STUDIES IN ANAPHYLAXIS

by

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A. B. University of Kansas, 1928.
A. M. University of Kansas, 1930.

Submitted to the Department of
Bacteriology and the Faculty
of the Graduate School of the
University of Kansas in partial
fulfillment of the requirements
for the degree of Doctor of Philosophy.

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ACKNOWLEDGMENT

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Introduction.

It has been recognized from the studies of active immunization that the parenteral introduction of foreign substances may call forth variable responses in species and individuals. The early work dealt with the treatments of animals, with bacteria or their products, for the purpose of increasing the tolerance or resistance of the animals. However, the most extensive studies of antibody formation have been made with antigens which were entirely innocuous, such as blood cells and serum. It appeared, for a time that the antibody content of the blood, and the resistance of the animal to foreign substances bore a parallel relationship.

However, it was soon recognized that the treatment of animals with any antigen, cellular or otherwise, may lead to increased tolerance under certain conditions and within definite limits, but may, under other conditions, give rise to the very opposite, that is, to an intolerance or increased susceptibility. The accumulation of this information has come from isolated observations scattered throughout the literature, which were often regarded as accidents or technical errors. This phenomenon of hypersusceptibility was further confused by the fact that some of the earliest work was carried out with substances toxic in themselves, such as Diptheria and Tetanus toxin, thus obscuring the basic principles involved.

Historical.

Perhaps the first observation of protein hypersensitivity was that of Magendie[1] in 1839, who found that rabbits which had tolerated two intravenous injections of egg albumin without any ill effects

immediately succumbed to a third injection made after a number of days.

Flexner [2] in 1894 made an accurate statement of the phenomenon in rabbits when he wrote, "animals that had withstood one dose of dog serum would succumb to a second dose given after the lapse of some days or weeks, even when this dose was sublethal for a control animal."

Knorr [3] in 1895 found that guinea-pigs developed an increasing sensitiveness to tetanus toxin.

Hericourt and Richet [4] in 1898 in studying the effects of eel serum on dogs found they were not able to immunize them against the serum, but that on the contrary there was an increasing sensitivity to it so that finally the dogs died.

Berhing and Kitashima [5] in 1901 while repeating some of Knorr's work also found an increasing sensitiveness to tetanus toxin on the part of guinea-pigs.

In 1902 Portier and Richet [6] found that if dogs were given a very small dose of a glycerin extract from the tentacles of actinia, and then in 15 or 20 days given a second small dose, the animals quickly succumbed. The dose given was so small as to cause no symptoms in a normal animal. They appear to be the first to use the word "anaphylaxis" to indicate hypersensitiveness to a poison. It means "against protection", to express its antithesis to prophy- laxis or "protective effects". This work constitutes the beginning of our modern understanding of anaphylactic phenomena, since they set forth the following principles.

1. A definite incubation period is necessary before anaphylaxis
    can be induced.

2. The anaphylactic state lasts many weeks.

3. There may be some similarity between anaphylaxis and immunity.

4. Anaphylaxis is to a certain extent specific; that is to say, the
    second injection should be of the same nature as the first.

5. The symptoms of anaphylaxis are immediate and intense, while the
    symptoms of primary intoxication are mild.

Arthus[7] in 1903 found that horse serum injected into rabbits by
any of the usual paths of entrance was entirely innocuous. It was
possible to inject even 40 c.c. without harm. If, however, one re-
peatedly injected small amounts, at intervals of several days,
eventually the later injections would give rise to infiltration,
edema and even gangrene at the points of injection. He recognized
that this was not due to cumulative action, but that it was the
systemic nature of the phenomenon and regarded it as analogous to
the observations of Richet.

The "phenomenon of Theobald Smith"[8] was described by this
worker in 1904 in the course of the standardization of Diptheria
antitoxin in guinea-pigs. He noticed that surviving pigs exhibit-
ed a great susceptibility to a subsequent injection of horse serum
made several days or weeks later.

Almost simultaneously appeared the papers of Otto[9] in Germany
and Rosenau and Anderson[10] in the United States on anaphylaxis in
the guinea pig using horse serum as an antigen. These studies not
only confirmed previous work, but set down the basis of our present
knowledge of anaphylaxis. Their clearly drawn conclusions were:

1. A single injection of horse serum into guinea pigs, harmless in itself, renders these animals hypersusceptible to a subsequent injection given after a definite interval or incubation time.

2. This interval, with the ordinary dosages employed (about 1 to 2 c.c.) was about 10 days. Properly carried out injections after this period were usually fatal.

3. The known antibodies, antitoxins, hemolysins, and precipitins, are not responsible for the reaction.

4. The reaction is specific, injections of horse serum sensitizing to horse serum only.

5. The sensitive condition is transmissible from mother to off-spring, the young of sensitized mothers being hypersusceptible to the first injection of horse serum.

6. The reaction is extremely delicate.

7. The hypersusceptible state is not a transient condition, but may last a long time.

With the basic principals of the hypersensitive state established, in the years following a great number of papers appeared which extended our knowledge, and described the phenomena as they appeared in other animals.

Biedl and Kraus [11] in 1909 and Pearce and Eisenbrey [12] 1910 were among the first to describe accurately the symptoms in dogs.

Manwaring [13] 1911 claimed to have actively sensitized 25% of a series of cats to horse serum, and Schultz [14] in 1911 described a drop in blood pressure in sensitive cats by injecting a shock dose of horse serum.

In 1924 Parker and Parker [15] apparently sensitized white rats by

a single intraperitoned injection, or by 3 intraperitoneal injections
at 3 day intervals.

Gahringer[16] in 1926 reported sensitization of pigeons, at times
sufficiently high to give lethal anaphylaxis, by a single intravenous
injection with 0.25 c.c. dog serum. Maximum sensitization appeared
about the fourteenth day. Hanzlik, Butt and Stockton[17] in 1927 were
able to demonstrate the reciprocal action of the crop muscles in
sensitized pigeons.

In 1925 Goodner[18] was able to demonstrate considerable slowing
and diminition in amplitude of the excised sensitized frog heart,
when brought in contact with the specific sensitizing substance. This
reaction seemed to resemble light peripheral parasympathetic stimulation.

Sherwood[19] in 1928 passively sensitized 3 to 4 day old chick embryos
with high titered immune rooster serum. The characteristic response
was a marked slowing of the whole heart in diastole and occasionally
cardiac standstill and death. This response was evident within 2 1/2
minutes after addition of the non-toxic dose of antigen and did not occur
when the embryos were tested for desensitization.

In 1928 Sherwood and Downs[20] passively sensitized sand turtles with
high titered rooster serum. The heart was utilized in situ and the
shock dose introduced directly into the ventricle. The response was
specific and consisted of a marked slowing of the heart, increase in
diastole and a decrease in amplitude. Every heart showed densensitization,
upon second injection after return to the normal rythm. Downs[21] in the
same year actively sensitized turtles to mammalian serum with 3 or 4
injections into the coelom given about three days apart. The response
was specific and similar to that reported for passive sensitization.

Definition of terms

Thus we have seen that states of increased susceptibility have been described for many animal species. In the vast accumulation of literature on this subject are to be found descriptions of many and varied responses to the injection of almost any types of substance.

Because of these many types of altered responses, and the fact that they are diversely classified by authorities of note, it seems fitting to discuss them here.

Von Pirquit [22] in his studies of serum sickness, introduced the word allergy, meaning "altered reactivity". He used the term in connection with protein reactions and implied antigen-antibody reactions. Doerr [23] took over the term allergy, but expanded its meaning to embrace all types of altered reactivity whether due to antigens or not. His classification in brief is:

1. Hypersusceptibility (and lessened susceptibility) to non-antigenic substances.

2. Hypersusceptibility to antigenic substances.

    a. Substances - toxic in themselves

    b. Protein antigens not primarily toxic

This classification was changed somewhat by Coca. [24] He used the term hypersensitiveness to include all the conditions and divided them into:

1. Anaphylaxis - - Phenomena in which an antigen antibody reaction has been proved.

2. Allergy - - Hypersensitive conditions in which the antigen-antibody mechanism has not been shown to be the underlying cause.

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Kolmer thought that since the fundamental change appeared to be a state of altered reactivity of the body cells, which was usually an increased susceptibility, but may be the reverse, allergy was the most appropriate term.

26
Zinsser in his classification of increased susceptibility used the term true anaphylaxis to denote a protein hypersensitiveness in which antigen-antibody reactions were involved, and in which the inciting agent was undoubtedly an antigen, and as far as was known, inheritance from both parents played no role.

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Wells definitely limited the term anaphylaxis to known antigen antibody reaction and discussed separately other conditions in which the actual mechanism was somewhat in doubt.

In this paper anaphylaxis is used to denote a hypersensitive state induced by a single or multiple injections of a soluble protein of antigenic nature, and made manifest by a further injection of the "shock dose" of the same protein after the elapse of a suitable period of time. This elapsed time between the administration of the sensitizing dose and the shock dose will be called "incubation period".

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The criteria of true anaphylaxis as expounded by Wells, and which are accepted as a standard, are:

1. The observed toxicity of the injected material must depend upon the sensitization of the animal; i.e., the substance must not produce similar symptoms in non-sensitized animals.

2. The symptoms produced must be those characteristic of anaphylactic intoxication as observed in the usual reactions with typical soluble proteins, being therefore the same for all antigens with the same test animal, but differing characteristically with each species of

animal.

3. It should be possible to demonstrate passive sensitization with the serum of sensitized animals.

4. It should be possible to demonstrate typical reactions in the virgin guinea pig uterus strip.

5. It should be possible to demonstrate amelioration or prevention of the bronchial spasm in guinea pigs by proper use of atropin and epinephrin.

6. The possibility that the observed symptoms are caused by capillary thrombosis or embolism must be excluded.

7. After recovery from anaphylactic shock there should be exhibited a condition of densensitization under proper conditions".

Anaphylactoid Reactions.

Numerous cases have been reported in the literature as anaphylaxis which do not conform to the criteria of Wells. Many of these cases are those following a single primary injection of some colloidal non-protein substance. Although they induce at times, the entire train of symptoms typical to true anaphylaxis, the fact that no sensitizing injection is necessary and that desensitization does not occur excludes them from the true anaphylactic phenomena. This sort of reaction has been investigated by Hanzlik and Karsner[29] and designated by them as "anaphylactoid phenomena". They described some 30 substances among which were althea (Marshmallow), gelatin, agar, acacia, etc., which induced this type of reaction when injected intravenously in animals. Hanzlik and Karsner have shown that the anaphylactoid phenomena are dependant on capillary thrombosis, agglutination emboli or capillary toxicity.

Nature of the antigens.

Any protein capable of serving as an antigen in other immunological reactions may be used to produce the typical anaphylaxis reaction, and, as far as now established nothing else will do it. The amount of protein necessary to produce the reaction is extremely small. The proteins concerned must be foreign to the circulating blood of the injected animal, but they may be tissue proteins of the same animal which are not normally present in its blood, such as placenta or lens proteins. Since positive results cannot be obtained with most of the fractions of protein cleavage (peptones, polypeptids, amino acids), it is not easy to accept the statement that anaphylaxis can be produced by relatively simple synthetic polypeptids. There are also derived proteins such as gelatin which not being antigenic, do not produce anaphylaxis. This is believed by Starin[34] to be due to deficiency of tryptophane and tyrosine and phenylalanine.

The protein involved may be either non-cellular or cellular. Of the first group, various sera and egg albumin have undoubtedly been most studied. Plant and animal extracts have also been utilized in an effort to establish relationships between biological and chemical specificity. The cellular proteins most studied are erythrocytes and bacteria. Anaphylaxis in the rabbit has been produced by coca[30] in 1919 and by Grove[31] 1932 by the injections of red cell suspensions.

Zinsser and Parker[32] have demonstrated both clinical and isolated smooth muscle responses by the use of bacterial bodies. Sherwood and Stoland[33] have likewise demonstrated these facts but in contrast to the first observes, conclude that sensitization with bacterial extracts is much more difficult to demonstrate in the isolated uterine horn than with clinical symptoms. They also report "we feel justified in the

conclusion that the smooth muscle reaction of Dale is not a necessary criterion of sensitization with bacterial extracts".

Sensitization

Active: Active sensitization is a term analogous to active immunization in that it signifies that the animal is sensitized by the injection of the antigen, and develops its sensitiveness in physiological response to the injection. It is usually accomplished by the parental introduction of foreign proteins by any one of the common methods.

In guinea pigs it is usually a single subcutaneous or intra-peritoneal injection. In dogs it may be accomplished by two or three subcutaneous injections on successive days, or by one subcutaneous injection followed in 48 hours by an intravenous injection. Multiple injections are usually required to produce the hypersensitive state in rabbits. Multiple injections have also been used in the attempted active sensitization of cats.

For several days, usually seven to twelve, after the sensitizing dose, subsequent injections of the homologous protein produces no symptoms of anaphylactic shock. If a second injection is administered within this period the animal is more liable to become immune than hyper-sensitive. The maximum hypersensitivity is usually reached from fourteen to 21 days following sensitization. After the maximum is reached, perhaps the sensitivity slowly decreases, but persists in some degree indefinitely.

Passive: A normal animal may be passively sensitized by introducing into its body serum which contains anaphylactins or the anaphylactic antibody. This antibody may be found in:

1. The serum of actively sensitized animals.

2. The serum of an animal not yet sensitive - in the pre-anaphylactic period.

3. The serum of a desensitized animal.

4. The serum of an immunized animal.

One species of animal may be passively sensitized by the serum of another species. The period of incubation must be at least four to six hours. The maximum hypersensitivity is reached from 24 to 48 hours. Passive sensitization may persist for four to six weeks, after which it usually cannot be demonstrated.

Antibody involved.

