THE PHYSIOLOGY OF THE IMMEDIATE REACTION OF ANAPHYLAXIS IN THE GUINEA-PIG.¹

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PLATES VI-IX.

Introduction.—If a guinea-pig be given a subcutaneous, intraperitoneal, or intravenous injection of normal horse serum in appropriate dose, and then, after an interval of ten days or more, this treatment be repeated, it is found that in the elapsed time the animal has undergone a change of such nature that, while the first injection has been without noticeable harmful effect, the second injection causes a very violent poisoning. This reaction is representative of a large group of similar phenomena which can be elicited in the guinea-pig and to a limited extent in other animals by repeated treatments with many native, non-toxic, soluble proteids. The fact as above stated was first observed by Theobald Smith² in 1903, and the first systematic work in extension of it was published by Otto³ in 1906. This was shortly followed by the valuable publications of Rosenau and Anderson of independent work along similar lines.⁴ Since then a very voluminous literature has accumulated in regard to this “reaction of anaphylaxis” as it is called, most of which need not concern us at the moment. The work and opinions of others which bear on the points developed by us will be discussed in the course of the paper.

Even considered superficially, this complex reaction presents several distinct phases for examination. The progress and nature

¹Received for publication January 4, 1910. The chief results here reported in detail were summarized in a note published in the Jour. of the American Med. Assn., 1909, liii, 458.
of the changes on the part of the animal from apparent indifference to extreme sensitiveness have been the subject of much experimentation and discussion. The reaction to the second injection may be considered quite independently of the preceding changes as an extremely characteristic intoxication due to some substance or group of substances as yet unidentified. The writers heretofore who have paid most attention to this intoxication per se have considered it particularly from the point of view of the pathological anatomist; to a less extent and with little decisive experimentation, the functional disturbances involved have attracted attention. The work of Richet and Biedl and Kraus demands especial mention in this connection. These authors have presented careful studies of the functional changes associated with anaphylaxis in the dog. Their results obtained on this animal, as contrasted with our results with guinea-pigs, show that the reaction in the two animals, guinea-pig and dog, is superficially dissimilar, and only further work can show where lie the fundamental similarities which probably exist. In regard to the finer anatomical changes found, widespread fatty degeneration, endotheliolysis, and hemorrhage, it may be said at once that they are consecutive to functional changes and that there is little which decisively distinguishes them from the consequences of the action of a number of other intoxicating agents.

The experiments which we wish to record in the following pages were made in the hope of gaining more definite information respecting the functional manifestations of the reaction of anaphylaxis in the guinea-pig. Moreover, the reaction approached from this point of view is still complex. The results obtained when hypersensitive guinea-pigs are given the second or intoxicating injection of specific proteid vary remarkably, the variations depending on several unstable factors which must be briefly reviewed.

There is expressed in the resulting reaction a relationship at least roughly reciprocal between the sensitiveness of the animal and the amount and injection site of the specific proteid. The subcutaneous injection is least active, the intraperitoneal more so,

*Portier and Richet, *Comp. rend. Soc. de Biol.*, 1902, liv, 170.
and the intravenous injection perhaps most effective. A highly sensitive animal injected intravenously with a dose of maximum efficiency dies in from two to five minutes, showing a definite and characteristic chain of symptoms, largely respiratory, which will be described in great detail in the following pages. This form of reaction has been variously termed acute anaphylaxis or anaphylactic shock. The term “shock” having already a well defined meaning in physiological literature, and the word “acute” applied to any condition implying that there is a definitely known chronic condition due to the same cause, it seems less confusing to call this fulminating reaction the “immediate” reaction of anaphylaxis.

If the intoxicating dose be given subcutaneously in animals ordinarily hypersensitive, the course of the intoxication is prolonged and its symptoms are quite different. In a most extreme example, the animal becomes sick in about an hour after the injection, and dies in from four to six hours, or after the sixth to the twelfth hour shows distinct and finally rapid recovery. In this type of reaction the respiratory convulsions may be quite lacking. The animal’s coat becomes rough, he is cold, and sleepy. He shivers, lies down frequently and stretches full length. In the interval he gets up, huddles in the straw, or with his fellows in the corner of the cage. The respiration becomes more and more feeble and finally disappears. The anatomical changes, fatty degeneration and hemorrhage are usually extreme in this type of case.

The average result of a subcutaneous intoxicating injection of the proteid, the usual result of intraperitoneal injection, and a very unusual consequence of the intravenous administration of a certainly fatal dose, is a complex of this slow type of reaction and the convulsive immediate reaction which we are particularly concerned with in this paper. We wish to emphasize duly the point that our results bear only upon the immediate reaction following most characteristically upon the intravenous injection of the intoxicant in excess, and that we have no definite data which seem at the present writing to account for the slow form of the intoxication just described. Naturally, in the average complex case resulting, let us say, from an intraperitoneal injection in a moder-
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Anaphylactic sensitive animal, our work explains a part of the symptomatology, but not the whole.

Experiments.—All of our experiments were carried out with guinea-pigs, for in these animals the symptoms of immediate anaphylaxis may be produced with great ease and comparative certainty. Sensitization was caused by the subcutaneous injection of either one to five cubic centimeters of horse serum or by three to four milligrams of edestin dissolved in \( \text{N/20 sodium hydrate} \), so as to form a one per cent. solution. The lethal dose was almost invariably injected intravenously, usually through a cannula, into the jugular vein; this dose varied, with horse serum, from 0.1 cubic centimeter to one cubic centimeter, and with edestin, from 0.5 milligram and less to ten milligrams. The interval between the sensitizing and toxic doses varied from three weeks to over six months.

Symptoms of Immediate Anaphylaxis.—The picture presented by immediate anaphylaxis in guinea-pigs varies somewhat with the position of the animal. If the sensitized animal is at once released from the holder after an intravenous or intracardiac injection of horse serum or edestin, it at first remains quiet, but within one minute restlessness develops; the hair begins to bristle over the neck and head; it sits up on its hind legs and vigorously rubs the nose, giving frequently a spasmodic moist ringing sneeze; occasionally there is a jump. Within two minutes violent tonic and clonic convulsions develop, and the animal can no longer stand, but falls on its side; the legs are neither rigid nor flaccid, and a sharp kick is caused by a moderate squeeze of the toes. Now the mouth opens with each respiration, which is very slow and finally ceases usually within three minutes after the intracardiac injection. The heart still beats regularly for many minutes after all respirations have stopped.

