles usually show subserous hemorrhages of variable extent. Stimulation of the cut surfaces of the ventricles is sometimes feebly successful on the left side, but only rarely on the right. The right ventricular muscle shows, as a rule, a peculiar soft, paper-like stiffness as it folds when the fluid blood is removed; its color is gray and the muscles may be almost as resistant to the finger nail as connective tissue. The left ventricle is fairly well contracted; its color is reddish brown and its muscle can easily be scraped by the finger nail.

On excision of the trachea and lungs, the latter look faintly mottled and the surfaces and borders show numerous areas of elevation; closer inspection shows that these hillocks are composed of large distended air sacs easily visible by the unaided eye; they are areas of emphysema. Occasionally slight hemorrhages are seen on the surfaces of the lung. From the cut surface of sections, pressure brings a moderate amount of air and more or less fine foam, as if there were some slight pulmonary edema.[28]

The trachea looks bluish, and on slitting it open the mucosa is always found to be strongly congested; this congestion extends into the pulmonary bronchi.

The blood is usually very dark and its coagulation delayed. The clot which forms after thirty minutes to two hours or longer is never firm.

This autopsy may be considered typical of the usual findings in acute anaphylactic death in rabbits.

[28] Also noted by Scott, *loc. cit.*, p. 40.

Finer Analysis of Symptoms and Signs.—The clinical picture and autopsy findings given above obviously point to two organs whose failure separately or collectively might be the immediate cause of death,—the heart and the lungs. To get further insight, therefore, an animal was prepared so that the heart and lungs could be inspected. This was done by splitting the chest transversely and giving artificial respiration. This experimental arrangement not only permitted observation of the two organs, but also served to differentiate which of them caused death. Shortly after the injection of five cubic centimeters of horse serum into the jugular vein, followed by two cubic centimeters of Ringer's solution to wash clear the cannula, the lungs did not collapse as well during the expiratory phase of artificial respiration. At the same time the heart slowed and the right ventricle appeared fuller and tenser than before. A few minutes later, inspection showed a few small hemorrhages on the right ventricular surface. About thirty minutes after the injection of the horse serum, the heart suddenly slowed considerably, the right auricle apparently did not contract at all and the right ventricle filled up strongly and stopped. During this time, the lungs were expanding and collapsing quite well under artificial respiration. During the cardiac stoppage, the animal made a few convulsive movements and the heart began to beat again, but now the ventricles beat only very weakly in groups of two, the second contraction being stronger than the first. The right auricle now beat four times faster than the ventricle.

At autopsy, the abdominal organs showed the picture described earlier in this paper.

The right ventricle was full and distended with blood; the left ventricle showed a moderate tonus. The ventricles contracted very feebly occasionally; both auricles were beating slightly, but much more rapidly than the ventricles. Unfortunately no notes were made in this experiment regarding the irritability of the heart muscle, except the statement that no contraction occurred on cutting open the heart chambers. The heart contained fluid blood and showed no coagula.

The blood was dark and still fluid ninety minutes after autopsy.

The lungs showed typical areas of emphysema on their surfaces and borders, as was described before.

This experiment pointed unmistakably to the heart as the cause

of death, for the lung functioned sufficiently well to be excluded in this instance as a very important factor in the production of anaphylactic death. (See also figure 3 for a graphic record.)

Peripheral or Central Action of the Horse Serum.—While the evidence so far submitted all indicated that the heart was at fault, the data are not conclusive that this organ is primarily responsible for acute anaphylactic death. It might, for example, be assumed that the stoppage of the heart was due to nervous influences from the medulla through the vagi and accelerator nerves. Again it might be assumed that dilatation of the splanchnic blood-vessels played a vital part, especially as Biedl and Kraus[29] have shown that splanchnic dilatation due to a peripheral vasomotor paralysis was the most important action of anaphylaxis in dogs. To answer these questions, a number of experiments were carried out in rabbits whose basal portions of the brain, medulla, and spinal cord had been destroyed by pithing; in addition, the thoracic aorta and vena cava inferior were clamped in order to exclude the splanchnic circulation. Figure 5 gives a graphic record of such an experiment under artificial respiration. Examination of the blood pressure curve shows that the blood pressure rose shortly after the injection of five cubic centimeters of horse serum into the jugular vein from thirty millimeters to eighty millimeters of mercury, the pulse pressure increasing moderately at the same time; then the blood pressure gradually sank, the pulse pressure decreasing markedly. Four minutes after the injection of the horse serum, the blood pressure record shows no heart beats. This experiment demonstrates that the heart itself is the vital cause of death in acute anaphylaxis in rabbits. On immediate autopsy, the heart was found to be full of fluid blood; there were no beats; a prick with the needle or faradic stimuli caused no ventricular contractions. The lungs showed the areas of emphysema always found; the tracheal mucosa was strongly congested. The blood was dark, and a sample taken above the clamp in the thorax did not coagulate during thirty minutes, while a similar specimen taken from the abdominal vena cava clotted in fifteen minutes.