Doerr and Russ[35] were the first to show that there was a direct relationship between the power of a serum to convey anaphylaxis passively and its contents of precipitins. They were inclined, therefore, to assume that precipitin and anaphylactic antibody were identical. This was in keeping with Friedberger's[36] purely theoretical idea that precipitins and anaphylactic antibody might be the same. Opie[37] in 1924 stated "In animals with either passive or active immunization there is a very close but not exact parallel between precipitin content of the serum and the occurrence and severity of specific inflammation".

Zinsser[38] held that anaphylactic sensitizers and precipitins are identical.

However, Spain and Grove[39] found that precipitation and anaphylactic reactions in rats might possibly represent two different immunological reactions. Manwaring and others[40] showed that the sensitizing antibody in dog serum was not the same as the specific precipitin of test tube reactions. Sherwood and Stoland[41] have been unable to correlate

the precipitin content of dogs with sensitization. Kurotchkin and Linn [42] in 1930 and Lim and Kurotchkin [43] in 1932 in active sensitization of guinea pigs with two yeast-like fungi (Monilia Pinoyi and Monilia Psilosis) found that sensitization appeared before demonstrable precipitins. Grove [44] concluded, "active sensitization of rabbits does not depend entirely upon the degree of antibody production because animals showing high power of antibody production may be wholly insensitive and vice versa." In our studies, we were unable to show strict correlation of precipitin content and sensitizing power.

Symptoms.

The clinical and experimental symptoms of true anaphylaxis have been clearly worked out for the guinea pig, rabbit and dog. A brief review of each would be fitting before the meager information is discussed concerning anaphylaxis in the cat.

Guinea pig: a short time after the sensitized guinea pig receives the shock dose, the animal grows restless and uneasy, and usually rubs its nose with its forepaws. It may sneeze and occasionally emit short coughing sounds. At the same time an increased rapidity of respiration is noticeable and the fur appears ruffled. There may be a discharge of urine and feces. In light cases the animal may remain in this condition for a few minutes, then gradual slow recovery sets in and may be complete in 30 minutes. In fatal cases the preliminary stages are followed by great weakness. The animal falls on its side, the leg and trunk muscles twitch irregularly and the respiration becomes slow and shallow. The very apparent dyspenea is of an inspiratory character. General convulsions set in and the animal usually dies.

An immediate opening of the thorax shows the lungs distended and
the heart still beating. Gay and Southard[45] were the first to describe
this feature and spoke of finding "pulmonary emphysema as a constant
feature at autopsy", and attributed death to a cessation of respiration
in the inspiratory phase under the influence of respiratory central
intoxication. Auer and Lewis[46] found that the pigs died of asphyxia,
due to tetanic contractions of the smooth musclature of small bronchioli
and alveolar ducts. The asphyxia was due to peripheral causes. It
was manifest when both vagi were sectioned and when the medulla and
spinal cord were destroyed. They recorded a preliminary rise in blood
pressure with a subsequent slow fall. Anderson and Schultz[47] showed that
the asphyxia could be prevented by atropine, adrenaline and chlorahydrate
plus urethane. Schultz[48] demonstrated that isolated intestinal segments
from sensitized animals contract more strongly in presence of antigen
than do normal segments. Dale[49] developed the "uterine horn technique
which is now cited by Wells as a required criterion of true anaphylaxis.
By its use, Dale was able to demonstrate the specific contraction of
sensitized virgin uterine horns of the guinea pig in the presence of
homologous antigen.

Manwaring[50] and others have reported specific contraction of smooth
musculature of the urinary bladder in anaphylactic guinea pigs. Grove,[51]
however, has shown that asphyxia in guinea pigs by ligation of the
trachea, will cause the bladder to contract. This reaction can be ob-
tained in one minute. However, she demonstrates a specific contraction
of smooth muscle in isolated strips of guinea pig bronchiole.

Rabbits: When a sensitized rabbit receives a shock dose of specific

antigen the following train of symptoms are manifest. The respiration quickens and the animal lies down upon its abdomen for a time, often with the hind legs outstretched. A greater or smaller number of dry fecal pellets are passed. Within a few minutes, however, the respiration slows, and the animal suddenly falls over on its side with clonic convulsions of short duration. The head is retracted strongly, the iris vessels, gums and tongue are pale, and the pupils are wide. The convulsions are sometimes preceded or accompanied by feeble cries. After the convulsions the animal lies motionless without respiration. In less than one minute the terminal group of gradually weakening respirations appears. These are preceded and accompanied by openings of the mouth. The animal now shows no visible or palpable heart beats or respirations. The animal is completely relaxed, and the abdominal walls bulge when it is placed on its back. Usually very active peristalsis of the cecum is evident.

Aside from a rather characteristic and universally described train of symptoms shown in the unanesthetized hypersensitive rabbit, perhaps the circulatory system has, deservedly, received more attention in the anesthetized anaphylactic rabbit than any of the other physiological systems. Auer[52] pointed out that cardiac disturbances played a very important role in the acute cases and described the heart as follows: The heart examined in situ immediately after respiration has ceased, is found to be in diastole, the ventricles contracting feebly or not at all, while the auricles beat fairly strongly and at a more rapid rate than the ventricles. He further stated that the entire right side of the heart was much ingorged with blood. Auer and Robinson[53] by

electrocardiographic methods demonstrated a slowing of conduction and auricular block. Manwaring and Marino [54] said there was usually a distinct or marked rise in blood pressure immediately following the shock dose. This rise gave way to a gradual fall which reached a minimum in from eight to twenty minutes. Coca [55] while working with washed stroma was probably the first to recognize the constriction of pulmonary blood vessels as a part of rabbit anaphylaxis. This was confirmed in 1914 by Airila [56] who recorded an increase of pulmonary arterial pressure following the injection of the shock dose. Coca [57] from perfusion experiments concluded there was a pulmonary capillary constriction in anaphylactic shock of rabbits. Bally [58] confirmed the blood pressure findings previously reported. He also described a peripheral circulatory "blanching reaction", as well as an increase in the clotting time of anaphylactic blood and a definite decrease in body temperature during shock. Grove [51] has recorded specific contraction of isolated pulmonary artery strips when in contact with homologous antigen. Thus it appears that the active smooth muscle in rabbit anaphylaxis is that of the pulmonary arterial system.

Dog: Anaphylaxis in dogs has been studied quite extensively. The shock dose administered to sensitized dogs causes them at first to become restless, vomit, and discharge urine and feces. They then become rapidly weak, fall to the floor, continue to twitch and vomit. The respiration becomes labored and irregular. There is general weakness of the muscles but not paralysis. The preceding symptoms were described by Biedl and Kraus [11] together with a characteristic fall of blood pressure. Pearce and Eisenbrey [12] also observed this drop of blood pressure followed by objective symptoms referable to cerebral anemia. By experiments in

which the peripheral and central vasomotor mechanisms were separated,
(decapitation, destruction of the cord, etc.) it was shown that the chief
influence was exerted on the peripheral vaso-motor system. Eisenbrey and
Pearce[59] used myocardiographic records to show that the functional
activity of the heart was not primarily affected by the injection of the
shock dose. The rate and range of contractions remained unchanged until
after the blood pressure had started to fall. Subsequent changes were
due to incomplete filling of the right heart. Pepper and Krumbhaar[60] held
that the increase of coagulation time in anaphylactic dog blood was due
to lack of thromboplastin or excess of antithrombin. More recently Man-
Waring and Coworkers have reported smooth muscle contractions of the in-
testinal tract and bladder,[61] also increased perfusion pressure of isolated
organ tissues.[62] However, Sherwood and Stoland[63] conclude from perfusion
experiments that the phenomena consisting of 50 to 75 per cent reduction
in rate of flow of perfusion fluid, the development of a rubbery con-
sistency of the lungs and the appearance of a tracheal exudate, all in
four to seven minutes are not peculiar to the sensitized dog as judged
by the blood pressure and coagulation time phenomena. However, these
authors were able to demonstrate an altered chronaxie of the vagi in
sensitized dogs. Simonds[64] has shown that the smooth muscle of the
hepatic veins of the dog is particularly abundant. His experiments tend
to confirm the view that the fundamental mechanism of anaphylaxis in the
dog has its physiological basis in the constriction and anatomical dis-
tribution of the smooth muscles of the hepatic veins.

Cats: Since this paper deals particularly with anaphylaxis in
the cat, a more detailed review will be given of the few studies per-
taining to that subject.

Brodie in 1900 described a sudden fall in blood pressure and abnormal respiration following intravenous injections of horse serum in cats. This reaction was also produced by all other mammalian sera and by egg white. This toxic action of serum was a matter of great importance in this connection, as it may complicate to a greater or less extent every injection of serum in the cat. Since it has been carefully described by Brodie, it is therefore known as "The Brodie Reaction". This reaction was not found in the dog or rabbit, but only in the cat, and was obtained from the intravenous injection of serum or egg-white which produced a marked inhibition of the heart and a severe fall in blood pressure. Recovery began in ten seconds and usually was complete in ten minutes.

Manwaring [13] in 1910 investigated anaphylactic shock in cats and published typical Brodie reactions to horse serum. He also described another type of reaction, which was a slow sinking in blood pressure that reached its lowest level in twenty minutes after the shock dose. Recovery was complete in 90 minutes after which time the animal was immune to a second injection. He also recorded loss of coagulibility of the blood.

The symptoms in the intact cat as described by Schultz [14] were as follows: The gross symptoms of serum intoxication in the cat are practically the same as those observed in the sensitized dog. If one injects cats intravenously with sterile horse serum, grave symptoms result, both in non-sensitized and in sensitized animals. The difference between the macroscopic reaction of the former with that of the latter is chiefly one of degree. Within one minute after intravenous injection the cat is lying limp on the floor unable to walk, pulse very

thready. Animal passes feces and urine. The respiration is greatly increased and somewhat dysponeic. The cat remains in extreme shock for five to ten minutes then there is usually slow gradual recovery.

Schultz also reported that horse serum caused constriction of the pulmonary arteries, coronary arteries, and systemic arteries, and also acted directly upon the heart muscle. Normal cats usually recovered from an intravenous injection of 2.5 c.c. of horse serum per kilo, while sensitized cats usually died. The action of the serum was peripheral, since destruction of the brain and spinal cord did not materially alter the end results. The abdominal blood vessels played at best only a secondary part in causing the low blood pressure since a fall of blood pressure was obtained when all abdominal vessels were clamped off. Atropin sulphate may or may not influence the circulatory phenomena. Schultz described only the rapidly fatal type of anaphylaxis.

Edmunds [66] in 1914 studied the affect of egg white on normal and sensitized cats. He found that as little as five tenths to one cubic centimeter produced a drop in blood pressure of as much as 20-25 m.m. hg in the normal cat. The heart was weakened and usually slowed from 20 to 30 beats per minute. These results could be brought out as often as an injection was given. In sensitized animals he described a slow drop of blood pressure which reached its lowest level in fifteen minutes. There was little tendency toward improvement. In these cases there was some acceleration of the heart and some weakening. A second injection of egg white produced no effect, and the blood had lost its property of coagulation. There was some impairment of the lungs, which occurred in both phases, they neither inflated nor collapsed well.

Edmunds also reported a decrease in liver volume following the

injection of the shock dose, but did not attach much significance to this observation. He concluded that apparently cats are not sensitized very easily.

Drinker and Bronfenbrenner [67] in 1924 investigated the pulmonary arterial pressure of actively sensitized cats. They found extraordinary reactivity of the pulmonary circulation to forgein proteins such as guinea pig, rabbit, horse, dog and sheep sera and egg albumin. They reported a sharp rise in pulmonary arterial pressure, with a fall in systemic blood pressure subsequent to the injection of dog and sheep serum in sensitized cats. The reactions are similar to those in rabbits but less marked.

It is readily seen from the preceding review that the anaphylactic phenomenon in cats is complicated by the natural sensitivity of this animal to the injection of forgein proteins. So confused and vague are the available reports on this subject, that some doubt remains as to whether true anaphylaxis has been observed in the cat.

Theories of the Mechanism of Anaphylaxis.

Numerous theories have been proposed to explain the mechanism of anaphylaxis. Many of the earlier theories conceived regarding the phenomena developed along lines which now seem fantastic. However, none, with the exception of possibly Sherwood's [68] and Stoland serves to explain all phases of the phenomena.

The chief point of controversy originally was, whether or not a poisonous substance was produced which was responsible for the reaction. If a poison was produced, whether it was produced in the circulating blood, humoral theory, or in the body cells, cellular theory. The former postulated the presence of enzymes or cleavage action forming

the toxic substance. The latter is explained by disturbances of the colloidal or electrolyte balance of the cell. A summary of the theories advocating the humoral theory will be given first.

Vaughan and Wheeler[69] thought that following the initial injection of a protein, enzymes were produced which quickly split the protein of the shock dose into a toxic and a non-toxic fraction. It was the toxic fraction which produced the symptoms of shock.

Friedberger[70] and Friedman[71] explained anaphylaxis on the basis of Ehrlich's side-chain theory. The foreign protein called forth the production of receptors, which remained sessile in the blood. Upon the injection of the shock dose, the sessile receptors united with antigen in the presence of complement to form anaphylotoxin.

Nicolle held that sensitization produced in the tissues two substances, albuminolysin and albuminocoagulen. After the administration of the shock dose the antigen was rapidly dissolved by the albuminolysin with the formation of toxic substances.

Jobling, Petersen and Eggstein.[73] concluded that the "intoxication is brought about by the cleavage of serum proteins through the peptone stage by a nonspecific protease" and that "the specific element lies in a rapid mobilization of this ferment and the colloidal serum changes which bring about the change in antiferment titer." This is very similar to that of Vaughan and Wheeler.