If, on the other hand, the animal is kept stretched out on its holder, the train of symptoms is somewhat different, and signs come into evidence which have been largely masked when the animal has been at liberty. To illustrate this difference the toxic dose of serum or edestin has been injected into the circulation after the animal has recovered from the ether anesthesia used for intro-
ducing a cannula into the external jugular vein. In less than one minute the respirations quicken and the animal becomes restless and squeaks shrilly. Now it can be noticed that the sides of the chest sink in moderately with each inspiration. This sinking in of the chest with each inspiration becomes rapidly more pronounced, until finally the sides and lower portion of the sternum are depressed very strongly with each inspiratory effort. In this stage the respirations are slow, labored, and the animal shortly shows tonic and clonic convulsions, but gives vent to no sound, or at most to a choking squeak. At the same time, the pupils dilate. The mucous membranes of the mouth and the tongue become bluish, and often a spurt of urine is seen. The convulsions now cease and the animal lies motionless; it is not yet dead, for the heart is always seen beating with strong, regular, but slow pulses. After a respiratory stoppage which usually lasts one minute, respirations again appear, this time accompanied by opening of the mouth. These respirations are slow and cause apparently but little movement of the chest; they gradually become weaker and in another minute or two only the mouth is seen opening slightly a few times. Now all respiratory attempts have disappeared permanently, but the heart is still beating regularly, though usually more slowly and weaker than during the respiratory stoppage which just precedes the last attempts of the animal to breathe. These heart beats may still be observed many minutes after all respiration has stopped. The entire process from injection of the lethal dose to the permanent cessation of respiration lasts less than five minutes.

From the two descriptions of immediate anaphylaxis given above, it will be seen that the two methods of observation lay stress on two different sets of organs. When the animal is loose the paralytic symptoms of the skeletal motor mechanism dominate the picture; when the animal is fastened on its back on a suitable holder, marked respiratory symptoms force themselves upon the observer, which are largely masked in the first method of investigation. On account of the prominence of these changes in the respiration we investigated this function carefully during the anaphylactic state. Before entering upon this, however, we will briefly mention the autopsy findings in a typical case of anaphylaxis in the guinea-pig.
Anaphylaxis in the Guinea-Pig.

Autopsy Picture.—The peritoneal cavity usually offers but little of interest. The gut is usually found moderately congested, especially the beginning of the colon. The small intestine may show active, coordinate peristalsis, which at times is quite marked and almost resembles Van Braam Houkgeest's "Rollbewegungen." These last but a short time, when present. No definite peristalsis of the colon, cecum or stomach were seen. The ureters were usually congested and responded readily with a peristaltic contraction to a touch. As a rule no hemorrhages were seen in the stomach or colon of guinea-pigs which died within five minutes after injection of the toxic dose. The diaphragm often shows hemorrhages and is much less arched than in normal animals after death. On opening the chest the lungs present a striking sight; the lungs do not collapse, as normal lungs do when the thoracic cavity is opened, but remain almost fully distended. They look pale bluish pink, and apparently form a cast of the thoracic cavity. Even when excised in toto there is practically no collapse and the posterior surfaces often clearly show the markings of the ribs. The lungs are light, soft and spongy and float on water like a cork. On cutting away pieces of lung tissue these pieces do not collapse, but remain distended; the cut surface is usually dry and on pressure a good amount of air may be expressed. Occasionally this pressure reveals some small foci of white foam, as if there were beginning pulmonary edema; occasionally small hemorrhages were seen on the surface of the lungs. The trachea and bronchi usually were dry, but showed often a marked congestion of the mucosa. The blood in the lungs and in the aorta was black; the heart was usually still beating vigorously when the autopsy was performed; incision in the aorta, abdominal or thoracic, showed spurts of black blood. The heart muscle often showed hemorrhages, which in some instances were very extensive.

From the details which we have given above it will be seen that we are largely in agreement with the anatomical findings given by other writers on the subject, especially Gay and Southard. We differ, however, in one particular, which we think vital, and that is the significance of the condition of the lung in immediate anaphylaxis. None of the previous investigators, as far as we are aware, have attached sufficient importance to this organ; nor has its appearance been accurately described; the striking fact that the lung in acute anaphylaxis seems to remain in an inspiratory, distended condition with open thorax, with unobstructed trachea and large bronchi, and without obvious pulmonary edema, has been noted, as far as we are aware, only by Gay and Southard. These authors call attention to the lungs, describing the condition as an emphysema.

1 Houkgeest, Arch. f. d. ges. Physiol., 1872, vi, 266; described also as "Peristaltic Rush" by Meltzer and Auer, American Jour. of Physiol., 1907, xx, 289.
They are under the impression that this condition is produced by an extrapulmonary mechanism in which the diaphragm is an important factor. The significant fact that the lungs on removal from the body do not collapse does not seem to have impressed them particularly.

This immobilization of the lungs we consider the most characteristic sign of immediate anaphylaxis in the guinea-pig, and, indeed, we use it as an indicator of the immediate anaphylactic state in conditions when the animal is motionless, as when under the influence of curarin or when pithed. In the course of this paper we will bring forward evidence that this condition of the lungs forms the anatomical basis for the explanation of immediate anaphylactic death in guinea-pigs.

Respiratory System.—The respiratory changes during immediate anaphylaxis were investigated by various methods. Sometimes the animal was allowed to breathe from a bottle of four to six liters capacity, care being taken that the tubing between bottle and trachea was as short and as wide as possible. Registration was secured by connecting a Marey tambour with this bottle. The air capacity of this Vorlage sufficed for the needs of a guinea-pig during five minutes; if a longer period was necessary the bottle was quickly ventilated. Another method of recording respiration was frequently employed, often in conjunction with the previous one; a Meltzer pleural cannula was inserted in a pleural cavity and the intrathoracic pressure changes were recorded by a Marey tambour. Negative pressure in the opened pleural cavity was only partially reestablished in order to prevent the lung from plugging the opening of the pleural cannula. This method recorded the volume changes of the pleural cavity. Under special conditions (medulla and cord destroyed or curarin), the volume changes of the lung under artificial respiration were sometimes recorded by placing the animal up to the neck into an air plethysmograph or indicated by means of a receiving tambour fixed directly to the chest.