[29] Biedl and Kraus, *Wien. klin. Wchnschr.*, 1909, xxii, 366.

Action on Cardiac Nerve Endings or Cardiac Muscle.—In the preceding sections, it was demonstrated that the toxic injection of horse serum in rabbits affects the heart so that this organ swiftly fails to perform its work. The question arises now whether this is due to an action on the cardiac nerve endings or upon the heart muscle itself or perhaps upon both structures. The evidence at my disposal does not permit any statement regarding a possible effect on the nerve endings, but there are, on the other hand, quite conclusive data that the heart muscle itself is affected. It has already been stated before that the heart of a rabbit which has died of acute anaphylaxis, responds only feebly or not at all to mechanical or faradic stimulation, the tests being performed immediately or within a few minutes after cessation of respiration. It has also been stated that the right ventricle usually shows a definite change in consistency. These two facts show clearly that the heart muscle itself has undergone a profound functional and anatomical alteration, due to the toxic injection.

Nature of the Change in the Heart Muscle.—What this vital change in the cardiac muscle was, formed an annoying puzzle for some time. The solution was indicated numerous times by the observation that the phrenic nerves lost their irritability very soon after the death of the animal, and that the diaphragm itself swiftly failed to contract to direct faradic stimuli, even with the coil pushed home. In addition, it was noticed that the diaphragm looked crinkled and grayish, and felt stiffer than normally to the touch. The significance of all this was not appreciated until it was noticed that an anaphylactic rabbit, whose death did not occur until about one hour after the injection of horse serum, showed on passive flexion a definite stiffness of the hind legs at the hip and knee. It must be added that this animal was still alive at the time, with a weak heart beat and a blood pressure of about twenty-five millimeters of mercury. Immediate examination of the thigh showed that the white muscles looked grayish and opaque, did not react to direct faradic stimuli (0 coil distance), and that the cut surface of these muscles was acid to litmus paper moistened with a 0.9 per cent. saline. These muscles, therefore, were in typical rigor while the animal was still alive. After the death of the animal (cessation

of respiration), the diaphragm also showed the typical signs of rigor: increased firmness, loss of contractibility, and acid reaction to litmus paper. It now became evident that the changes seen in the heart after acute anaphylactic death were also of a rigor type. These changes are especially well shown, as a rule, in the right ventricle, as mentioned before; the right ventricular wall looks grayish and opaque and falls into peculiarly soft yet stiff parchment paper-like folds when the contained blood is removed; mechanical or electric stimulation yields little or no contraction; on testing its consistency, the right ventricle shows an increased toughness, so that in marked cases the muscle resists the finger nail like connective tissue.

The changes described above in the right ventricle are by no means pronounced in the left. In typical cases, the left ventricle shows a moderate tonus; its muscle looks fairly normal in color; it responds to stimulation usually in the same way as the right ventricle, but it was often noticed that a faint contraction could be obtained from the left ventricular muscle when the right was perfectly unirritable; the left ventricle usually shows but little change in consistency when tested with the finger nail shortly after death. About fifteen minutes after cessation of respiration, the left ventricle was firmly contracted to a little gray teat. It is thus seen that while in typical cases the right ventricle shows practically all the signs of rigor shortly after the cessation of respiration, the left ventricle shows practically only one,—loss of irritability on direct stimulation. This fact that the right ventricle passes into full rigor sooner than the left is interesting because it is a reversal of the usual course in post mortem rigor. Joseph and Meltzer[30] have shown that post mortem rigor sets in later in the right ventricle than in the left, when cats, dogs, and rabbits are bled to death. Their data, unfortunately, are not as complete for rabbits as for dogs and cats, but the facts they furnish make it very improbable that rabbit ventricles do not behave in the same way (see especially their tables on pages 20, 24, 28, and 29). This is, therefore, additional proof that cardiac anaphylactic rigor in the acute fatal cases is probably not a *post mortem* but an *intra-vitam* phenomenon, and

[30] Joseph and Meltzer, *Jour. Exper. Med.*, 1909, xi, 32.

further evidence is given by those cases where the heart stops suddenly (figure 3).