Abel and Kubata[74] advocated the production of histamine as a protein cleavage product responsible for the shock. Dale objected to an enzyme explanation, but does not offer any other explanation. Dale[75] has listed the chief respects in which histamine fails to account for all

phenomena of anaphylaxis.

1. It fails to desensitize sensitized animals or tissue, yet produces strong reactions in the uterus strip that has been thoroughly desensitized.

2. Histamine does not produce the temperature reactions usual in anaphylaxis.

3. Histamine does not produce the change in coagulability of the blood usual in anaphylaxis.

Manwaring [76] believed the smooth muscle contraction were due to histamine-like substance (hepatic-anaphylatoxins) explosively formed or liberated by the anaphylactic liver. As was mentioned, Simonds [64] explained this by the anatomical distribution of smooth muscle in the hepatic veins of the dogs.

While these theories differ in many respects, they are all apparently dependent on enzyme or cleavage action forming a toxic substance responsible for the phenomena of anaphylaxis. Much evidence has been produced in favor of these theories. The anaphylactic response is closely simulated by the injection of histamine or peptone, however, Wells [28] has outlined the evidence against the humoral theory as follows:

1. "It does not fit the latent period of passive sensitization. Intracellar formation of anaphylatoxin might account for this, however."

2. "Complement is not essential since animals deprived of complement in the circulating blood may still give anaphylactic reactions. Here again one may suggest intracellular or reserve complement."

3. "All attempts to prove that complement is a proteolytic ferment have failed."

4. "Anaphylatoxin activity has been produced in serum by
    digestion in the absence of complement, in the absence of
    antigen and in the absence of antibody. On the other hand,
    if antigen and the specific antibody are injected simultan-
    eously into the opposite jugular vein of a guinea pig the
    animal shows no evidence of intoxication."

5. "In the anaphylatoxin experiments the existence of capillary
    embolism or endothelial intoxication has not been excluded
    and there is reason to believe that most of the observed
    symptoms are anaphylactoid."

In addition to the above descrepancies, Sherwood has suggested
that the specific contraction of sensitized isolated smooth muscle is
inexplicable by anaphylatoxin formation.

The early cellular theories also postulated the formation of a
poisonous substances in or on the body cells. The later theories
explain the phenomena by other means. One of the theories assumed a
nervous mechanism. The exponents of this theory were Ricket,[77] Gay and
Southard[78] and others.

Richet suggested that when the sensitizer or anaphylactogen was
first injected it caused the production of a substance which he called
toxogenin. This toxogenin, on the second injection, combines with the
protein to produce a poison called apotoxin, which through its action
on the nervous system produces the symptoms of anaphylaxis.

Gay and Southard thought that every antigen consisted of two
elements, one toxic, anaphylactin, and the other non-toxic or sensitiz-
ing. After the initial injection the toxic anaphylactin was eliminated

from the body and the non-toxic portion was retained in the cells. Subsequent to the injection of the shock dose, the toxic anaphylactin portion was rapidly absorbed by the sensitized cells and anaphylactic shock resulted.

The mechanical irritation theory of Weil and of Coca assumed the formation of a specific precipitate in or on the tissue cells. The precipitate acting by physical means was responsible for the anaphylactic symptoms.

Opie [79] held that anaphylaxis was essentially caused by inflammation of the tissue produced when antigen and antibody met within them.

Kritschensky, Doerr and Moldovan and to some extent Novy and De-Kruif [68] assumed that a change in colloidal dispersion of the cells occurred and was either directly or indirectly the cause of anaphylactic symptoms.

The theory of Sherwood [68] and Stoland seemed to explain all manifestations of anaphylactic phenomena. It was as follows: If an animal is sensitized and then given a shock dose of antigen, the union of antigen and antibody in or on the tissue cells, brings about a colloidal change in which electrolytes take part. This disturbs the electrolyte balance in or on the tissue cells. Since calcium is a bivalent ion, and potassium a monovalent one, there is a one hundred to one chance of calcium entering into the reaction, rather than the monovalent potassium. It has been suggested that an increase in the ratio of potassium to calcium is the easiest way of stimulating the para sympathetic nervous system. Consequently, a disturbance in the afore-mentioned balance could easily be the spark that initiates the symptoms manifested in anaphylaxis.

The general trend has been in the explanation of anaphylactic shock, from a chemical or humoral basis to that of a physical or cellular. It has been shown fairly conclusively by the evidence outlined by Wells that the site of the reaction is in the tissue cells. Furthermore, the evidence which has accumulated seems to point to an intrinsic nervous mechanism stimulation as responsible for at least a large part of the visible phenomena. The fact that atropin and adrenalin ameliorates the anaphylactic symptoms supposedly by blocking the parasympathetic and stimulation of the antagonists of the parasympathetic respectively supports this hypothesis. However, both the cells and the circulating blood play a part. Undoubtedly, the blood is the means of conveying the antigen and possibly antibodies to the tissue cells, so both must be concerned in the phenomena of anaphylaxis.

Object of these studies.

It has been pointed out that all preceding studies of anaphylaxis in the cat have been carried out using complex substances as an antigen, such as horse serum, dog serum or egg white. And that these substances when injected even in small amounts into normal cats produce a perceptible loss of arterial blood pressure. The "Brodie Reaction", as described is then a very disconcerting and complicating factor in the study of anaphylaxis in the cat. It is a question whether the blood pressure response, which has been reported by earlier investigators, is one of true anaphylaxis or of an exaggerated Brodie type.

The ambiguous reports suggested the question, as to the possibility of actively sensitizing cats with a chemically pure antigen such as crystalline egg albumin. By the use of this antigen it was hoped to

eliminate the Brodie Reaction, and to secure simultaneous physio-
logical responses of other organs. If cats could not be actively
sensitized, then it was hoped to ascertain the reasons.

The question also arose as to the possibility of passively sensitiz-
ing cats to crystalline egg albumin. If passive sensitization was
possible, the various physiological responses were to be studied. If
the cats were not passively sensitized, was it because of incapable
absorption or some other reason?

Some theories of the mechanism of anaphylaxis hold that protein
cleavage products such as peptone or histamine are responsible for the
symptoms of the phenomenon. Observations of the physiological responses
of the cat to injections of peptone and histamine were to be made.
These responses were to be compared with those of anaphylaxis in the
cat. From this comparison some evidence as to the validity of the
above mentioned theories was hoped to be advanced.

In all experiments the results were obtained under as nearly
identical conditions as experimentation would permit. A description
of the physiological methods employed accompanies the tabulation of
the results of the anaphylactic study. A particular effort was made
to draw blood samples for clotting time and to take the temperature
readings at regular periods subsequent to the injections.

Part II.

Physiological Studies of the hypersensitive cat

Section I. Active Sensitization.

Brodie[65] in 1900 described the exaggerated sensitivity of normal cats to intravenous injections of foreign proteins. Apparently this type of reaction was peculiar to the cat, since the threshold of toxic reactions was much higher for the dog, rabbit, or guinea pig. All investigators[13, 14, 66, 67] who have reported studies of the anaphylactic phenomena in cats have used as sensitizers complex protein material such as horse serum, sheep serum, dog serum or fresh egg white. These substances even in small amounts, produce a decided drop of arterial blood pressure when injected intravenously into the normal or hypersensitive cat. This fact is a very complicating factor then, in the production and study of true anaphylaxis in cats as a species.

Nevertheless Manwaring[13] and Edmunds[66] have described a slow drop of blood pressure in sensitized cats following the injection of the shock dose, and thought it was characteristic of true anaphylaxis. Edmunds sensitized his animals by infecting two or three cubic centimeter of horse serum subcutaneously two or three times at five days intervals.

More recently Drinker and Bronfenbrenner[67] have reported the increase of pulmonary arterial pressure in anaphylactic cats. They produced sensitization by injecting 0.5 c.c. of dog serum subcutaneously in three periods each of from three to five consecutive days with two or three days elapsing between the periods of injection.

Because a small percentage of animals became hypersensitive and

because of the complicating Brodie reaction, Manwaring found the cat to be an entirely unsuitable animal for experimental studies in anaphylaxis. Other investigators have expressed similar findings.

This work was undertaken with the hope of finding some sensitizing substance which would not induce the "Brodie Reaction" when injected intravenously in amounts sufficient to produce shock in sensitized animals. With such an antigen the physiological response of the hypersensitive cat could be more clearly described and the prevailing gaps in this phenomenon more nearly spanned. It was thought that pure crystalline egg albumin would fulfill these requirements.

To this end a series of cats was sensitized and the shock dose of antigen injected with the hope of securing the simultaneous physiological responses of the arterial blood pressure, heart rate, coagulation time, rectal temperature, kidney volume, intestinal and intracystic pressures.

The precipitin content of the blood, together with the reactions of excised intestinal and uterine horn smooth muscle strips were also determined. A description of the results obtained will be set down in the paragraphs to follow.

Experimental.

This series was composed of 20 normal cats all of which were grown except one that was used for smooth muscle experiments alone. This was a young female weighing 1200 grams. The adult cats varied in weight from 1800 to 3520 grams. Their average weight was 2745 grams. There were 16 females and four males included in the adult series. The various physiological studies were performed simultaneous-

ly upon 18 of the cats, the other two being used for smooth muscle experiments alone. Smooth muscle reactions were also obtained for a number of the other cats. An exact tabulation will be included in the summary of results.

Sensitization: The sensitizing antigen was a solution of 4% crystalline egg albumin [80] in distilled water. The sensitizing dose was 0.5 c.c. of 4% crystalline egg albumin per kilo body weight. Several methods of injection were utilized in attempting to sensitize the animals of this series.

The various methods used were:

1. One subcutaneous injection followed at three day intervals by two intravenous injections.

2. Three intravenous injections given two days apart.

3. Eight to thirteen subcutaneous injections given in three periods of three to five injections on consecutive days with three days rest between periods.

4. Three subcutaneous injections on consecutive days followed by an intravenous injection the fourth day, allow three days to elapse and repeat.

5. Five to seven subcutaneous injections given at two day intervals and followed by two intraperitoneal injections of the same spacing.

Incubation period: The incubation period varied from eight to 74 days. The greater number of the animals studied had an incubation period falling between the eighteenth and twenty-sixth day limits.

Anesthesia: For each animal ether was administered from a cone

until complete surgical anesthesia was established, after which the trachea was cannulated and an ether bottle attached.

Shock dose: The shock dose was two cubic centimeters of 4% solution of crystalline egg albumin per kilogram body weight. A few received only one cubic centimeter per kilogram. It was injected by means of a cannula tied in the right femoral vein. Sufficient warm Ringer's to bring the total volume injected to ten c.c. followed, to make sure that all the albumin had entered the circulation.

Experimental technique.

Blood Pressure: The mean arterial pressure was measured by means of a cannula tied into the left carotid artery, and connected with a mercury manometer which recorded the pressure changes on a revolving kymograph drum.

Heart rate: When a light mercury manometer was used to record the blood pressure changes, it was possible to count the heart rate from the blood pressure graph. To insure accurate counts, a lense magnifying 20 diameters was employed. The heart rates were determined immediately preceding the injection and at the low point of the drop.

Coagulation time: The right carotid artery was ligated and cannulated centrally so that blood could easily be drawn. The coagulation time was determined by drawing blood into a clean test tube freshly rinsed with physiological saline. The tube was allowed to stand without agitation and observed every fifteen seconds. Time was recorded when the blood had coagulated sufficiently to permit inverting the tube without rupturing the surface film. Samples of blood were drawn immediately preceding, and five minutes after each

injection.

Rectal temperature: By aid of a thermometer the rectal temperature was determined immediately before, and five minutes after each injection.

Kidney volume: The kidney volume changes were recorded by enclosing the left kidney in a metal oncometer containing a rubber dam. By connecting the oncometer with a piston recorder which was adjusted to write on a timed kymograph drum, a very sensitive method was perfected.

Intestinal pressure: The intestinal smooth muscle responses were determined by tying off a loop of the ileum in such a manner as not to embarrass the circulation. A three way cannula was inserted and connected to a rubber membraned tambour. The loop was then filled with warm mineral oil so that a slight positive pressure was registered on the kymograph drum.

Intracystic pressure: To measure the smooth muscle reactions of the urinary bladder, a no. 16 hypodermic was carefully forced through the bladder wall and connected to a membrane tambour. After the hypodermic was in place the uretheral orfice was tightly clamped with a hemostat. The tambour was adjusted to record the pressure changes on a revolving kymograph drum.

Precipitin titration: Samples of blood were drawn immediately before and five minutes after the injection of the shock dose. Their precipitin content was determined by use of the ring test and over night settling. Three tenths of a cubic centimeter of antigen dilution were stratified above one tenth cubic centimeter of clear undiluted cat serum in small fermentation vials. They were examined for the presence of a ring after 20 minutes incubation. The contents

of the Vials were then mixed, incubated in the 37° C. waterbath for one hour, allowed to sit in the ice box over night, and the final reading made.

Results.

The blood pressure invariably showed an injection rise of from four to twenty M.M.Hg. This rise was maintained for from 30 seconds to ten minutes. This was essentially the same reaction as of a normal animal when injected with an identical dose. Figure #3 shows the blood pressure response of a normal control cat to an intravenous injection of two c.c. of 4% egg albumun per kilogram body weight in comparison to the response of the same cat to an injection of one c.c. normal rabbit serum per kilogram. The heart rate usually exhibited slight slowing. The maximum decrease of rate was ten beats per minute. The coagulation time of the blood and the rectal temperature progressively decreased throughout the duration of the experiments.

The intraintestinal and intracystic pressures were consistently without change.

Table #1: Results of the physiological studies of active
sensitization in cats.