Examination of the various curves obtained give much information about the functional changes going on in the pulmonary

\[1\] Meltzer, Zeit. f. Instrumentenkunde, 1894; abstract in Cent. f. Physiol., 1896, x, 536.
mechanism during acute anaphylaxis. Fig. 1 (Plate VI) shows the oscillations of intrathoracic pressure which are produced by the action of the respiratory muscles, and the blood pressure curve of an anaphylactic guinea-pig. The respiratory curve (inspiration = downstroke) shows graphically what has already been described, namely, the initial quickening of the respiration after the toxic dose, followed by a swiftly developing slowing of the rate with active expiration, then the respiratory stoppage which may last one to two minutes and which is occasionally broken by single respirations with powerful active expiration; finally, the terminal group of respirations. It will be noticed that all of the respirations, excepting the last few of the terminal group, produce a greater negative pressure in the thorax than the normal respirations. Under ordinary conditions this would mean that a larger quantity of air would enter and leave the lungs in the respirations during anaphylaxis, for normally the lungs follow passively the changes in volume of the thoracic cavity which the action of the rib-muscles and diaphragm produce. In the present instance these changes in intrathoracic pressure do not represent respirations, but only respiratory attempts. This is shown clearly in Fig. 2 (Plate VIII). In this experiment the animal breathed the air contained in a large bottle and its respiration was recorded by connecting a tambour with this Vorlage. A tracing obtained by this method, therefore, gives a roughly quantitative record of the air which leaves the bottle during an inspiration and of the air which enters during an expiration. This instructive curve shows strikingly that during the stage when the respirations are slowed less air enters and leaves the lung, not more, as a casual interpretation of the intrathoracic pressure changes seems to show. Again, Fig. 2 shows beautifully that the air in this stage of slowed respiration enters and leaves the lung with increasing slowness and difficulty, for inspiration (downstroke on curve) and expiration (upstroke on curve) take place only gradually, as a glance at the record will show.

Moreover, air enters and leaves the lung slowly in spite of the fact that the negative intrathoracic pressure is greater than normal in these respirations (see Plate VIII, Fig. 3) and this increased negative pressure is established at once and not gradually during a res-
piration, so that conditions seem very favorable for a prompt and speedy entrance of air into the lungs. In the terminal group of respirations we see that practically no air leaves the bottle during an inspiration, while the intrathoracic pressure shows changes at first which may be even stronger than those registered when the animal was breathing normally, before injection of the toxic dose. These facts which we have brought forward indicate clearly that some stenosis is gradually produced in the pulmonary passages in immediate anaphylaxis, so that in the final stage practically no air enters or leaves the lung in spite of violent respiratory attempts. Since air enters and leaves the lung with greater and greater difficulty, until finally practically none is obtained, it is clear that an asphyxia must swiftly develop. This is the case. The evidence presented thus far amply demonstrates that this must be true, but there are other facts in support of this which may be mentioned. When a blood pressure tracing is taken it will be noticed that the blood in the cannula swiftly darkens and finally becomes black; again, there are convulsions during this stage (Fig. 3), the tongue becomes bluish, the pupils dilate widely, and the blood pressure usually, though not always, shows a considerable rise (Fig. 1). All these facts find their explanation in the speedy development of an asphyxia caused by a pulmonary stenosis, which is brought on by the injection of the toxic dose. It may, therefore, be considered established that the primary cause of immediate anaphylactic death in guinea-pigs is due to asphyxia; cessation of respiration is secondary to this asphyxia.

Section of Vagi: Curarin.—In numerous experiments the effect of the vagi upon the lungs was studied. At this point we may state that section of both vagi in the neck had no preventive effect upon the production of immediate anaphylactic death, such as one might legitimately expect, if the action of the injected toxic dose were in the medullary centers. These experiments, however, do not form a rigid proof of the peripheral nature of the vital change in the lungs; this will be given later.

In many experiments it was desirable to immobilize the animal. For this purpose a liberal dose of curarin (one or two milligrams) was injected into the circulation and accomplished its effect perfectly without interfering to any noticeable extent with the cardiac vagus. In these curarized animals, also, the effect of the toxic injection was promptly and characteristically shown; arti-
ficial respiration being, of course, given after the curarin. These curarin experiments, it may incidentally be stated, refute the theory of Gay and Southard that immediate anaphylactic death seems to require stimulation of the medullary or phrenic centers, thus producing a diaphragmatic spasm and pulmonary emphysema. In these curare experiments the diaphragm was excluded, the phrenic nerves being physiologically cut, yet the typical and death-bringing lung condition developed with promptness when the second injection was given.

Peripheral or Central Action.—In a preceding section we have demonstrated that asphyxia is the killing agent in immediate anaphylactic death, and that this asphyxia is produced by a stenosis of the pulmonary air passages. How is this stenosis produced? Is it the result of a stimulation in the central nervous system, as is generally assumed, or is it produced by action upon the peripheral mechanism itself in the lung, or do both factors, a central and a peripheral action, join in bringing about this condition? A survey of the recent literature bearing upon this question shows that practically all observers agreed that the main phenomena in acute anaphylaxis were due to some disturbance of the medullary centers. Thus, for example, Richet in a recent paper defines the "poison" which produces all the phenomena of anaphylaxis (apotoxin) as a poison which paralyzes the central nervous system and especially the vasomotor functions of the central nervous system. Rosenau and Anderson suggest repeatedly that the "essential lesion of serum anaphylaxis is probably localized in the respiratory center." Besredka explains the phenomena under discussion as the result of changes occurring in the nerve cells. Gay and Southard speak of a local anaphylaxis of the respiratory nervous center. The only investigators who considered the peripheral nature of anaphylaxis were Biedl and Kraus, who used the dog as the experimental animal. Biedl and Kraus furnished evidence that the characteristic anaphylactic effect in dogs, the prompt drop in blood pressure, was caused by a peripheral paralysis of the vasomotor system.