In summing up the last section, it may be said that the change in the cardiac muscle which causes death in acute anaphylaxis is probably a rigor. This rigor may be classed as a chemical rigor.[31]

Blood Pressure.—With the animal prepared as described on a preceding page, the blood pressure and respiration were recorded in numerous experiments. The blood pressure curve is fairly characteristic and is as follows: After or even before the toxic dose of warm horse serum has been completely injected into the external jugular vein, the pressure begins to rise, the respiratory oscillations disappear, the pulse pressure increases, and the heart slows moderately. The rise usually does not exceed twenty millimeters of mercury, but it may at times exceed this considerably; it usually does not last longer than one minute, and then the blood pressure falls gradually, the pulse pressure usually decreasing swiftly while the heart rate increases. From now on the pressure curve takes one of two courses: (a) The pressure continues to sink. Within another minute, the twenty millimeter level is reached, but at the same time the pulse pressure again increases; usually the terminal group of respiration occurs during this stage. The increase in pulse pressure is accomplished by another marked temporary slowing of the heart rate. From now on the pressure keeps on gradually sinking while the heart beats become smaller and still more rapid. Three minutes after the injection, the curve shows a pressure of about ten millimeters, and the pressure waves are hardly discernible. Six minutes after injection, the curve is a straight line. Figure 1 gives a graphic record of this type of blood pressure curve. (b) The second type is illustrated by figures 2 and 4. The fall of blood pressure suddenly slows, and at the same time there is a marked increase in the rate and a striking diminution in the size of the pulse pressure. The pressure may remain stationary for a short period, but then slowly drops so that five to ten minutes later the pressure curve has reached about the ten millimeter level. Dur-

[31] See Meltzer and Auer, *Jour. Exper. Med.*, 1908, x, 48–49, for a description of the various kinds of rigor.

ing the final drop the pressure waves become still smaller and are often irregular in size and rhythm (figures 2 and 4).

At times the heart may stop abruptly after the toxic injection; figure 3 gives an example of this. This animal had received three milligrams of curarin and the vagi were intact. With an average blood pressure of about seventy millimeters, there were a few dropped beats and then the heart stopped suddenly and the blood pressure sank to the twenty millimeter level within a few seconds. The curve now shows only a few irregular spasmodic waves, and within two minutes after the drop, only the oscillations due to the artificial respiration are recorded.

This sudden cardiac failure was observed a number of times, and always in rabbits with intact vagi. It might, therefore, be assumed that the stoppage was due to a stimulation of the cardiac vagus endings. This explanation alone, however, is not sufficient, for a permanent cardiac stoppage by vagus stimulation cannot be obtained in mammals, at least by artificial means. Another factor probably enters into consideration, and that is a sudden complete functional failure of the heart muscle. Additional evidence for this is furnished by the behavior of the ventricles of these animals to direct stimulation, which has already been described.

When the influence of the central nervous system, as well as the splanchnic circulation is excluded, as described previously, the blood pressure exhibits greater regularity. Figure 5 gives an example of this. In this animal the blood pressure naturally was low, about thirty millimeters of mercury; but the heart beats were regular and the respiratory oscillations are well shown. After the injection of the horse serum, the pressure rose in about one minute to eighty millimeters, the pulse pressure increasing, and the heart beating more rapidly (from 220 to 310 per minute). The respiratory oscillations were abolished during this rise. After another minute, the pressure began to sink slowly and, accompanying this drop, the pulse pressure rapidly decreased, until four minutes after injection the pressure is about twenty millimeters, and the record shows only a few irregular heart contractions. Five minutes after injection, the pressure curve shows only the oscillations which are produced mechanically by artificial respiration. This curve shows

well the main affects of lethal cardiac anaphylaxis upon the functional power of the heart.

Respiration.—The respiration was recorded in one way only, by means of an intrapleural cannula. The respiratory record in the tracings therefore represents only the intrapleural pressure variations during respiration, but in the present investigations these pressure variations fairly accurately represent the volume variations of the lung. That this is true has been shown in a previous section where the lungs were inspected during acute anaphylaxis and where it was shown that the toxic injection of horse serum exerts only a moderate influence upon the collapse and expansion of the lung under artificial respiration (see figure 3 for a graphic record).

In a typical case of acute lethal anaphylaxis, the respiration behaves as follows: Shortly after the horse serum has been injected and during the initial rise of blood pressure, the respirations decrease in amplitude and either quicken or slow slightly, depending apparently upon the respiratory rate preceding the injection (see figures 1 and 2). There usually are a few short, sharp struggles. Now the respirations begin to slow and the amplitude increases considerably; during this stage, which lasts a number of minutes, the blood pressure falls to a low level. This stage of slow, deep, respirations may be terminated by tonic and clonic convulsions followed by a respiratory stoppage (figure 1), or the stage of slow respirations is broken by a number of short sharp convulsive struggles, after one of which the respiratory pause appears (figure 2). When the respiratory stoppage occurs which takes place two to five minutes after the serum injection in highly sensitive animals, the blood pressure is still falling gradually and shows abrupt changes in the rate of beat. These changes in the rate of beat show the establishment of a block, for the respiratory tracing records three or four auricular contractions before the ventricles contract (see figure 1). The respiratory stoppage lasts about one half minute and then the terminal group of swiftly decreasing respirations appears (figures 1 and 2). Respiration now ceases permanently, but the heart is still beating very feebly and the blood pressure has practically reached its lowest level. There is no recovery from this stage.