Serial Number	Sex	Weight	Method of Sensitization		Incubation period		Anesthetic
4	Male	3500 Grs.	Normal control				Ether
50	Female	2520 "	"	"			"
51	"	2070 "	"	"			"
57	Male	2700 "	"	"			"
33	Female	2850 "	#1		21 Days		"
34	"	2450 "	#1		21	"	"
35	"	2400 "	#1		22	"	"
36	"	1800 "	#2		22	"	"
38	"	2850 "	#1		26	"	"
52	"	2230 "	#3		19	"	"
53	"	2750 "	#3		24	"	"
56	"	2200 "	#4		14	"	"
58	"	3000 "	#4		28	"	"
59	"	2850 "	#3		24	"	"
60	Male	3050 "	#3		25	"	"
62	Male	3520 "	#4		20	"	"
63	"	2080 "	#4		24	"	"
64	Female	2550 "	#4		22	"	"
77	Male	3200 "	#4		74	"	"
79	Female	3020 "	#5		9	"	"
80	"	2970 "	#5		12	"	"
81	"	3000 "	#5		14	"	"

Table #1: Results of the physiological studies of active
sensitization in cats. (continued)

Serial	Shock Dose	Coagulation Time Normal	After Shock	Rectal Temperature Normal	After Shock
4	1 c.c. of 4% egg alb.per Kg.	4' 45''	4' 30''	99.6°F	98° F
50	"	—	—	—	—
51	2 c.c. of 4% egg alb.per.Kg.	7'	2'	99.8°	98.°F
57	"	10'	1' 30''	100.2°F	99.2° F
33	1 c.c. of egg alb. per Kg.	6' 30''	3' 30''	99.2°F	98.2° F
34	"	7' 30''	1'	99.2°F	98.8° F
35	"	4'	2'	100.7°F	100.5° F
36	"	5'	1'	99.5°F	99.0°F
38	"	5'	1' 30''	100° F	99.7° F
52	1 c.c. egg alb.perKg	2' 30''	45''	100.2°F	99.4° F
53	2 c.c. egg alb. per Kg.	5'	50''	100.2°F	99.6°F
56	"	3' 50''	1' 30''	98° F	—
58	"	4'	1'	100.2° F	98.8°F
59	"	5'	1'	99.4°F	9818°F
60	"	5'	2'	99.8°F	99.°F
62	"	2' 30''	1' 30''	99.4°F	98.2°F
63	"	3' 30''	1' 20''	97.°F	95.6°F
64	"	2'	2'	99.5°F	99.°F
77	"	2' 40''	2' 50''	99.° F	98.4° F
79	"	1'	1' 30''	99.8° F	99.5° F
80	"	1' 50''	3'	97.6°F	96.6° F
81	"	3'	2' 50''	97.5° F	96.8° F

Table #1: Results of the physiological studies of active sensitization in cats. (continued)

Serial number	Blood Pressure	Kidney Volume	Intestinal Pressure	Bladder Pressure
4	Rose 10 MM Hg.	—	No change	No change
50	Rose 12 MM Hg.	Slight increase	Slight loss of rythm	No change
51	Rose 20 " "	No change	No change	No change
57	Rose 18 " "	" "	" "	" "
33	Rose 8 MM Hg	Very slight increase	No change	No change
34	Rose 16 " "	No change	" "	" "
35	Rose 4 " "	No change	" "	" "
36	Irregular little change	" "	" "	" "
38	Rose 2 MM Hg.	" "	" "	" "
52	Rose 8 MM Hg.	Very slight increase	" "	" "
53	Rose 12 " "	" "	" "	" "
56	Rose 36 " "	" "	" "	" "
58	Rose 9 " "	No change	" "	" "
59	Rose 24 " "	Very slight increase	" "	" "
60	Rose 10 " "	No change	" "	" "
62	Rose 11 " "	Very slight increase	" "	" "
63	Rose 20 " "	" "	" "	" "
64	Rose 30 " "	" "	" "	" "
77	Rose 20 " "	" "	" "	" "
79	Rose 28 " "	" "	" "	" "
80	Rose 22 " "	" "	" "	" "
81	Rose 14 " "	" "	" "	" "

Table #1: Results of the physiological studies of active sensitization in cats. (continued)

Serial number	Precipitin content Before shock	Aft.Shock	Beats per minute Heart Rate Before shock	After	Intestinal strips	Uterine Horns
4	–	–	–	–	–	–
50	–	–	240	242	–	–
51	–	–	240	240	–	–
57	–	–	284	290	–	–
33	None	None	No count	No count	–	–
34	"	"	180	177	±	±
35	"	"	226	226	–	–
36	"	"	No count	No count	–	±
38	"	"	253	250	–	–
52	"	"	265	265	–	–
53	"	"	240	234	–	–
56	"	"	No count	No count	"	–
58	"	"	216	216	–	–
59	"	"	271	267	±	*
60	"	"	No count	No count	–	–
62	"	"	240	230	–	–
63	"	"	226	216	–	–
64	"	"	262	262	–	–
77	"	"	169	169	No reaction	–
79	"	"	No count	No count	"	No reaction
80	"	"	160	150	"	"
81	"	"	206	213	"	"

Table #1: Results of the physiological studies of active
sensitization in cats. (continued)

Serial number	Sex	Weight	Method of Sensitization	Incubation Period
75	Female	2250 Grs.	Normal Control	
76	Female	1200 Grs.	#3	17 days.
78	Female	2650 "	#5	8 "

Serial number	Precipitin Content Before Shock	After Shock	Intestinal Strips	Uterine Horns
75	—	—	No Contraction	No Contraction
76	None	—	"	"
76	None	—	"	"

The kidney volume usually showed no change, however, a very slight increase sometimes accompanied a pronounced injection rise of blood pressure. A decrease in volume never followed the injection of the shock dose. The intestinal and intracystic pressures were consistently without change.

Two intestinal strips from each of seven cats, and six uterine horns from the same were removed and suspended in Ringer's at 37° C. under light tension until the physiological experiments were completed. At this time they were tested by the method of Schultz and Dale for specific contraction with the homologous antigen, crystalline egg albumin. One c.c. of 2% albumin solution was found to be non-toxic for the intestinal strips, and 0.3 c.c. of 2% albumin was non-toxic for the uterine horns when added to a 20 c.c. bath of Tyrode's solution. All the intestinal strips as well as the uterine horns failed to respond when tested by this method.

Guinea pigs were injected with the sera of six cats in an effort to passively sensitize them to crystalline egg albumin. The blood was drawn from the sensitive cats both before and after injection of the shock dose as described for the precipitin titration. The cat sera were injected intraperitoneally in 5 c.c. amounts into 400 gram normal healthy guinea pigs.

Figure 1:   Blood pressure and kidney volume responses of an actively
            sensitized cat to the injection of the shock dose of
            crystalline egg albumin.

Figure 2:   Intestinal and intracystic pressure responses of an actively
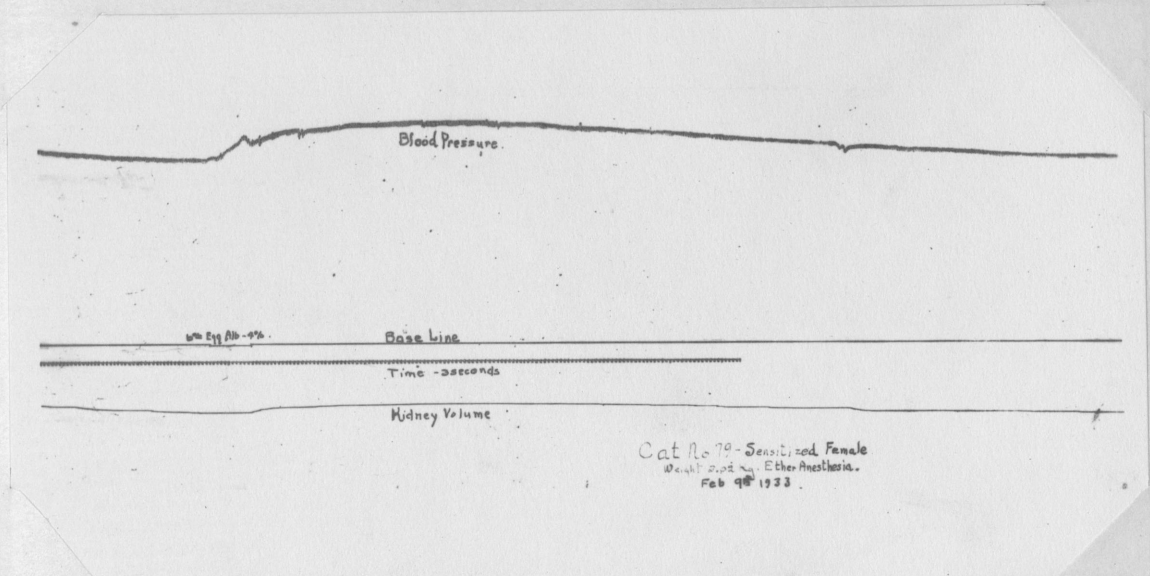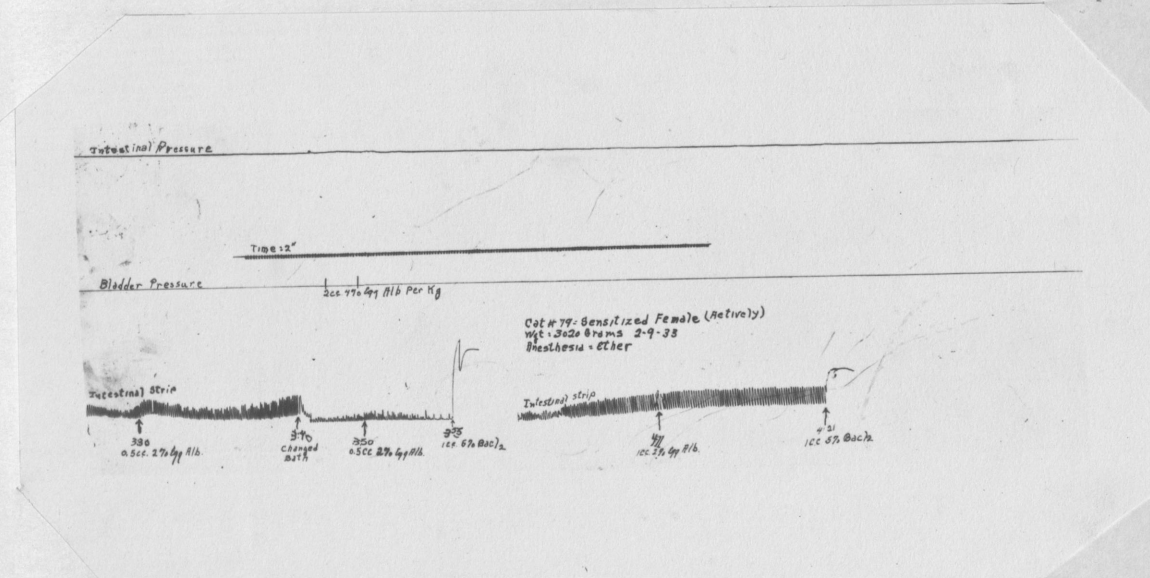   sensitized cat to the injection of the shock dose of
            crystalline egg albumin. The response of excised intestinal
            strips to the addition of albumin is to be seen at the bottom
            of the graph.

After 24 hours incubation, the guinea pigs were injected intra-
cardially with one cubic centimeter of 4% egg albumin, and were ob-
served for clinical symptoms of anaphylaxis. None of the guinea pigs
responded with anaphylactic symptoms.

The sera of 21 cats were tested for the presence of precipitating
antibodies for crystalline egg albumin. One sample of blood was drawn
immediately before injecting the shock dose, and another sample was
drawn five minutes after the injection. Both samples were examined by
the Ring test and over night settling methods as described. All the
tests were consistently negative.

Discussion.

It is quite evident from the preceding results that no cat in
this series displayed any of the recognized symptoms of anaphylactic
shock. The possibility that this lack of sensitization was due to
non-antigenicity of the crystalline egg albumin had to be ruled out.
This was accomplished by at least three biological methods:

a. Guinea pigs could be sensitized by a single subcutaneous
injection of one cubic centimeter of 4% crystalline egg
albumin. An identical dose when injected intracardially
twelve days later, produced fatal clinical anaphylaxis.

b. Typical specific contractions of the excised uterine horns
from sensitized virgin guinea pigs were demonstrable by
Dale's technique.

c. Multiple intravenous injections of crystalline egg albumin
in rabbits stimulated the production of easily demonstrable
precipitins for that antigen. This method will be described

in detail in the following section. These findings seemed to prove the antigenicity of the crystalline egg albumin. If this were true, the question arose as to why the cats were not sensitized by its injection. It has previously been pointed out that apparently the cat produces no precipitating or passively sensitizing antibodies to crystalline egg albumin. Is there likewise no hemolysins or bacterial agglutinins produced in response to introduction of their respective antigens? With the hope of ascertaining the answer to this question, a series of three cats was given five intraperitoneal injections of 10% sheep cells at three day intervals, and another series of three cats was given five intraperitoneal injections of a formalized suspension of E. Typhi. (Rawlins strain.)

It was found for the first series, that all the cat sera preceding injection contained hemolysins for sheep cells when undiluted but not in a dilution of one to ten. After the round of injections there was complete hemolysis of the sheep cells in a dilution of one to ten but only a trace in a dilution of one to 50.

None of the animals of the second series showed any agglutinins for E. Typhe before immunization. After five injections the suspension of E. Typhi was agglutionated by 1-200, 1-100, and 1-32 dilutions of the respective sera.

Thus it is shown that at best the cat produces antibodies in very small quantities. It was thought that this might be explained by an inadequate absorptive mechanism, or by a complete inability to absorb foreign substances from the peritoneal cavity. However, when trypan blue was injected intraperitoneally, it appeared in the mucous membrane

and skin as early as five hours after injection.