19 Besredka, Bull. de l'Inst. Pasteur, 1908, vi, 948.
From this short survey it will be seen that practically all investigators (all of those who experimented with guinea-pigs) were committed to the theory that the vital effects of immediate anaphylaxis were exerted in the central nervous system.

Numerous experiments were made to strengthen this hypothesis, but none were conclusive. Yet technically it was much easier to attempt to demonstrate a possible peripheral action in acute anaphylaxis; all that is necessary is to destroy the central nervous system, keeping the animal alive by means of artificial respiration. If a characteristic reaction is now obtained after injection of the toxic dose, incontestable proof will have been furnished that the central nervous system is negligible in its production; in other words, that the action is peripheral. But, for a successful demonstration by this means, a characteristic reaction, if possible the vital reaction, must be known, and we think that we have this vital reaction, as far as immediate anaphylaxis in guinea-pigs is concerned. We have already stated, and advanced the proof, that the most characteristic, the vital reaction of immediate anaphylaxis in guinea-pigs is the production of a stenosis in the pulmonary air passages, so that in the final stages very little or no air enters or leaves the lungs in spite of violent respiratory attempts, and that anatomically this condition is easily recognized. This striking behavior of the lung we have used as an indicator that immediate anaphylaxis had developed as a result of the toxic dose. The course, then, of an experiment to demonstrate the peripheral action of the toxic dose was as follows: Sensitized guinea-pigs were anesthetized with ether, suitable provision being made to maintain the animal’s temperature (electric pad); a cannula was tied into the trachea; both vagi were cut in the neck, and artificial respiration was started. Now the animal was turned on its belly, and the cord, medulla, and the lower portions of the brain were destroyed by pithing. Then the animal was returned to its original position, on its back, and a cannula tied into the external jugular vein. Great care was exercised that the artificial respiration (40 to 60 per minute, occasionally more) was sufficiently strong to give a well defined chest expansion to the animal. Now after determining that the heart was beating, the toxic dose was injected into the cannula, the cannula being
washed clear by one cubic centimeter of normal salt or Ringer's solution. Careful observation showed that within one to three minutes after the injection, the chest expansion gradually grew less, the chest becoming fuller, until finally the blast of air driven rhythmically into the trachea caused no further expansion or collapse of the chest. The chest was fixed motionless in a more or less inspiratory condition. Fig. 4 (Plate IX) illustrates this well. This tracing was obtained from a pithed animal by means of a tambour fixed over one side of the chest. Each oscillation represents a blast of air from the respiration machine, upstroke being produced by an expansion of the chest. Shortly after the intravenous injection of 0.2 cubic centimeter of normal horse serum it may be noticed that the respiratory oscillations increase slightly in size, then a rather rapid diminution in size of the respirations occurs, until finally practically none are seen, which in this instance is one and a half minutes after injection of the toxic dose. Inspection of the tracing will also show that the quiescent chest now traces a line distinctly higher than the line formed by the bases of respiratory oscillations (the expiratory level) which were obtained before injection of the toxic dose; this means that the chest is now at rest in a more expanded condition than during the period of expiration before injection. Autopsy of this animal showed the typical picture of anaphylaxis of the lung which we described before.

A more striking tracing, and one which usually shows more details, may be obtained, if the pressure changes in the thoracic cavity are recorded by means of a pleural cannula. Fig. 5 (Plate IX) (pithed animal) is a tracing obtained in this way. This curve shows shortly after injection of the horse serum that the oscillations, produced by the effect of artificial respiration upon the volume of the lung, at first become slightly less, then increase in size and finally rapidly decrease in extent, until nothing but the volume changes of the heart are recorded. These changes indicate that the toxic dose first causes a slight decrease in the volume changes of the lung, then an increase in the volume changes, and finally, one and three quarter minutes after the injection, a decrease to such an extent that no volume changes of the lung are recorded at all, although artificial respiration is still continued.
exactly as before, the small waves visible being those caused by systole and diastole of the ventricles.

Since we have obtained the characteristic lung picture of immediate anaphylaxis invariably in these pithed animals, of which Figs. 4 and 5 give a graphic presentation, we have furnished absolute proof that the central nervous system is not essential for the production of the characteristic and death-dealing lesion of immediate anaphylaxis; the action is surely peripheral in the lung. But this evidence permits no conclusion regarding a possible effect on the central nervous system; it is quite conceivable that the medulla does aid in the production of immediate anaphylactic death, but we have demonstrated that this action, if present, is not essential, for not even a delay in the onset of the pulmonary inspiratory immobilization after the toxic dose is to be noted in these pithed animals. Rigid proof for this hypothetical central action, which our experiments have proven to be unnecessary for the explanation of acute anaphylactic death, has been furnished by no one.

_Causation of Lung Condition._—How is this remarkable condition of the lungs produced? By what mechanism is the air imprisoned in the alveolar sacs, so that the lungs remain distended for a long time when excised? There are several conditions conceivable that would prevent the air from escaping and thus produce this condition: (1) pulmonary edema; (2) emphysema; (3) submucous edema in the bronchi and bronchioli; (4) tetanic contraction of the musculature of the bronchioles, occluding their lumen.

The first possibility, pulmonary edema, may be dismissed at once. The two pictures, pulmonary edema and the lung in immediate anaphylactic death, have nothing in common. In an outspoken edema of the lung, such as may easily be produced in a guinea-pig by an intravenous injection of a fraction of a cubic centimeter of adrenalin, the lungs are dark, mottled, heavy; pink foam usually exudes from the nares of the intact animal; on section the trachea is usually full of a pinkish foam composed of fine bubbles; section of the lung shows it to be extremely juicy. On the other hand, the lung of a guinea-pig dead from immediate anaphylaxis is a pale bluish-pink in color; very light; the trachea contains no foam, and shows often a marked congestion of the blood-vessels; sections of the lung show a fairly dry surface, and on pressure much air, but little fluid, escapes. At times, it is true, some small foci of a fine white foam may be noted in certain sections on pressure, but these were never ex-
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tensive nor widespread. These small areas possibly show a slight degree of pulmonary edema in certain areas, but their extent is too small to explain the entire picture.