When the volume changes of the lung during artificial respiration are recorded indirectly by means of a pleural cannula, the animal being immobilized by curarin, no changes are noticed in the record during acute anaphylactic death (see figure 3). This indicates that no very marked stenosis of the pulmonary air passages occurs in rabbits during acute anaphylaxis; surely none which could in itself cause death.

The respiratory changes are due probably to influences upon the respiratory centers. Whether this is merely the effect of a failing blood supply, for the alteration in respiration sets in about the same time that the heart begins to slow (figure 2), or whether it is due to a hypersensitiveness of the respiratory nerve centers cannot be determined from my experiments.

Effect of Some Drugs.—I have only a few experiments regarding the effect of drugs upon the development of acute lethal cardiac anaphylaxis, This section of the work was hampered by the fact that I never could feel certain that the animal would succumb acutely. This necessarily excluded the use of prophylactic injections, for if the animal survived there was no guarantee that recovery was not due rather to a relatively low sensitiveness than to the protection of the drug. I was therefore compelled to inject the drugs during the terminal stages when the heart was already surely damaged.

The drugs used were digalen and strophanthin. Both were injected intravenously during the terminal stages usually, and both exerted apparently a distinctly harmful effect. This was especially noticeable when, for example, strophanthin (Thoms) was injected during the time when the blood pressure was still good but when the heart beat was very rapid and the pressure oscillations small. Under these circumstances, the pressure rose moderately and the heart increased still more in rate for a short period of time; then the pressure sank rapidly and very soon no beats were recorded. I received the impression that this injection directly caused death. While these few experiments are insufficient to permit definite statements, there is enough evidence to urge great caution in the employment of cardiac stimulants (digitalis group) in cases of cardiac anaphylaxis.

DISCUSSION.

In the preceding sections, experimental facts have been described which show that in acute lethal anaphylaxis of rabbits the fatal outcome is primarily due to a failure of the heart to perform its work. It was also shown, by destroying the central nervous system and excluding the splanchnic circulation, that the cause for this failure resided in the heart itself. This was still further strengthened by demonstrating that the heart itself immediately after cessation of respiration, responded only feebly or not at all to mechanical and electrical stimuli, and that there was also as basis for this functional change, an alteration of the anatomical properties of the heart muscle which was especially marked in the wall of the right ventricle. This anatomical change was interpreted as a rigor of the heart muscle, because this muscle showed a marked change in color, translucency, consistency, and irritability.

This work, therefore, agrees with the interesting research of Cesaris-Demel which has been described previously. I may be permitted, however, to point out that Cesaris-Demel limited himself to the demonstration that the isolated heart was affected in anaphylaxis; he did not show that this also occurs in the intact animal, nor did he study the nature of the cardiac change produced in anaphylaxis.

The question might now be asked, how it was known that these animals were really anaphylactic. This is easily answered. In the first place, the largest dose of horse serum injected was about twenty cubic centimeters, and such a dose is tolerated by normal animals without any obvious respiratory or circulatory effect; any disturbance which arises in a sensitized animal after the injection of the antigen may therefore legitimately be ascribed to a state of hypersensitiveness or anaphylaxis.

Diagnostic Character of the Blood Pressure and Respiration.— Perhaps the most striking characteristic to be noted in the blood pressure curve, when recorded adequately, is the initial increase and then the rapid progressive diminution of the pulse pressure associated with an increasing fall of blood pressure (figures 1, 2, 4, and 5). This characteristic cannot, however, be considered diagnostic of anaphylaxis *only,* for other substances which produce a similar

change in the heart muscle will surely cause a similar blood pressure picture. The blood pressure curve can only be said to be characteristic of a certain cardiac functional alteration. This viewpoint will be considered more in detail later.

The respiratory picture may be regarded in the same fashion (figures 1 and 2); it shows nothing which can be considered characteristic *only* of acute lethal anaphylaxis in the rabbit.

Both blood pressure and respiration may, however, be considered perfectly characteristic of anaphylaxis if the conditions under which they are produced are clearly kept in mind. This point will be discussed more fully in the following section, but before this can be done it is necessary to have a clear conception of what should be understood when the word anaphylaxis is used.

Basic Conditions for the Diagnosis of Anaphylaxis.—The diagnosis of anaphylaxis is at present only justified when the injection of the substance used for sensitization causes symptoms and signs which are not obtained, or at least in a less degree, when the same substance is injected into a normal animal. There is nothing new in this statement, for it is simply a definition of what the word anaphylaxis means. The two fundamental conditions, therefore, are that on first injection a substance may be harmless or only slightly harmful, but that a second injection, after a proper interval, should exert a distinctly harmful effect.[32] These basic conditions for a legitimate employment of the term anaphylaxis have been ignored in much of the recent work. Thus Friedberger's "anaphylatoxin" is misnamed, for this substance, produced by various biological manipulations from normal sera, causes death in Friedberger's hands when injected into *normal* guinea pigs. The mere fact that Friedberger claimed that he obtained the lungs characteristic of acute anaphylactic death in guinea pigs with anaphylatoxin[33] cannot be considered legitimate proof that his "anaphylatoxin" causes true anaphylaxis, any more than it can be claimed that barium chlorid and eserin cause anaphylaxis because these substances pro-

[32] It is obviously possible that anaphylaxis might also be beneficial in regard to some functions as yet unknown.