Three cats were then injected intraperitoneally with five c.c. of 10% suspension of chicken cells. One of the cats was killed after the elapse of six, twelve and twenty-four hours, the spleen and liver removed, embedded, sectioned, and stained. Definite phagocytosis of the chicken cells were observed by the fixed tissue cells of the spleen and liver from the cats killed at 12 and 24 hours. It appears then that the cat has an adequate absorption as well as phagocytic mechanism, although it does not respond with active generation of demonstrable antibodies to the introduction of foreign proteins.

The apparent inability of the cat to generate antibodies may account for the entirely negative series just reported. It seems very reasonable that if hemolysins, bacterial agglutinins, and precipitens are not generated in demonstrable quantities, that likewise the sensitizing antibody of anaphylaxis is also absent. This assumption is certainly born out by the preceding physiological studies of anaphylaxis.

Conclusions.

The preceding physiological studies of active anaphylaxis in the cat seem to warrent the following conclusions:

1. That the cat has an adequate absorptive mechanism and an actively functioning phagocytic system.

2. That antibodies are produced only in small quantities by the cat in response to the parenteral introduction of foreign proteins.

3. That the cat is an unsuitable animal for the demonstration

of active anaphylaxis when a pure crystalline substance such as
egg albumin is used as a sensitizer.

4. That crystalline egg albumin is relatively non-toxic for cats as
judged by the absence of the "Brodie Reaction" following comparative-
ly large intravenous injections.

Section II. Passive Sensitization.

Historical.

Passive sensitization is the transferrence of the hyper-
susceptible condition to a normal animal by injecting into it serum
from an actively sensitized one. The normal animal is thus merely the
passive recipient of the reaction antibodies produced in the sensitive
animal by preliminary treatment.

That passive sensitization is possible, was first pointed out
perhaps by Nicolle in 1907.[81] He found that if a normal rabbit was in-
jected with the serum of a rabbit sensitized to horse serum, and 24
hours later injected subcutaneously with horse serum a typical arthus
phenomenon resulted at the site of injection. Richet[82] soon after this
succeeded in transferring hypersensitivity toward mytilocongestin from
a senesitized dog to a normal animal by, transferring a large amount of
blood from the first to the latter. Almost simultaneously Otto[83] was
successful in passively transferring hypersensitivity to guinea pigs in
a similar manner.

In 1908 Rosenau and Anderson[84] showed that sensitivity could be
transmitted from mother to offspring in guinea pigs.

These observations were confirmed and extended by many invest-
igators. It was also brought out that serum from refractory animals

and from immunized animals, as well as from sensitive ones might be used for passive sensitization purposes. Also that sensitization may be passively transmitted from one species to another. It is sufficient to transfer the clear serum, in order to obtain sensitization, since the corpuscles are not the carriers of the antibody.

More recent work of this nature in rabbits has been done by Opie,[85] in the study of the mechanism of the Arthus phenomenon. Likewise, Manwaring[86] and Coworkers have contributed to the knowledge of this phenomenon in dogs as have Sherwood and Stoland.[63]

It has been pointed out that the literature concerning active anaphylaxis of the cat is very meager, thus it is not surprising that the passive phenomenon is apparently omitted. We have offered an explanation as to why the cat does not readily yield itself to active sensitization. However, it appears that foreign substances are quickly absorbed from the body cavities of this animal. Thus the question arose as to the possibility of passively transferring the anaphylactic sensitizer to the cat.

With the hope of obtaining some information on this question a series of physiological experiments were undertaken. These experiments were of such a nature as to secure a correlated physiological study of the responses of the arterial blood pressure, heart rate, coagulation time of the blood, rectal temperature, oncometric kidney volume, intestinal and intracystic pressures together with the precipitin content and passively sensitizing power of the sera, as well as the specific contraction of excised intestinal strips and uterine horns by the method of Schultz and Dale.

Experimental

This series was composed of fifteen adult healthy cats, ten of which were females and the remaining five were males. These animals ranged in weight from 1800 to 3,050 grams, with an average weight of 2520 grams. In each experiment the various physiological studies were performed with a few exceptions which will be noted with the appropriate analysis.

Sensitization: High titered anti-crystalline egg albumen sera were produced by repeated injections of 4% egg albumin solution into the marginal ear vein of rabbits. Seven sera were prepared which showed a precipitin titer of from 1-17,500 to 1-27,500, and which were capable of passively sensitizing 400 gram guinea pigs when injected intraperitoneally in two c.c. amounts. An analogous dose, or five c.c. per kilogram body weight was chosen as the sensitizing dose for cats and was injected intraperitoneally.

Incubation Period: The incubation period varied from 24 to 72 hours. Positive reactions were secured in each period.

Shock Dose: For each animal the anesthesia and the methods of recording the various physiological responses were the same as those described in the section on active sensitization, as were also the determinations of the precipitin content and passively sensitizing power of the cat's serum as well as the smooth muscle reactions of the excised intestinal strips and uterine horn. The shock dose, which consisted of two c.c. of 4% crystalline egg albumin solution, was injected through a cannula into the right femoral vein. The cannula was then washed clean of antigen with sufficient warm Ringer's

solution to bring the total volume injected to ten c.c.

The results, which will immediately follow, are based on the physiological responses of six animals which reacted in what appeared to be a typical anaphylactic manner. It will suffice to say that all data for the remaining member of this series were the same as that described for negative animals in the section on active anaphylaxis, and merits no further mention.

Results.

Blood pressure: Six cats showed a profound drop of arterial blood pressure following injection of the shock dose. Three of the cats responded with a "three phase" drop as previously described, and three with a single phase drop. Every animal exhibited an appreciable injection rise of blood pressure, which was maintained until the decrease of pressure was initiated. This decrease became evident from 30 seconds to one minute 40 seconds after the injection of the shock dose was begun. The average time was 52 seconds. The average drop of blood pressure was 42.7% with a maximum value of 51% and a minimum of 33%. The low point of the blood pressure curve was reached on an average of two minutes 30 seconds after injection of the shock dose. From this point a gradual recovery was evidenced in every animal until the normal blood pressure was restored. 28 minutes was the greatest time necessary to consumate complete recovery and 4 minutes was the least. The average duration of the shock was twelve minutes 30 seconds.

Two of the animals which exhibited the "three phase" blood pressure response, showed an interesting phenomenon in that the preliminary

Table #2: Results of the physiological studies of passive
sensitization in cats.

Serial Number	Sex	Weight	Sensitizing antisera	Incubation period
65	Female	2070 Grs.	#152	24 Hours
66	"	2090 "	#156	24 "
67	Male	3000 "	Composit	48 "
68	Female	2200 "	#152	48 "
69	Male	2800 "	#152	72 "
70	Female	2700 "	#155	72 "
71	Female	2900 "	#152	72 "
82	Male	3000 "	#157	72 "
83*	Pregnant Female	3300 "	#157	48 "
84	Female	2300 "	#157	48 "
85	"	3050 "	#158	72 "
86	"	2500 "	#160	48 "
87	Male	2600 "	#161	72 "
88	Female	1800 "	#160	72 "
89	"	2250 "	#160	48 "
90	Male	2500 "	#159	48 "

* Cat didn't survive the operation.

Table #2: Results of the physiological studies of passive
            sensitization in cats. (Continued)

Serial Number	Anesthetic	Coagulation time Normal	Shock	Rectal temperature Normal	Shock
65	Ether	3'	1'	98.6°F	96.8°F
66	"	2' 30''	45''	97.6°F	95.°F
67	"	3'	2' 50''	98.°F	97.2°F
68	"	4'	2'	97.6°F	96.°F
69	"	3'	1' 30''	100.8°F	100.2°F
70	"	6' 15''	1' 30''	99.°F	99.6°F
71	"	2'	2'	98.°F	97.6°F
82	"	2' 50''	3'	97.8°F	97.°F
83	"	0	0	0	0
84	"	3'	3'	100°F	99.5°F
85	"	3'	1' 30''	95.8°F	95.4°F
86	"	4'	2'	99.6°F	99.°F
87	"	4'	1' 15''	95.8°F	94.4°F
88	"	5' 15''	45''	99.6°F	98.6°F
89	"	4'	1' 15''	101.6°F	101.°F
90	"	2' 45''	1' 15''	99.2°F	98.4°F

Table #2: Results of the physiological studies of passive
sensitization in cats. (continued)

Serial number	Shock Dose	Blood Pressure		
		Response	Type curve	Recovery
65	2 c.c. of 4% egg albumin	Drop 51%	Single Phase	28 mins.
66	"	Rose 22 MM Hg	0	0
67	"	Rose 40 " "	0	0
68	"	Drop 38.4%	Three Phase	8 mins.
69	"	" 49.4%	Three Phase	8 mins.
70	"	Rose 10 MM Hg	0	0
71	"	Drop 34.6%	Three Phase	20 mins.
82	"	Rose 20 MM Hg	0	0
83	0	0	0	0
84	2 c.c. of 4% egg albumin	Rose 50 MM Hg	0	0
85	"	Rose 24 " "	0	0
86	"	Drop 50%	Single Phase	7 mins.
87	"	Rose 22 MM Hg	0	0
88	"	Drop 33%	Single Phase	4 mins.
89	"	Rose 14 MM Hg	0	0
90	"	Rose 2 " "	0	0

Table #2: Results of the physiological studies of passive
sensitization in cats. (continued)

Serial Number	Heart Rates Normal	Shock	Kidney Volume	Intestinal Pressure	Bladder Pressure
65	167	161	Marked decrease	Loss of rythm	No change
66	170	158	Slight increase	No change	" "
67	194	188	"	" "	" "
68	186	186	Marked decrease	Increase	Increase
69	270	265	"	"	"
70	180	177	Slight increase	No record	No change
71	216	135	Marked decrease	No change	" "
82	187	170	Slight increase	" "	" "
83	0	0	0	0	0
84	211	208	Slight increase	No change	No change
85	189	177	"	" "	" "
86	189	98	Marked decrease	increase	" "
87	174	160	No change	No change	" "
88	206	180	Marked decrease	Increase	" "
89	224	213	Slight increase	No change	" "
90	0	0	"	" "	" "

Table #2: Results of the physiological studies of passive
sensitization in cats. (continued)

Serial Number	Precipitin Content Before shock	After shock	Intestinal Strips	Uterine Horns
65	None	None	O	O
66	"	"	O	O
67	"	"	O	O
68	"	"	O	O
69	"	"	O	O
70	"	"	O	O
71	"	"	O	O
82	"	"	Negative	O
83	"	O	"	O
84	"	None	"	Negative
85	"	"	"	Toxid Reactions
86	"	"	Specific contraction	Hyper irritable
87	"	"	Negative	O
88	"	"	Specific contraction	Specific contraction
89	"	"	Negative	Negative
90	"	"	"	O

recovery amounted to an overcompensation of 54 and 26 M.M. Hg respectively. This overcompensation was immediately replaced by a slow drop which has been described.

                            *

The second injection, consisting of 2 c.c. of 4% crystalline egg albumin per kilogram body weight, invariably produced only a transient injection rise of blood pressure. This injection rise was similar in magnitude and duration to that of a normal animal in response to an identical injection. The absence of a blood pressure drop following the second injection would suggest complete desensitization of the animal by the shock dose of the specific protein.

Heart rate: Of the six positive animals, everyone showed a decrease in heart rate during the decrease of pressure. In three of the animals the reduction of rate was marked, amounting to almost 50% in one. This reduction of heart rate might suggest a change in conductivity of the nerve bundle or a change in the irritability of the cardiac musculature.

Coagulation time of the blood and rectal temperature: The value of both the coagulation time of the blood and the rectal temperature progressively decreased throughout the duration of the experiments. They apparently were responses governed by experimental conditions rather than vital reactions of the animal to the injections of egg albumin.

Kidney volume: Following every injection of the shock dose, there was a slight increase in kidney volume as the injection rise of blood

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* This is the term used to denote the injection of the specific protein to test for desensitization of the animal.
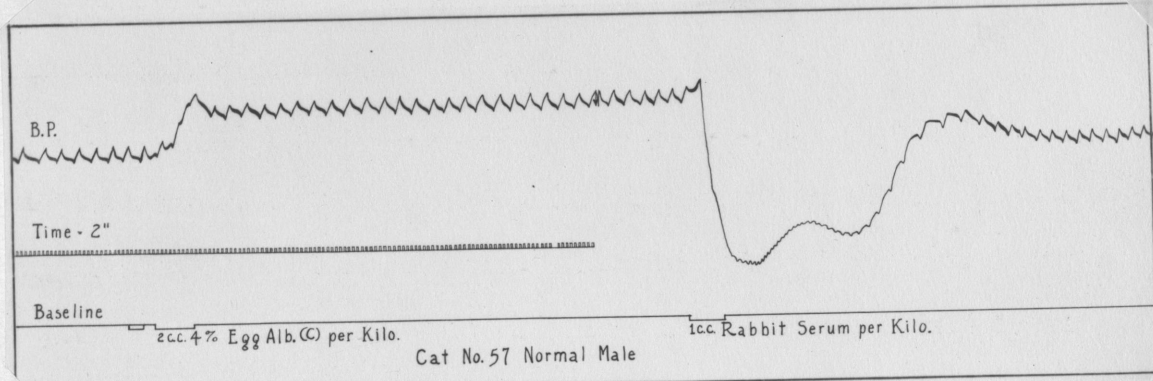
B.P.

Time - 2"

Baseline

2 c.c. 4% Egg Alb. (C) per Kilo.   1 c.c. Rabbit Serum per Kilo.

Cat No. 57 Normal Male

Figure 3: The blood pressure responses of a normal control cat to
           the injections of 2 c.c. of 4% egg albumin and to 1 c.c.
           of rabbit serum.

Blood Pressure.