The second possibility, emphysema, has been noted in immediate anaphylaxis by Gay and Southard. They are even "inclined to regard this emphysema as the effective cause of death in the quickly fatal cases." In the extensive histological studies which these authors give of the lesions found in various organs after acute anaphylactic death, a detailed consideration of the lungs is not given, an omission all the more striking since they attribute such importance to the lungs; moreover, in no place do they explain how an "emphysematous" lung can cause death within a few minutes. We have already shown before that their conception of how this "emphysema" is produced, is erroneous (p. 160).

While Gay and Southard undoubtedly have seen the typical anaphylactic lungs, and although they justly, though with no published evidence, brought the lung condition into causal relation with acute anaphylactic death, it must be pointed out that these anaphylactic lungs are not emphysematous, at least as that term is ordinarily understood. Only two conditions come into consideration if these anaphylactic lungs are emphysematous: acute vesicular emphysema and acute interlobular emphysema. In the acute vesicular type the surface of the lung is raised into little hillocks formed by the overdistended lobules and the areas between these elevations are compressed and even atelectatic; these hillocks are especially noticeable at the free borders of the lobes. In the lung of acute anaphylaxis nothing of the kind is seen; the surface is smooth and the borders of the lobes are clean cut and sharp; in short, the lung looks like a normal lung which has been fully inflated; the histological picture shows no areas of compression or atelectasis, and the alveoli are only moderately distended. Nor is this condition due to interlobular emphysema; in no instance were the characteristic subpleural blebs of air noted on the surface of the lungs. Since there is no other well defined acute emphysema of the lungs, we think that it must be admitted that the lungs of immediate anaphylaxis are not emphysematous.

The third possibility, submucous edema in the bronchi, and especially the bronchioi, is not so easily disproved as the other two possibilities. It is well known from the labors of v. Pirquet and Schick that serum injections may cause edema of the skin in man, especially if the subject has been sensitized by a previous injection of serum. They make no mention, however, of such a condition in the lungs, nor are we aware of any such observation based on anatomical findings. It is conceivable that the sudden development of submucous edema in the bronchioi could practically occlude their lumen, so that air could neither enter nor escape. But while it is impossible to dismiss this explanation, there are a number of facts which speak against submucous edema as a predominant factor in the production of the anaphylactic lung. Thus, for example, we have stated before that after injection of the toxic dose a period of increased lung expansion occurs shortly before the final and complete

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cessation of lung expansion (Fig. 5). How is this increased expansion of the lung to be explained on basis of this theory? The increased expansion obviously means that more air is driven into the lungs by the blasts from the artificial respiration machine; yet, how can more air enter, if, as the hypothesis demands, a submucous edema is being formed, which must to some degree obstruct the lumen of the finer air passages and thus hinder the entrance of more air? Again, how is this theory to explain the fact that an intravenous injection of atropin causes, in suitable cases, a rather prompt resumption of pulmonary oscillations (pithed or curarized animal)? How does the atropin bring about the disappearance of the submucous edema? Some other opposing facts might be mentioned, and will be referred to later, but it seems sufficiently clear now that submucous pulmonary edema alone will not explain all of our experimental facts. It is possible, perhaps we may say probable, that the production of such an edema does take place, but conditions do not yet force us to take this factor into consideration in our attempts to explain the experimental data, and under these conditions it is unnecessary to call upon two mechanisms when one of them is sufficient to explain the results.

There remains for consideration the fourth possible explanation, and this is the mechanism which we consider fully capable of explaining the remarkable lung condition in immediate anaphylaxis, namely, a tetanic contraction of the muscles of the finer bronchioles, so that the air is imprisoned in the alveolar sacs. The anatomical basis for this is clear: the finer bronchioles are practically nothing but muscular tubes,19 moreover muscle fibers are also present in the alveolar ducts20 and, according to some anatomists, may even form sphincter-like structures about the alveoli.21 The contraction of these structures must have a profound effect upon the volume of air passing to and from the alveoli. That this is indeed true has been demonstrated by numbers of observers, especially conclusively by Einthoven22 and Dixon and Brodie.23 These investigators have shown that stimulation of the vagi in the neck produces a constriction of the pulmonary passages, so that air enters the lung with difficulty, and that this stenosis was produced by a contraction of

19The effect of atropin in immediate anaphylaxis will be considered in a later paper.
21Oppel, loc. cit., p. 653.
23Dixon and Brodie, Jour. of Physiol., 1903, xxix, 97.
the bronchial musculature and not by vascular changes as has been assumed by v. Basch and his pupils.\(^2\)

An examination of our lung data will show, we think, that they are easily explainable on basis of this theory. For example let us consider Fig. 5. This curve was obtained from a pithed guinea-pig which had been sensitized by edestin. In one pleural cavity a cannula was fixed and the volume changes of the lungs, produced by artificial respiration from a machine, recorded by a Marey tambour on a smoked drum. The large oscillations represent these changes, upstroke being inflation, downstroke the elastic recoil of the lungs during the respiratory pause. During the time indicated by the broad white mark, one-half milligram of edestin, dissolved in N/20 sodium hydrate was injected into the external jugular vein; the cannula was then washed out by a second injection of one cubic centimeter saline solution. During and after these injections the tracing shows that the oscillations became slightly but definitely smaller; then they increased to an extent greater than normal. Then another slight decrease in amplitude occurred, which lasted about thirty seconds; now within twenty to thirty seconds the amplitude decreased slightly until the pleural cannula recorded no pulmonary volume changes, but only the volume changes of the heart, in spite of the fact that artificial respiration was still continued. These rhythmic changes are now easily explained; the injected substance caused first a broncho-constriction of moderate degree, this was followed in turn by a well defined broncho-dilatation, a slight broncho-constriction, and finally a broncho-constriction of maximal degree occurred so that artificial respiration no longer caused any lung volume changes. Such rhythmic contractions of the bronchial muscles have been described by Einthoven\(^2\) and by Dixon and Brodie;\(^6\) the latter give a curve illustrating this. During the course of this investigation we also have had opportunity to notice such changes after stimulation of the vagi in guinea-pigs; Fig. 6 (Plate IX) shows this very well.