[33] This is vigorously denied by Biedl and Kraus, *Ztschr. f. Immunitätsforsch.*, 1910, vii, 220–221, 408–413.

duce a greater or less approximation to the lung picture found in acute anaphylaxis of guinea pigs. *It must be remembered that the lung condition which Lewis and I described in guinea pigs that die acutely of anaphylaxis is characteristic of this condition only when a sensitized guinea pig is injected intravenously with its antigen.* In other words, the inspiratory immobilization of guinea pig lungs is characteristic of anaphylaxis only when the conditions for its production are fulfilled: intravenous injection of the substance used to produce sensitization in guinea pigs.

These considerations hold good at present for every sign and symptom which have been described in anaphylaxis in any species of animal; in order to be characteristic, they must be obtained in the only manner legal for anaphylaxis: on second injection of the substance used to sensitize. It should be noted that I stated that these considerations hold good "at present." They will not be valid when the real anaphylatoxin[34] has been isolated. But this anaphylatoxin must, in my opinion, fulfill certain conditions: it must be biologically isolated from the blood or tissues of an animal which had a true attack of anaphylaxis, and this substance must not be found in normal animals, but it must produce the typical symptoms when injected into them.

Attention may be called in this connection to another error. It is perhaps not generally appreciated that the symptoms and signs of anaphylaxis differ considerably in the three species of animals which have so far been carefully studied. Thus, for example, the characteristic drop of blood pressure in the dog is not found in the acute cases of anaphylaxis in the rabbit and guinea pig; the large, pale, fully inflated lungs of the guinea pig are not found in the dog or the rabbit; and again the intravital rigor of the heart muscle in the rabbit is not seen in the dog and the guinea pig. There are numerous other differences, but those cited are sufficient to indicate clearly that each species of animal must be measured with its own yardstick when examined for anaphylaxis. It is, therefore, not permissible to apply indiscriminately a characteristic sign of one species to another species, as Friedberger and Gröber do when they

[34] Whether the assumption of an "anaphylatoxin" is necessary or not, I do not care to discuss.

state that the drop of blood pressure seen in acute lethal anaphylaxis in the rabbit cannot be referred to a pulmonary inspiratory rigidity, and that this pulmonary rigidity is not characteristic of anaphylaxis anyway, because all sorts of poisons cause this sign in rabbits and guinea pigs.[35]

The considerations given above clearly show, it seems to me, the necessity of limiting at present the scope of the word anaphylaxis to its original restricted meaning which demanded two injections of the same substance, the first one producing only sensitization, while after an appropriate interval the second injection caused powerful toxic symptoms. Only under these conditions will confusion be avoided, and the diagnostic value of the various signs and symptoms established for anaphylaxis be preserved.

SUMMARY.

Acute lethal anaphylaxis in the intact rabbit is caused by a failure of the heart.

This failure of the heart is due to a change in the heart itself; it is peripheral and independent of the central nervous system for its production.

This change in the heart is shown anatomically and functionally by decreased translucency, change in consistency, and by failure to respond to stimuli, and is probably to be classed as a chemical rigor.

The rigor of the heart is most pronounced in the right ventricle, the wall of which may be gray, stiff, very tough to the finger nail, and non-irritable.

Cardiac stimulants of the digitalis group seem to exert a harmful effect when injected in acute anaphylaxis.

Blood coagulation is delayed; a loose clot forms after one half to two hours.

Anti-anaphylaxis is produced when the animal does not succumb to the injection.

When anaphylactic death is delayed for about one hour, a well developed rigor of the white muscles of the thigh, and of the diaphragm may occur while the animal is still alive.

Reasons are brought forward to show the necessity of more caution in employing the word anaphylaxis.

[35] Friedberger and Gröber, *loc. cit.*, 236.

Friedberger's statement, that the lungs of guinea pigs dead from acute anaphylaxis are not characteristic of anaphylaxis for this animal, is shown to be baseless.

EXPLANATION OF PLATES.

In the tracings which show two curves (figures 1, 2, and 3) the upper curve represents respiration, registered by means of a pleural cannula; the straight line transecting this is the atmospheric pressure line: above the line is positive, below is negative pressure.

The curve with smaller oscillations is the blood pressure curve, written always by a Hürthle spring or a membrane manometer. The straight line below it is zero pressure. The calibration scale at the end of the curve gives the value of the different levels in millimeters of mercury.