Base Line   Egg Albumin 4% crys.
                     1 c.c. per kg.

Time - 3 seconds.

Kidney Volume.

Cat No. 88 Female
Passive Sensitization.
Ether Anesthesia Wt 1.9 kgs
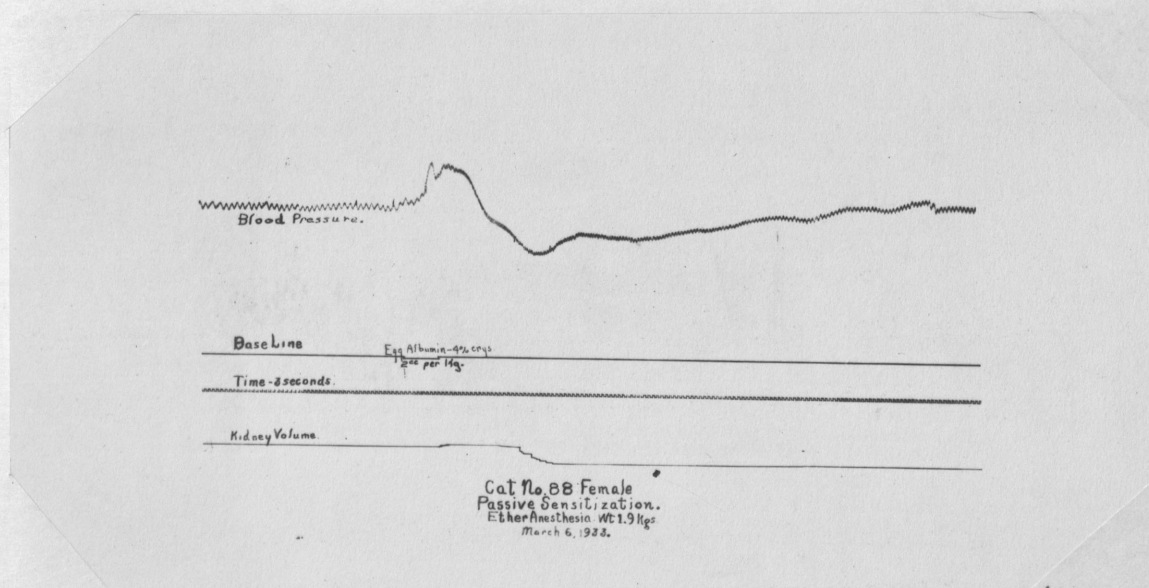March 6, 1933.

Figure 4: The blood pressure and kidney volume responses of a passively
           sensitized cat to the injection of the shock dose of
           crystalline egg albumin.

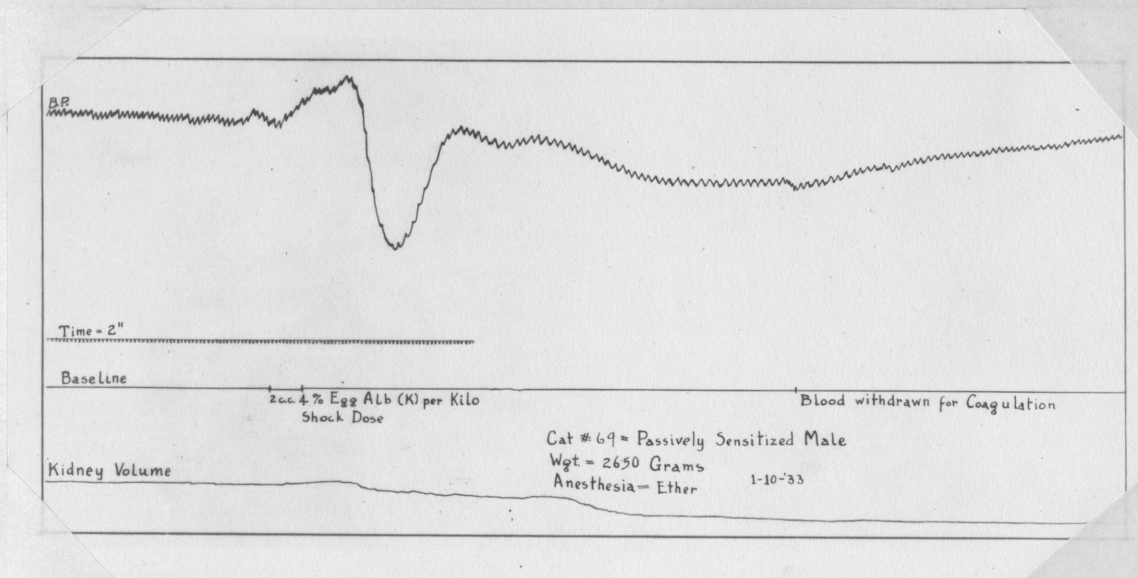Figure 5:   The blood pressure and kidney volume responses of a
            passively sensitized cat to the injection of the shock
            dose of crystalline egg albumin. The blood pressure
            shows the "three phase" curve.
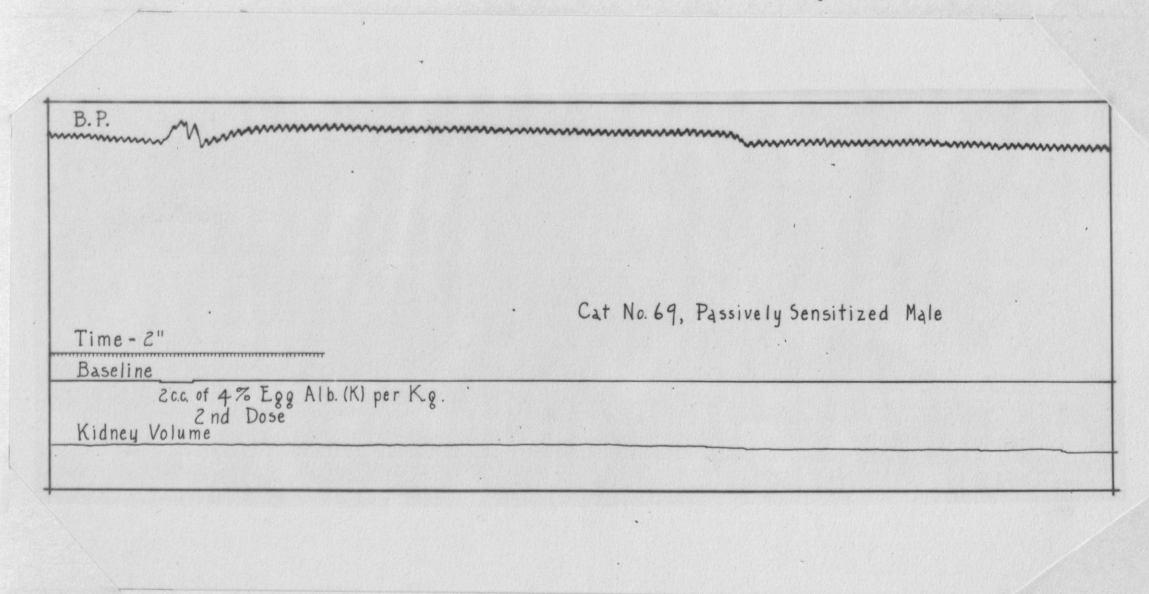

Figure 6:   The blood pressure and kidney volume responses of the
            same cat as shown in Figure 5 to a second injection of
            crystalline egg albumin.

pressure became evident. There was a direct relation since the sensitivity of the piston recorder was very delicate.

Likewise there was a pronounced decrease in renal volume as the blood pressure fell, however, the curve of the kidney volume did not coincide with that of the blood pressure exactly. Usually the volume of the kidney remained greatly reduced long after the blood pressure had started recovery. It would appear that there was an active constriction of the renal vessels, with a subsequent decrease in volume. Following the second injection there was occassionally no change, but usually there was a slight increase which was quickly restored to its normal volume. In no case was there a decrease in kidney volume following the second injection.

Intestinal pressure: Of the six cats responding with a drop of arterial blood pressure, four showed a definite increase of intestinal pressure following introduction of the shock dose. The intestinal loops of the remaining two animals showed no change of tone. A loss of rythmic contraction and relaxation of tone was not observed. These observations support the view that the smooth muscle of the intestinal wall was sensitized and responded with a specific contraction, since there was no change of pressure following any of the second injections.

Intracystic pressure: Two animals showed a definite increase of intracystic pressure after injection of the shock dose of specific antigen. The four remaining animals showed no change in bladder pressure. There was never any increase of intracystic pressure following the second injection. The bladder response appears to be an inconstant physiological reaction and thus cannot be considered a

Intestinal Pressure 1st

Intestinal Pressure 2nd

Bladder Pressure 1st

Time -2"   2 c.c. 4% Egg Alb. (K) per KG - Shock Dose

Bladder Pressure 2nd
2 c.c. 4% Egg Alb. (K) per KG - 2nd Dose
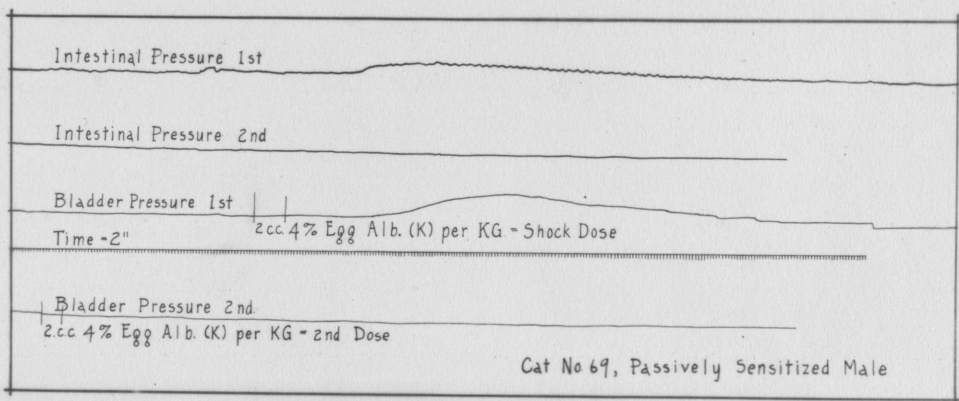
Cat No 69, Passively Sensitized Male

Figure 7: The Intestinal and intracystic pressure responses of a passively sensitized cat to the injection of the shock dose of crystalline egg albumin, and to the second injection of the same antigen.

criterion of anaphylaxis in the cat.

Precipitin content and passively sensitizing power for guinea pigs: The sera of fifteen cats were titrated for precipitin content. Samples drawn immediately before injecting the shock dose and five minutes after injection were tested. Both the Ring test and over night settling method were employed. All the sera were consistently negative, even when tested undiluted.

The passively sensitizing power of the cat sera for guinea pigs was tested as has been described. The sera of three positively reacting cats and of one negatively reacting animal were employed. A 24 hour incubation period was allowed to elapse before injecting the shock dose which consisted of one cubic centimeter of 4% crystalline egg albumin. None of the guinea pigs displayed anaphylactic symptoms following intracardial injection of the shock dose. Thus it is shown that the cat sera in five cubic centimeter amounts contained insufficient sensitizer to render the guinea pigs hypersensitive. Also that there is no demonstrable difference in the sensitizing power of the samples of cat sera drawn immediately before injecting the shock dose from the samples drawn five minutes after the injection.

Excised intestinal strips and uterine horns: Two intestinal strips from each of seven negative animals and from two positive animals were tested for specific contraction by the Schultz-Dale technique. None of the strips from the negative animals responded with a specific contraction while the strips from both positive cats reacted with a marked contraction when one c.c. of 2% egg albumin solution was added to the 20 c.c. Tyrode's bath. After renewing the bath with fresh Tyrode's, a second addition of an identical dose of albumin caused no
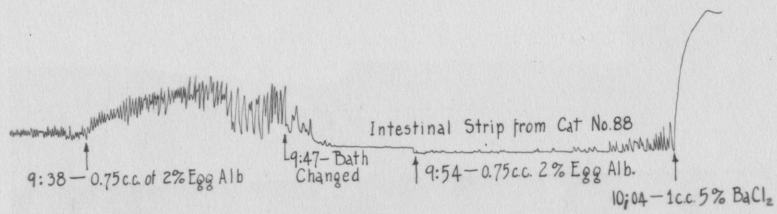
Figure: 8: Specific contraction of an intestinal strip from a cat passively sensitized to crystalline egg albumin.
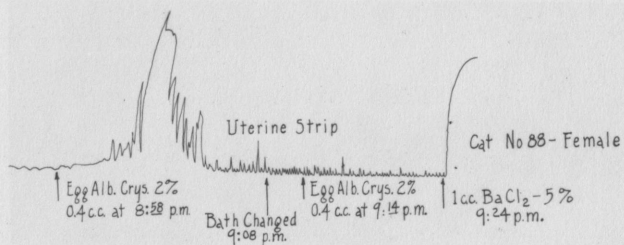

Figure 9: Contraction of the uterine horn from a passively sensitized cat.

contraction. A subsequent addition of barium chloride produced the characteristic shortening.

The uterine horns from three negative cats and from two positive cats were tested by the same method. The horns from one positive cat were hyperirritable even in a bath of physiological saline, thus relaxation was unobtainable and a satisfactory test was impossible. The horns from the other positive cat responded with a maximum contraction when 0.3 c.c. of 2% crystalline egg albumin solution was added to the 20 c.c. bath. After renewal of the bath, the addition of an identical amount of albumin induced no change in the tone of horn, however, upon the addition of barium chloride a marked contraction resulted. None of the horns from the negative animals showed any contraction except when barium chloride was added to the bath.