Fig. 5 shows some other points of interest; it will be noticed that

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the lung comes to rest about midway between passive expiration and the inspiration caused by the blast of air. This means that the lung is fuller than during a passive expiration, and more nearly in an inspiratory condition; in other words, air has been imprisoned in the lungs probably by the same agency which first caused a rhythmic change in the lung volume and which finally occluded the pulmonary air passages. In another tracing, Fig. 4, this final resting point was nearer the inspiratory level of the lung oscillations and more air therefore imprisoned. This latter tracing (Fig. 4) shows a slight broncho-dilatation following shortly upon the injection of the toxic dose of horse serum. Both figures show that the air enters and leaves with increasing difficulty by the decrease in size of the lung oscillations and by the increasing slope of these oscillations. Both of these points are well brought out in Fig. 4. This tracing was obtained from a pithed sensitized animal (cord, medulla and base of brain destroyed) by placing a tambour on one side of the chest and thus recording the chest oscillations produced by the expansion and collapse of the lung under artificial respiration from a machine which delivered air to the animal with a constant rate, strength and volume. The terminal oscillations in this tracing are small and slope much more than the normal oscillations which are almost vertical. This sloping upstroke is due to the gradually increasing resistance which the entering blast of air encounters and which can only slowly and slightly change the lung volume; the sloping downstroke shows the slowness with which the lung discharges the air, and finally no lung volume changes occur at all, although the artificial respiration continues exactly as before; no air enters or leaves the lung.

We have stated before that an increase in size of the lung volume oscillations occurs after injection of the toxic dose. This is true only under a certain condition, namely, when the pulmonary bronchioli are in a state of moderate tonus. In the numerous tracings which we have obtained in our study of the anaphylactic lung, practically only those in which the vagi had previously been stimulated have shown in a noticeable degree this primary increase in lung oscillations after injection of the toxic dose. Such bronchodilator effects may also be obtained by stimulation of the vagi, as
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has been shown by Beer and especially by Dixon and Brodie. The latter observers call attention to the fact that this dilator effect may easily be obtained provided that the bronchial muscles are in a state of tonus; a striking curve illustrates their statement.

This fact that a primary broncho-dilatation after injection of the toxic dose is only markedly shown after an effective vagus stimulation is another strong argument in favor of the theory that the bronchial muscles are affected in immediate anaphylaxis.

Finally, we may add that atropin under certain conditions is able to relax the rigid anaphylactic lung so that it is again able to expand and collapse. Now it has been shown by Beer and by Einthoven that atropin paralyzes the bronchial muscles and, therefore, this fact forms another link in the evidence that the bronchial muscles play an important rôle in immediate anaphylaxis in guinea-pigs.

The evidence which we have presented in the last section may be summarized as follows: After the toxic injection (a) the lungs of a sensitized guinea-pig which has been curarized or pithed shows within a few minutes a marked decrease in the lung volume changes caused by artificial respiration; this decrease progresses swiftly and finally no volume changes are recorded at all, although the artificial respiration continues with the same rate, force and volume; (b) this tremendous decrease in the lung oscillations is preceded under a certain condition by a stage of increased lung oscillations; (c) this stage of increased lung oscillations which precedes the final stage of complete absence of lung oscillations may be obtained with a fair certainty only when the broncho-constrictors have shortly before been excited; (d) atropin may again bring about lung oscillations even when injected after the final stage of complete absence of pulmonary movements has been established.

Since all the effects mentioned under the first three heads have been produced by stimulation of the peripheral vagus (Einthoven, Dixon and Brodie) and since it has been shown that blood-vascular


Dixon and Brodie, *Jour. of Physiol.*, 1903, xxix, 9, 139; tracing on p. 140.


changes will not alone account for these lung changes, but that the bronchial muscles are the main factors, and since atropin paralyzes the bronchial muscles, we feel justified in assuming that the second or toxic injection in a sensitized guinea-pig acts upon the bronchial muscles, producing swiftly a tetanic contraction of the finer bronchioles which completely occludes their lumen and thus prevents the entrance and escape of air. We do not care, as yet, to state whether the action of the toxic dose is exerted upon the vagus broncho-motor endings, or upon the muscles directly, or upon both.

**Blood Pressure in Immediate Anaphylaxis.**—The blood pressure in sensitized guinea-pigs was obtained from the carotid artery by means of a Hürthle spring manometer. Mercury manometers we found unsuitable, because the blood pressure oscillations obtained by vagus stimulation allowed a fair amount of the anti-coagulant to flow into the circulation and this introduced a factor of some importance in such a small animal as the guinea-pig, especially when magnesium sulphate or sodium carbonate solutions were employed to fill the tubing.

As anti-coagulant for the connecting tubing we employed chiefly half saturated sodium sulphate solution or 10 per cent. sodium citrate. Their action was not very successful in the guinea-pig, for clots were annoyingly frequent, especially in our earlier experiments when the animals were largely grain-fed.

The average blood pressure at the beginning of an experiment we found to be 80 millimeters of mercury, and the average pulse rate about 275 beats per minute. The animal weighed from 300 to 600 grams. These results agree quite well with those of Harrington.\textsuperscript{81} Harrington states that the average blood pressure in his experiments upon guinea-pigs was 75 millimeters (mercury manometer; sodium carbonate for tubing) and the average heart rate was 200.

The blood pressure of an anaphylactic guinea-pig is shown in Figs. 1 and 2. As soon as the respiration shows an increase in rate (Figs. 1 and 2), which occurs within a few seconds after the injection of the toxic dose, the blood pressure begins to rise. This is due to beginning asphyxia, for although Fig. 1 shows at

\textsuperscript{81} Harrington, *American Jour. of Physiol.*, 1898, i, 384.
this time an increased negative pressure in the pleural cavity. Fig. 2 shows at the corresponding point that the animal is already experiencing difficulty in getting air into the lungs, for the oscillations of the respiratory curve from the Vorlage are smaller and the slopes of the inspirations and expirations are greater. The pulse rate during this stage may not be altered, and the respiratory oscillations of the blood pressure are indicated. As the respiratory difficulty increases the heart may show some irregularities in beats, probably due to reflex vagus inhibition (Fig. 2); if this reflex inhibition is not marked the blood pressure now reaches its maximum (Fig. 1) and then begins slowly to drop, each respiratory effort, even though no air enters the lung, being clearly shown on the blood pressure curve. This drop continues so that five to eight minutes after the maximum the blood pressure has fallen to 10 to 20 millimeters of mercury.