Time is marked invariably in four second intervals.

The broad white lines below the time line show the duration of injections, stimuli, etc.

PLATE 44.

FIG. 1. Experiment of December 22, 1910. White rabbit, male, weight 1,200 grams. Sensitized by peritoneal injections of 3 c.c. of horse serum on September 29, October 7 (subcutaneous), 13, and 20. Cannulae in external jugular vein, trachea, left carotid artery, and left pleura.

Downstroke of respiration curve = inspiration. Vagi intact. Toxic dose of horse serum: 5 c.c. into the jugular vein. Further details are given at the head of this section. This tracing gives a good general picture of acute lethal anaphylaxis in the rabbit.

PLATE 45.

FIG. 2. Experiment of May 9, 1911. White rabbit, male, weight 1,660 grams. Sensitized by the intraperitoneal injection of 3 c.c. of horse serum on November 25, 1910, November 30, December 5, and December 10. The operative procedure was exactly the same as in the preceding animal, except that blood pressure was recorded from the right carotid artery. Vagi intact. Toxic dose of horse serum: 10 c.c. into the jugular vein, repeated once. Further details are given at the head of this section. This plate gives a modification of the type shown by figure 1.

PLATE 46.

FIG. 3. Experiment of March 22, 1911. White rabbit, male, weight 1,760 grams. Sensitized by the intraperitoneal injection of 3 c.c. of horse serum on November 25, 1910, November 30, December 5, December 10, and on February 24, 1911, 2 c.c. injected into ear vein. Cannulae were inserted into the left external jugular vein, trachea, right carotid artery, and right pleural cavity. Three milligrams of curarin given intravenously. Vagi intact. Artificial respiration recorded: upstroke represents inflation of lung. Toxic dose of horse serum: 9.5 c.c. into the jugular vein; after a few minutes, 5 c.c. Note the sudden stoppage of heart beats and the unvarying respiratory amplitudes. This plate shows well how swiftly the left heart may fail.

PLATE 47.

FIG. 4. Experiment of May 10, 1911. Gray and white rabbit, male, weight 2,170 grams. Sensitized exactly as preceding animal. Cannulae were inserted in the external jugular vein, trachea, and right carotid artery. Both vagi cut. Three milligrams of curarin were injected into the jugular vein; artificial respiration. Toxic dose: 10 c.c. of horse serum into jugular vein, repeated once. Note the change in character of the blood pressure curve after the injection.

FIG. 5. Experiment of March 17, 1911. White rabbit, female, weight 2,190 grams. Sensitized by the peritoneal injection of 3 c.c. of horse serum on November 25, 1910, November 30, December 5, December 10, and on January 9, 1911, 2 c.c. into ear vein. Tracheotomy; vagi cut; cord, medulla, and basal portions of brain destroyed by pithing. Artificial respiration. Cannulae into left external jugular vein and carotid artery. Chest opened through diaphragm and vena cava and thoracic aorta clamped. Toxic dose of horse serum: 5 c.c. into jugular vein. Note the rise in blood pressure and the abolition of respiratory oscillations, then the rapid decrease of the pulse pressure during the drop in pressure, and the development of irregularities and cessation of the heart beat.