Discussion

By correlation of the physiological responses of the passively sensitized cat to an intravenous injection of the homologous antigen, it is possible to describe anaphylactic shock in the anesthetized animal. Soon after the intravenous injection of the shock dose, the arterial blood pressure abruptly falls, and at the same time the heart rate is markedly reduced. The oncometric kidney volume is also greatly diminished. The intestinal pressure definitely increases and at times this is also true of the intracystic pressure. Marked specific contraction are exhibited by excised intestinal strips and uterine horns when brought in contact with small amounts of the homologous protein. The coagulation time of the blood, and the rectal temperature are apparently unaffected. There are no demonstrable circulating anti-

bodies for crystalline egg albumin present. This fact would indicate that the antibodies injected are either quickly fixed by the animals tissues or hastily excreted. Since anaphylactic shock could be demonstrated, the former suggestion seems more fitting. There is 100% correlation of the excised smooth muscle responses with those of the arterial blood pressure, kidney volume, etc.

It has been pointed out that all the rabbit anti-sera used for passive sensitization in these studies were capable of passively sensitizing guinea pigs to a subsequent injection of crystalline egg albumin, yet only 40% of the cats in this series were rendered hyper-sensitive to the same antigen. A perusal of the results shows that all cats which exhibited anaphylactic symptoms were sensitized by injecting antiserum #152 or #160. All animals injected with the other five anti-sera consistently failed to respond to the injection of crystalline egg albumin.

The guinea pig has long been considered the animal "par excellent" for demonstrating the anaphylactic phenomena. It has been shown by Spain and Grove[39], Sherwood and Stoland,[41] Tim and Kwiatchkin[43], and others that the titer of the anaphylactic sensitizer did not parallel the titer of the precipitating antibody in anti-sera. Our results in passively sensitizing cats with rabbit anti-sera, bear out these findings. It is likewise demonstrated that the cat does not yield to passive sensitization as readily as does the guinea pig. Sherwood and Stoland[63] have shown that some dogs are not passively sensitized while others are by injections of the same antiserum. This recalls to light the additional factor of individual variation.

Conclusions.

The preceding experimentation, in which the responses of the passively sensitized cat while under ether anesthesia, to an intravenous injection of a shock dose of crystalline egg albumin, were recorded, led to the following conclusions:

1. That the characteristic blood pressure response is a profound loss of pressure, which is followed by a slow return to normal. There may be a temportary partial or complete recovery, which produces the "three phase" curve as previously described.

2. That while the blood pressure is reduced, there is a marked slowing of the heart that tends toward the normal rate as the blood pressure is restored.

3. That the rectal temperature progressively decreases throughout the duration of the experiment, thus plays no active part in anaphylaxis of the cat.

4. That the precipitin content of the circulating blood is not an important factor in feline anaphylaxis.

5. That the increase of intestinal pressure in the cannulated loop suggests there is active participation of the intestinal smooth muscle in the anaphylactic phenomenon.

6. That the intracystic pressure responses are variable and show the need of additional study.

7. That the consistently marked decrease of kidney volume, suggests an active constriction of the renal blood vessels.

8. That the coagulation time of the blood displays a progressive

decrease throughout the duration of the experiment, and cannot be used as a criterion of feline anaphylaxis.

9. That the response of excised smooth muscle strips can be used as a criterion of anaphylactic shock in the cat.

10. That there is 100% agreement of the smooth muscle reactions with the physiological responses as judged by the drop of arterial blood pressure, reduction of heart rate, etc.

11. That hypersensitivity is passively induced in 40% of the cats in this study.

12. That anaphylaxis may be manifest in the cat while under ether anesthesia.

13. That the characteristic symptoms of anaphylactic shock in the cat are somewhat different from those of other species.

14. That the elimination of the "Brodie Reaction" by use of a pure protein such as crystalline egg albumin constitutes an important step in the study of the anaphylactic phenomenon of the cat.

Part III.

Studies on Histamine and Peptone Reactions in Cats.

Section 1. Histamine.

It has long been known that the introduction of histamine into the animal body produces a state of profound shock. Dale and others have called attention to the similarity of the symptoms of histamine schock to that of anaphylaxis. Following intravenous introduction the appearance of symptoms is almost instantaneous and more profound shock results than when injected subcutaneously or intraperitoneally.

Dale and Laidlaw [87] in 1910 described the symptoms of histamine shock of the intact animal for several species. They recognized a difference in the reaction of guinea pigs and rabbits from that of the carnivora. Because of this difference the response of the guinea pig and rabbit will be discussed first. Dale and Laidlaw observed that when 0.5 M.Gm. of histamine was injected intravenously in guinea pigs it produced labored and spasmotic breathing, with forced inspiratory movements. Death usually occurred in a few minutes. The heart remained beating after respiration had stopped. Death was due to asphyxia, and the lungs were distended with air. Preliminary injection of atropine, though it did not abolish the action, had decided protective value. They concluded, "Whether atropine actually weakens the bronchial spasm or merely modifies the effect of secretion must remain uncertain."

The same authors found that 0.2 Mgm of histamine injected intravenously in the rabbit produced marked prostration, irregular and labored breating. The heart beat was feeble and intermittent. If a second dose was administered before the symptoms had entirely disappeared the symptoms were greatly augmented and death ensued in a few seconds.

Death was apparently caused by right heart failure. They observed that the rabbit suffered bronchial spasms when unanesthetized following histamine injection. The conditions of anesthesia and the length of time the animal had been under the influence of anesthesia modified the blood pressure response. They concluded that the uncomplicated effect of histamine on the heart and vessels of the rabbit was to cause a rise of systemic pressure which could be shown to be due to arterial constriction, in which the intestinal vessels shared.

Feldberg[88] commented on the action of anesthetics, and noted that rabbits tolerated larger doses of histamine than did the cat, also that the rise of blood pressure in the rabbit was obviously due to arterial constriction.

Smith[89] in 1920 failed to show any change in body temperature or coagulation time (possibly some decrease) subsequent to histamine injection.

Bally[90] has conducted a physiological study of the response of the rabbit to histamine injections. He found that the typical response to histamine was an immediate increase in the mean arterial pressure followed by a slower fall, both of which bore a somewhat direct relationship to the dosage of histamine injected. That the anomalous rise in blood pressure of the rabbit following histamine injection was probably due to a combined action of arteriole constriction and increased capillary tone or possibly to cardiac stimulation. However, he reported that histamine injections produced a moderate lengthening of the blood coagulation time, Bally also found that in the majority of cases the intestinal smooth muscle of the rabbit was stimulated to

contraction by the intravenous injection of histamine. Dale[91] and Kendall[92] have found that histamine was a potent stimulant of excised smooth muscle tissue.

The reaction of the dog and cat to histamine injection is very similar and may be discussed together. Dale and Laidlaw[87] found that the injection of two to ten milligrams in the intact unanesthetized animal caused immediate vomiting, purging, profuse salavation, labored respiration with a subsequent period of collapse and light narcosis. A second injection produced similar symptoms but less marked. In the anesthetized animal using, morphine and A. C. E. mixture, or paraaldehyde, they found that injections of 0.25 Mgm. per Kg. produced a slowing of the heart, which did not act directly on the heart muscle. They found a constriction of the pulmonary arterioles with a rise in pulmonary pressure, while a drop was evident in the systemic blood pressure. The limb volume and intestinal loop volume increased as the pressure fell. The kidney and spleen registered a marked decrease in volume. Excised gastric and intestinal strips responded with contraction in the presence of a high dilution of histamine.

In 1918 Dale and Richards[93] concluded that the vasodilator action of histamine was purely peripheral effects on the blood vessels, independent of the integrity of any nervous connections.

They found that histamine constricted the arteries, but relaxed the tone of the capillaries. No exact line could be drawn where the characteristic arterial reaction gave way to that of the capillary reaction, and in 1919 Dale and Laidlaw[94] found that local application of histamine produced a typical reaction of local edema. Also that the systemic blood pressure drop was partly due to loss of volume in

the circulating fluid, because the increased permeability of the capillaries allowed the plasma to escape. This view was upheld by Manwaring[95] and others, who observed explosive edema of canine organs in blood free perfusion experiments. These authors described a profound drop in blood pressure of dogs within ten seconds following intravenous histamine injection. From 40 to 90 minutes was required for the blood pressure to return to normal. They observed no change in coagulation time of the blood. Rich[96] was able to demonstrate capillary dilatation and engorgement in the omentum of cats following both local application and general histamine injection. He concluded that when histamine was injected intravenously it caused a quickly progressive dilatation of both the visible and occult capillaries together with their adjacent arterioles and venules. That the circulatory failure of histamine shock resulted from dilatation of the peripheral vascular bed.

Dixon and Hoyle[97] reported a transient rise in both systemic and pulmonary blood pressure immediately following histamine injection in the dog. This was quickly followed by a fall in both, and he attributed the fall to an active constriction of the hepatic venules and an insufficient supply of blood to the right heart. However, they found that sufficient histamine to lower the systemic blood pressure of the cat always raised the pulmonary arterial pressure. One milligram of histamine raised the pressure 60 M.M. of half saturated sodium sulphate.

Emery and Griffith[98] found that injection of 0.5 mgm. of histamine per Kg. in the cat produced a fall in blood pressure and a decrease in liver volume, which might have been an active constriction, for in some records the liver began to contract before the blood pressure

started to fall. Injections into the hepatic artery produced in some cases a decrease in liver volume, whereas in others an active dilatation occurred. The action of histamine as summed up by Wells[99] is:"It causes bronchial spasm in guinea pigs, obstruction to pulmonary circulation in rabbits and a fall of blood pressure in dogs. It causes marked local uticaria of the skin in humans, and it does all these things in extremely minute dosage." It has been pointed out that the reaction of the cat is very similar to that of the dog following histamine injection.

Although the physiological responses of the cat to histamine injection have been extensively studied, it seemed fitting to study a short confirmatory series. In this study there has been an attempt to record various physiological reactions occurring simultaneously in the anesthetized, normal cat. With this intention the carotid blood pressure, heart rates, blood coagulation time, rectal temperature, oncometric kidney volume, intestinal smooth muscle tension, and intracystic pressure were recorded by the methods described in the section of anaphylaxis. To our knowledge the changes of intestinal smooth muscle tension and intracystic pressure following histamine injection have not been described.

Experimental.

This series included six normal healthy cats, which ranged in weight from 2200 to 4000 grams. The average weight was 2830 grams. Of the six animals, four were females and two were males. The various physiological experiments were performed simultaneously on each of the animals except in the first few the technique of recording changes of

kidney volume was not perfected.

Anesthesia: The animals of this series were given 55 Mgm. of sodium amytal intravenously for three of which the anesthesia was incomplete so the trachea was cannulated and an ether bottle was attached.

Injections: All injections were made by means of a cannula tied into the right femoral vein. Each histamine injection was followed by five c.c. of warm Ringer's solution to wash the cannula free of histamine and insure us that the entire injection had reached the circulation.

Results.

Blood Pressure: The first cat received a single injection of 0.5 M.gm of histamine per kilogram body weight. A fatal shock resulted. Each of four cats received two injections consisting of 0.25 mgm histamine per kilogram. One cat died 27 minutes after the second injection, but in all other animals there was complete or partial recovery of the normal blood pressure. One cat received three injections of 0.25 mgm. per kilogram, after each there was almost complete recovery in from eleven to 26 minutes. The time required for the blood pressure to recover progressively shortened with succeeding injection.

In every case with a single exception there was a rise of pressure of from six to ten M.M. Hg within six seconds following the start of injection. This was undoubtedly a rise due to the increase in volume of the circulating fluid, and was not a result of histamine action. The injection rise was immediately followed by an abrupt drop of pressure which began from five to eight seconds after the injection was started.

Subsequent to 67% of the histamine injections the blood pressure curve followed that described by Dale and Laidlaw[87] as the "three phase drop". This was an abrupt drop interrupted by a slight or marked recovery which was again followed by a slow decline to the minimum pressure. Four injections or 33% were followed by an abrupt drop which shaded into a slow gradual decline, after which slow recovery was initiated.

An analysis of the graphs showed the abrupt drop of blood pressure to start at an average time of six seconds following the start of injection. The decrease of blood pressure produced by the ten non-fatal injections showed a maximum value of 53% and a minimum value of 33%. The average drop was 46.9%. The maximum time required to consumated this decrease was six minutes and four seconds, the minimum was one minute. The average time required was two minutes 30 seconds. When multiple injections were given, a longer period of time was required for the cat to regain the normal blood pressure after the first injection than after the succeeding ones. An average of twenty minutes was required to recover normal pressure following the first injection while twelve to fifteen minutes were sufficient after the second. Four of the cats, however, did not show complete recovery of pressure following the second injection. There was no apparent difference in the physiological responses when under amytal from those of ether anesthesia.

Heart rate: Subsequent to 75% of the histamine injections, the heart rate was decreased from three to twenty-five beats per minute. Following one injection the rate was increased slightly and after two, both in the same cat, the rate was markedly increased. (55 beats per minute.) The heart rate was usually restored to its normal value

Table #3: Results of the Physiological Studies of Histamine injection in Cats.