All the blood pressure curves which we have obtained in sensitized guinea-pigs show the same general features: an initial rise, which varies from 10 to 60 millimeters of mercury, shortly after the injection of the toxic dose, a short maintenance of this level and then a gradual drop to 10 to 20 millimeters of mercury. The entire length of time consumed from the injection of the toxic dose to the point where the 10 to 20 millimeter level is reached, usually is less than ten minutes, provided that the animals are highly sensitized and that the body heat of the animal has been maintained during the experiment.

The course of the blood pressure curve in immediate anaphylaxis of guinea-pigs is strikingly different from that in the dog as described by Biedl and Kraus. These investigators noted a fall in blood pressure which occurs about thirty seconds after the toxic injection and reaches its maximum in about one minute. The blood pressure fall is considerable and may reach the 40 millimeter level and even less. Associated with this fall of blood pressure is a diminution in the size of the pulse waves and an increase in the pulse rate. During this stage of low blood pressure, stimulation of the peripheral splanchnic nerves or an intravenous injection

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of adrenalin produces no rise of the pressure level, but an intra-
venous injection of barium chloride does elicit a powerful increase
in blood pressure. From these data the authors justly conclude
that this fall in blood pressure in anaphylaxis in dogs is caused by
a paralysis of the peripheral vasomotor mechanism.

Since the general picture of immediate anaphylaxis in dogs is very
different from that of immediate anaphylaxis in guinea-pigs, we
need not enter into a further discussion of Biedl and Kraus's in-
teresting communication.

Heart Block.—Each of the blood pressure curves shows more or less well,
on mere inspection, that the pulse rate changes markedly during this drop in
blood pressure; the beats are large and slow. A count of these pulse beats
shows that their rate stands in a simple ratio to the normal number of beats.
Thus, for example, the number of beats observable shortly after a complete
stenosis of the pulmonary air passages may be 44 for ten seconds; when the
first slowing takes place, which occurs abruptly, the beats number 22 per ten
seconds; after another slowing these beats may now number 11 per ten seconds.
Fig. 5 shows these changes in the heart rate.

Inspection of the animal's heart, when the chest has been opened, shows
beautifully the development of a heart block; at first the ventricles beat regu-
larly after a preceding systole of the auricles; shortly the auricles beat two
times to every one beat of the ventricles; and a little later the auricles and
ventricles beat in a 3:1 rhythm. All of these changes may occur within one
minute after the lung bronchioles have become completely occluded by the
injection of the toxic dose; Fig. 5 illustrates this change in ventricular rhythm
very well. This tracing was obtained by a pleural cannula from a pithed
animal, and thus disturbing reflex vagus inhibition plays no rôle in this curve;
the blood pressure curves (Figs. 1 and 2) also show at least one change in
ventricular rhythm.

Cardiac Vagus During Immediate Anaphylaxis.—In a moderate number of
blood pressure experiments we observed the effect of peripheral vagus stimula-
tion upon the heart. Practically all of these experiments showed that during
the blood pressure drop the cardiac vagus gradually lost its irritability, so that
finally when the blood pressure was about 20 millimeters, we usually obtained
no effect on stimulation of the vagus with any strength of induced current.

Effect of Temperature.—In all the experiments which we have made, care
was taken to maintain the animal's temperature by means of an electric pad.
The rectal temperature noted, after the animal was on the holder, ranged
between 37 and 39° C., and this was maintained throughout the experiment
with only moderate fluctuations. This we found necessary because a cooled
guinea-pig shows a markedly delayed reaction to the toxic injection of serum,
and the symptoms which are produced under this condition are not so striking
as when the guinea-pig has a higher temperature.
Blood Coagulation.—In the valuable contribution by Biedl and Kraus\textsuperscript{2a} attention was called to the striking fact that the blood of an anaphylactic dog does not coagulate for days. This is, however, not true for the guinea-pig, as the same authors state in their second communication,\textsuperscript{4a} and we are able to corroborate this fact. Most of our blood pressure experiments illustrate this fact.

Controls.—In a number of normal guinea-pigs horse serum was injected into the external jugular vein and its behavior observed. In accordance with the result of numerous previous observers we found that the injected horse serum, which varied in quantity from four to six cubic centimeters, exerted no deleterious effect upon the animal. The animals struggled occasionally in the holder, now and then showed some dyspnea (no tracheotomy was performed), but not any more apparently than normal non-operated animals show when merely stretched out on the holder. The blood pressure (Hürtthle) after thirty to fifty minutes usually showed a drop of 10 millimeters of mercury. In short, the injected horse serum exerted no obvious harmful effect.

SUMMARY.

1. By an immediate anaphylactic reaction we mean the chain of symptoms which occur in highly sensitized guinea-pigs shortly after an intravenous or intracardiac injection of the toxic dose and usually end in death.
2. Immediate anaphylactic death occurs three to five minutes after the toxic injection in highly sensitized guinea-pigs.
3. Immediate anaphylactic death in guinea-pigs is caused by asphyxia; cessation of respiration is secondary to this asphyxia.
4. This asphyxia is apparently produced by a tetanic contraction of the smooth muscles of the bronchioles, which occludes their lumen gradually, so that finally no air enters or leaves the lung, in spite of violent respiratory efforts; the animal is strangulated.
5. The stage of complete broncho-constriction is preceded by a short broncho-dilatation, if the bronchioles have been in a state of tonus previous to the injection of the toxic dose.
6. Anatomically, the lungs of these guinea-pigs are typical and

\textsuperscript{2a} Biedl and Kraus, \textit{loc. cit.}, p. 367.
may be used as an indicator of the immediate anaphylactic state when the animal has been immobilized by curarin or by pithing.

7. The lungs of a guinea-pig killed by immediate anaphylaxis are distended and in an inspiratory position so that the diaphragm is pushed down; no marked collapse occurs when the chest is opened and when the lungs are excised in toto; their color is a pale bluish-pink; the surfaces and borders are smooth; no foam is in the trachea or large bronchi; pieces of lung cut off do not collapse, float lightly on water, and contain a good amount of air and little fluid which escapes on pressure. The blood in the lungs and heart is black when the autopsy is made at once after the cessation of respiration.