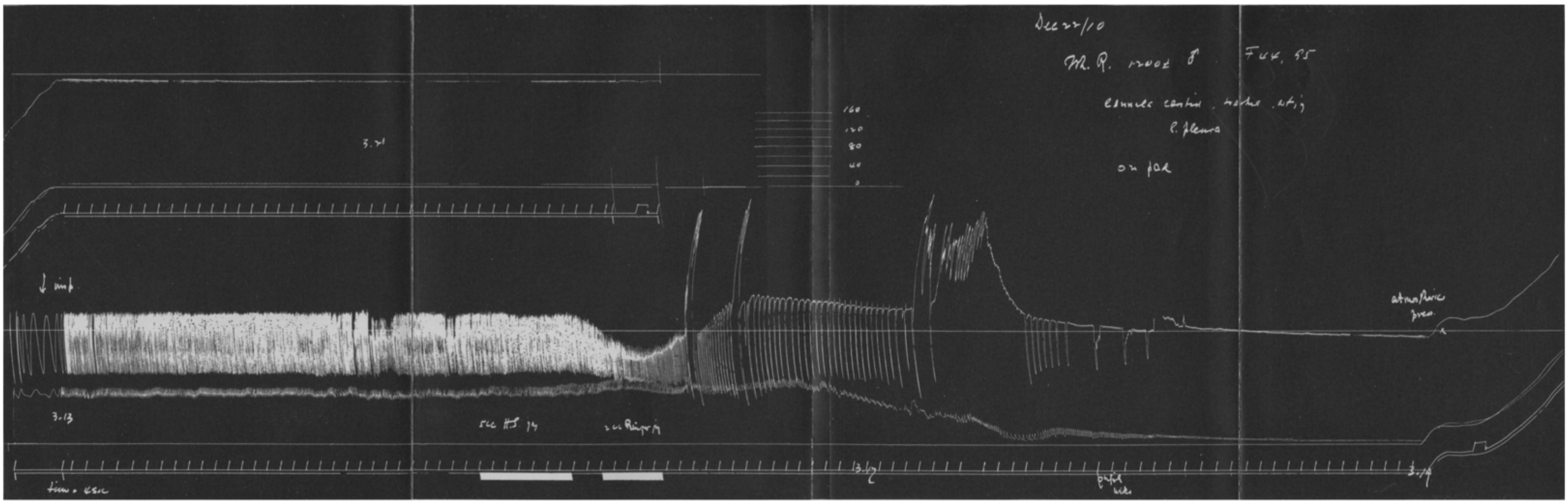

FIG. 1.

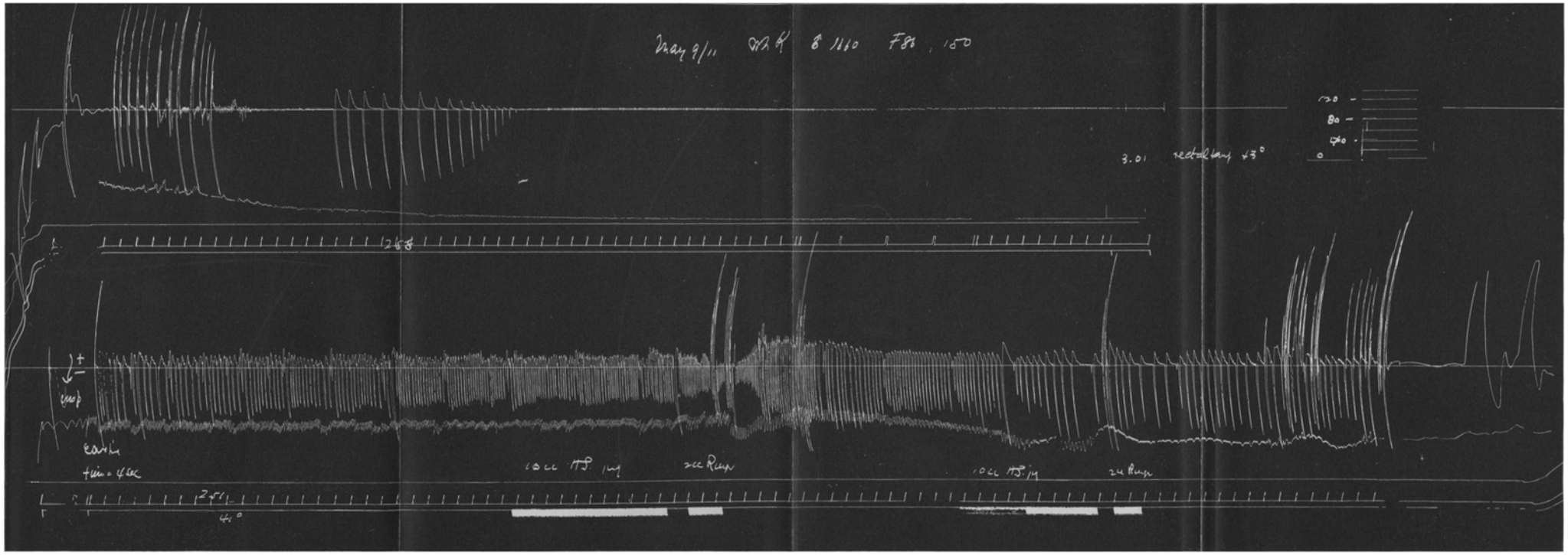

FIG. 2

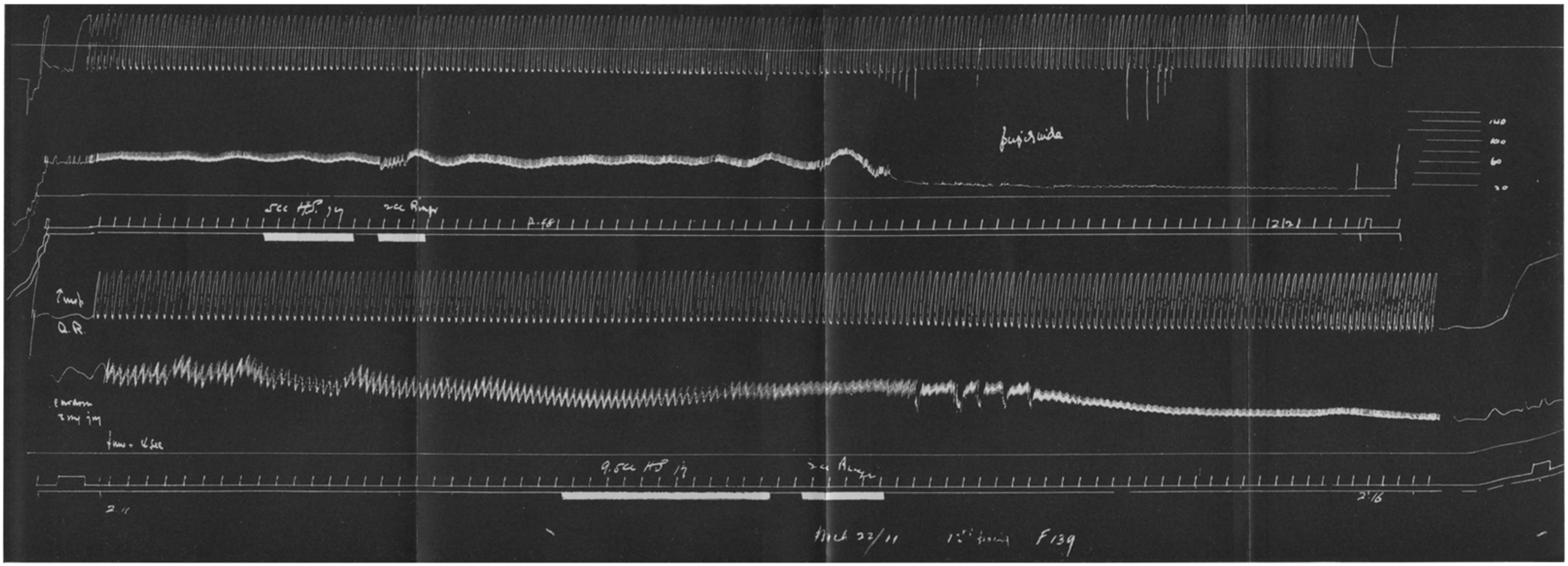

FIG. 3.

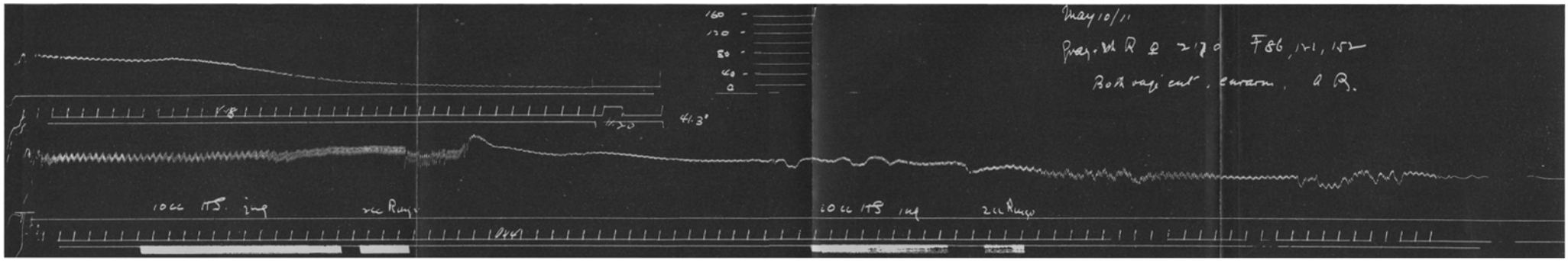
160
120
80
40
0
May 10/11
Both vagi cut, curare, A R.
41.3°
10 cc 1% inj
10 cc 1% inj

FIG. 4.

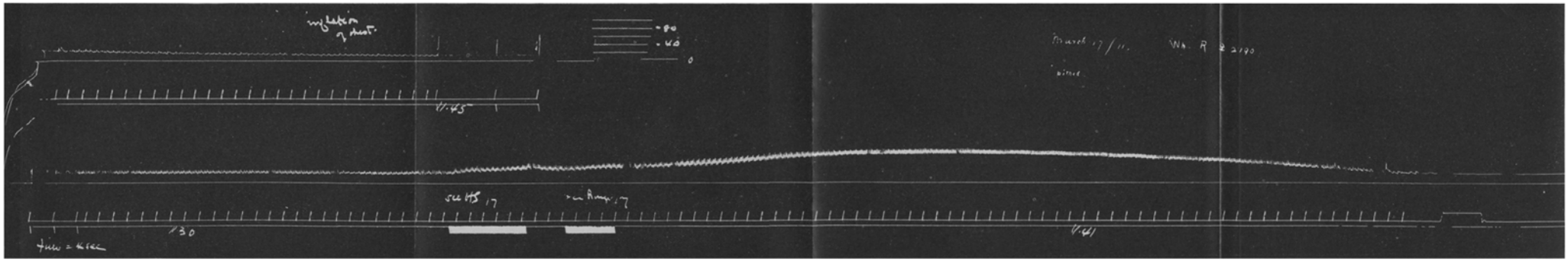
injection of thrust.
80
40
0
130

FIG. 5.