8. Section of the vagi in the neck, or curarin (artificial respiration) exerts no appreciable effect on the development of immediate anaphylaxis.

9. This immobilization of the lungs, which is due to a bronchoconstriction, is of peripheral origin, for destruction of the spinal cord and medulla affects in no appreciable way the promptness and extent of the typical lung response to the injection of the toxic dose. Artificial respiration is, of course, necessary.

At the present time we do not care to state whether the toxic dose exerts its effects upon the bronchial muscles alone or upon the vagus motor endings or upon both structures.

10. The blood pressure in immediate anaphylaxis first shows a rise, which may be considerable; a short maintenance of this high level and then a gradual drop to 10 to 20 millimeters of mercury and even less, within ten minutes after injection of the toxic dose.

11. Shortly after injection of the toxic dose a heart block develops, so that auricles and ventricles may beat in a 3:1 rhythm; the block is probably due to asphyxia.

12. The cardiac vagus gradually loses its irritability after injection of the toxic dose.

13. Cooling of the guinea-pig delays the reaction to the toxic injection.

We wish to express our thanks to Dr. W. H. Park for his kindness in furnishing us horse serum.
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EXPLANATION OF PLATES.

PLATE VI.

Fig. 1. In this tracing a simultaneous record of the intrapleural pressure and the blood pressure (Hürthle) was recorded. Time marking is in two second intervals. The unbroken line above the time line is the abscissa for the blood pressure tracing. The curve above this, intersecting the large respiratory oscillations, is the blood pressure curve; the blood pressure scale, showing the value of the curve in millimeters of mercury is at the termination of this curve. The curve showing large oscillations represents the fluctuations of the intra-thoracic pressure due to respiration; downstroke equals inspiration. The longitudinal, unbroken line near the top of the large respiratory waves is the atmospheric pressure line; above this line is positive pressure, below is negative pressure.

At the place marked by crosses, 1 c.c. of horse serum was injected into the external jugular vein; this was followed by 1 c.c. of Ringer's solution to wash out the cannula. The blood pressure curve is marred by a partial clotting, but the main features (see text) are well brought out. The respiratory curve is self-explanatory.

PLATE VII.

Fig. 2. Simultaneous record of the blood pressure (Hürthle) and of the air which enters and leaves the trachea, recorded by means of a tambour connected with the air bottle from which the animal breathed; downstroke equals inspiration. Time is in one second intervals. At one point noted in the curve the air in the bottle was renewed (unnecessarily). The respiratory oscillations immediately following this show very well the increasing difficulty of getting air into and out of the lungs until finally no air enters or leaves, as is shown by the straight line traced by the tambour lever, although the animal makes violent respiratory attempts, as is shown by the respiratory oscillations of the blood pressure curve. The blood pressure shows the same general features as before; note the change in the heart rate.

At the place marked by crosses, 1.25 c.c. of horse serum were injected into the external jugular vein; this was followed by 1 c.c. of Ringer's solution.

PLATE VIII.

Fig. 3. Simultaneous record of intrapleural pressure changes and of the air inspired and expired (Luft Vorlage); downstroke on both curves is inspiration. Time marking is in four second intervals. The upper curve, showing large oscillations, records the intrapleural pressure changes; the lower curve indicates the air which enters and leaves the lungs during respiration; the sudden drop at one point of this curve was due to the opening of a stop-cock. The broad white bands on the line beneath the time marking show when 1 c.c. of horse serum and 1 c.c. of saline solution were injected into the external jugular vein. Shortly after the serum injection the respirations became slower and dyspneic; the intrathoracic pressure changes (upper curve) are greater while the lower curve shows that less and less air enters and leaves the lung. Shortly after this no air enters or leaves the lung and the lever of the tambour
connected with the air bottle traces a straight line, while the intrapleural pressure curve shows that the animal makes active expirations and deep inspiratory attempts. The respiratory pause, preceded by a convulsion and followed by the terminal group of respiratory attempts is well brought out. At no point does the curve show an inspiratory tetanus of any duration. The straight line near the top of the curve represents atmospheric pressure. Above this line is positive pressure, below the line is negative pressure.

PLATE IX.

Fig. 4. This tracing was obtained from an animal whose cord, medulla, and basal portions of the brain had been destroyed by pithing. Artificial respiration was started before the pithing was completed and was recorded by means of a tambour fixed on the left side of the chest; upstroke equals inflation of the lung. At the places marked by broad white bands, 0.2 c.c. of horse serum and 1 c.c. of saline solution were injected into the external jugular vein. Shortly after this injection the lung volume oscillations increased slightly, then gradually decreased in amplitude until finally no oscillations were seen, although artificial respiration was still going on. The terminal oscillations also show increased slopes indicating slowness of air in entering and leaving the lungs. The lever finally comes to rest very near the inspiratory level of the curve, showing that the chest is considerably fuller than during expiration. Time line shows four second intervals.

Fig. 5. Tracing showing the volume changes of the lung in a pithed guinea-pig (cord, medulla and basal portions of the brain destroyed) obtained by means of a pleural cannula. Time is in four second intervals. At the places marked by broad white bands, 0.5 mm. of the edestin dissolved in N/20 sodium hydroxide, and 1 c.c. of saline solution were injected into the external jugular vein. (Artificial respiration was begun before pithing and steadily maintained; both vagi had also been stimulated by induction shocks to bring about a tonus of the bronchial muscles.) During and after these injections the lung volume changes caused by the artificial respiration became less; these gradually increased to more than before the toxic injections, then decreased again slightly, and finally decreased to such an extent that the artificial respiration caused no further changes in the lung volume. The small oscillations recorded now are due to volume changes of the heart; this curve of the heart beat shows abrupt changes in rate due to heart block.

This tracing shows graphically the peripheral attack of the toxic dose, and the rhythmic change in lung volume due to the action of the toxic dose upon the bronchial muscles.

Fig. 6. Tracing obtained from the pleural cavity of a curarized, sensitized guinea-pig. At the place marked by a broad white band both vagi were stimulated by an induced current (40 mm. coil distance; Petzoldt coil, 2 Daniell cells). Time is in four second intervals. The tracing shows well the rhythmic changes in lung volume which may be produced by stimulating the bronchial muscles through the vagi.