Serial Number	Sex	Weight	Anesthetic	injection number	Dose	Coagulation time Before	After
15	Male	3500 Grs.	Sodium Amytal	1	0.5 Mgr. per Kilo	1'	1'
17	Female	2500 Grs.	Sodium Amytal	1	0.25 Mgr. per Kilo	4' 30''	3' 30''
				2	"	0	1' 20''
18	Female	2200 Grs.	Sodium Amytal & Ether	1	"	7'	7'
				2	"	0	0
19	Female	2200 Grs.	Sodium Amytal	1	"	4'	2' 50''
				2	"	0	0
20	Male	4000 Grs.	Sodium Amytal & Ether	1	"	10'	5'
				2	"	0	4'
				3	"	4'	2' 30''
21	Female	2600 Grs.	Sodium Amytal & Ether	1	"	10'	3' 20''
				2	"	0	3' 20''

Table #3: Results of the physiological studies of histamine injection in cats. (continued)

Serial number	inj. no.	Temperature Before	Temperature After	Heart rates Before	Heart rates After	% Drop	Blood Pressure Type Curve	Recovery Time
15	1	101°F	100°F	215	180	65	Three phase	Fatal in 10'
17	1	98.6°F	98.0°F	140	140	48	" "	Complete in 20'
	2	0	97.1°F	No Count	No Count *	33	" "	" " 8'
18	1	103.4°F	100°F	205	190	53.5	Single Phase	" " 7'30"
	2	0	0	210	210	58	" "	Fatal in 27'
19	1	97.6°F	100.7'F	138	175	47	Three Phase	Complete in 17'
	2	0	0	No Count	No Count	43	" "	Incomplete in 30'
20	1	0	0	230	228	51	" "	Complete in 26'
	2	0	0	228	228	50	" "	" " 15'
	3	0	0	No Count	No Count	48	" "	" " 10'20"
21	1	96°F	95.2°F	170	175	47	Single Phase	" " 20'
	2	0	94°F	170	163	49	" "	" " 11'

* Pulse too weak to count heart rate.

Table #3: Results of the physiological studies of histamine injection in cats.(continued)

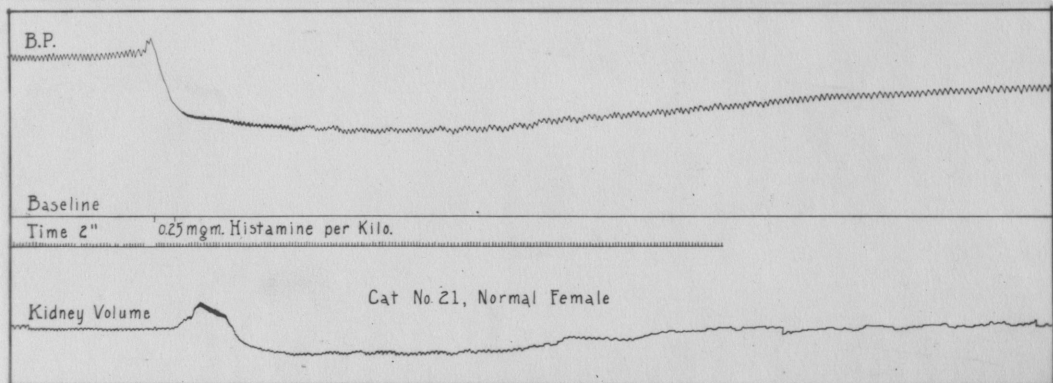| Serial number	inject number	Kidney volume		Intestinal pressure		Bladder pressure	
15	1	Apparatus inadequate		Marked increase		Slight increase	
17	1	"	"	"	"	No change	
	2	"	"	"	"	"	"
18	1	"	"	"	"	"	"
	2	"	"	"	"	"	"
19	1	"	"	"	"	increase	
	2	"	"	"	"	"	
20	1	Fleeting increase Marked decrease		"	"	#	
	2	"	"	"	"	"	
	3	"	"	"	"	"	
21	1	"	"	"	"	"	
	2	"	"	"	"	"	

Figure 10: Blood pressure and kidney volume responses of a cat to the first injection of histamine. Single phase blood pressure response.
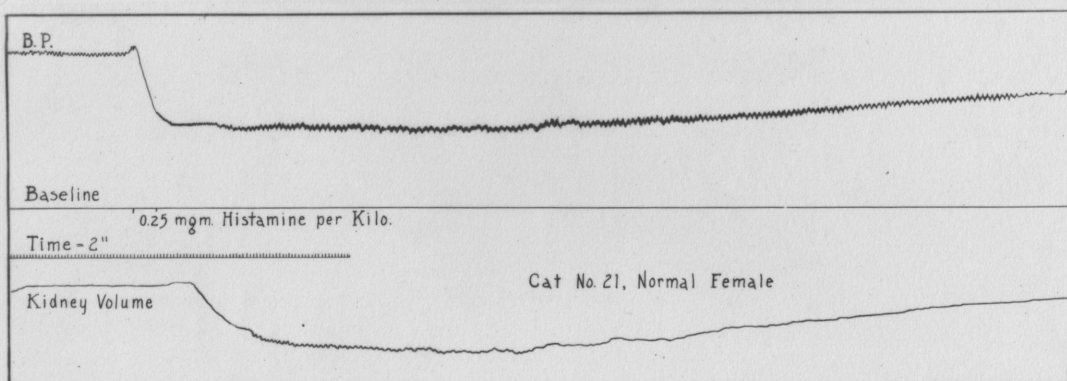

Figure 11: Blood pressure and kidney volume responses of a cat to the second injection of histamine. Single phase blood pressure response.

when the blood pressure was regained.

Coagulation time: Dale and Laidlaw as well as others have reported no increase of blood coagulation time following histamine injections in cats. In this study, two of the six cats showed no change of coagulation time, while the remaining four exhibited a progressive decrease as the experiments continued. Since this observation was also made of control cats not receiving histamine injections, the shortening of the coagulation time was not attributable to histamine action but to experimental conditions.

Rectal Temperature: The rectal temperature exhibited a slow progressive fall throughout the experiment for every animal. It was obvious that the amount of all varied directly with the period of time which the animal was on the operating table, the surgical maniputalion, etc.

Kidney volume: A marked decrease in kidney volume has been reported to follow intravenous injections of histamine in the cat. It was thought to suggest active constriction of the renal vessels. In our experiments, a fleeting definite increase in volume was observed. The slight injection rise of blood pressure was hardly sufficient to account for this increase of kidney volume. The increase was immediately replaced by a marked decrease in volume as the blood pressure fell. If this decrease in kidney volume is to be considered an active constriction, the evidence seems to suggest that it is preceded by a transient definite dilatation of the renal blood vessels.

Intestinal pressure: A definite increase of intestinal pressure followed every injection of histamine. For two cats, receiving four

injections, the increase was not evident until one minute after in-jection. Following the remaining eight injections, the increase was evidenced within 30 seconds.

Intracystic pressure: Four cats, receiving eight injections, responded with a slight or marked increase of intracystic pressure. Two cats, which received four injections, gave no response. It was of interest to note that the two cats which showed no reaction, were the same as those which exhibited delayed increase of intestinal pressure.

Death: Two of the six animals in this series died in histamine shock. Both animals exhibited a very low arterial blood pressure preceding death. A postmortem examination showed the large veins to be distended, the right heart engorged, and the left heart practically empty.

Narcosis: In animals under light anesthesia, the injection of histamine caused a loss of existing reflexes, such as the corneal reflex, etc.

Discussion.

In our experiments there is no appreciable difference in the response of cats to histamine injection, under amytal, ether, or mixed anesthesia. This is in accord with previous reports. The blood pressure response follows very closely that described by Dale and Laidlaw as the "three phase drop". However, not all animals produce this type of curve which is again in agreement with their findings. We were able to confirm the observation that apparently cats are less susceptible to the second injection of histamine than

B.P.

Time - 3"

Baseline

0.5 mgms. per Kilo

Kidney Volume

Cat No 15, Normal Male
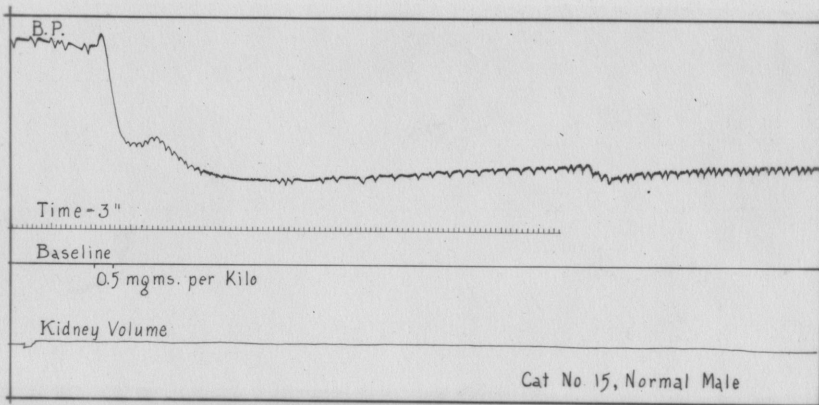
Figure 12: Blood pressure response of a cat to the first injection
of histamine. Three phase response. Kidney oncometer
was unattached.

Intestinal Pressure - 1st

Intestinal Pressure - 2nd

Time = 2"

Bladder Pressure - 1st

Bladder Pressure - 2nd

0.25 mgn. Hist. per KG

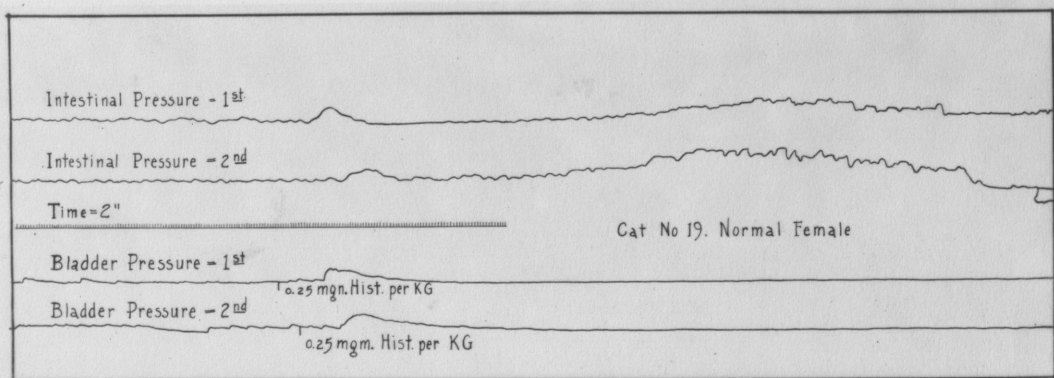0.25 mgm. Hist. per KG

Cat No 19. Normal Female

Figure 13: The intestinal and intracystic pressure responses of a
cat to the first and second injection of histamine.

to the first as judged by the time necessary for the blood pressure to be restored. Heart rates are usually reduced following histamine injections and return to normal as the animal recovers from shock. However, apparently a small percentage of animal respond with an increase of heart rate.

This study confirms previous reports of histamine injection in the carnivora, that it does not affect the coagulation time of the blood or the body temperature. Both the coagulation time and the body temperature decrease progressively throughout the duration of the experiment.

A fleeting definite increase of kidney volume has been observed which is immediately replaced by a profound decrease in volume. It seems this preliminary increase of kidney volume is hardly explicable by the mechanical effect of the slight injection rise of arterial blood pressure. It suggests that the preliminary action of histamine on the renal vessels of the cat is a dilatation which may be succeeded by an active constriction.

From the intact intestinal loop records it is shown that the intestinal smooth muscle of the anesthetized cat responds in a similar manner as the same when excised and tested in warm Tyrode bath. There is 100% contraction of the intestinal loop following histamine injections.

Since following 67% of the histamine injections there is a definite increase of intracystic pressure, it suggests that this response is due to the action of histamine. This is in opposition to the view of Dale and Laidlaw who thought histamine had no direct effect

on the bladder musculature.

We feel that the foregoing simultaneous physiological studies of histamine injection in the cat bear out the following conclusions:

1. That sodium amytal anesthesia may be satisfactorily used in laboratory studies.

2. The typical reaction of the cat to a single rapid injection of histamine is a three phase drop in blood pressure. There is an abrupt drop, interrupted by partial or complete recovery followed by a slow gradual fall to the minimum pressure.

3. The intravenous injection of histamine usually produces a slight decrease in heart rate, which returns to normal as the blood pressure is restored.

4. That the injection of histamine does not exhibit any noticeable effect on the coagulation time of the blood.

5. That it produces no evident change of the rectal temperature in the cat.

6. That histamine injection produces a fleeting dilatation of the renal blood vessels which is immediately displaced by what appears to be an active constriction with subsequent decrease of kidney volume.

7. That histamine injection produces an active increase of intestinal pressure.

8. That in the majority of cases, histamine induces a definite increase of intracystic pressure.

9. That cats dying in histamine shock, display an arterial blood pressure near zero. That the large veins are distended, the right heart engorged and the left heart almost empty.

10. A definite effect of narcosis is observed following histamine injection in the cat.

Section 2. Peptone.

Schmidt-Mulheim [100] in 1880 discovered that when peptone was introduced intravenously into the systemic circulation of a dog, it produced the remarkable result of delaying the coagulation time of blood drawn soon after the injection, and at the same time caused a very profound fall of blood pressure. From this classical experiment numerous investigators gained incentive, and a voluminous literature has accumulated on peptone shock especially in the dog.

Pollitzer [101] studied the reaction in the dog and concluded: "That the fall of pressure is due to vaso-motor paralysis cannot of course be questioned, and that the action is manifest, if not wholly, on the splanchnic region is reasonably certain."

Thompson [102] in 1896 showed that a dose of less than 20 mgm of peptone per Kilo was stimulatory while large doses produced a fall in pressure. He thought the loss of pressure was of peripheral origin, in which all blood vessels shared, and the effect was consumated by loss of irritability of neuro-muscular apparatus. In 1899 Thompson [103] called attention to the fact that the kidney volume of the dog was decreased following intravenous peptone injection. Also that speed of injection was an important factor. In 1900 [104] he showed that the vessels of the spleen and limbs were affected little if any by peptone. However, there was a marked increase in liver volume, which he attributed to the increase of onflow from the blood of the portal system.

Underhill [105] in 1903 summarized the preceding work on peptone in-

jection as follows: "Physiological reactions called forth by the intravenous injection of the 'peptone' of earlier writers are diverse and include the rendering of the blood incoagulable together with changes in its reaction and composition; an acceleration of lymph flow; a fall of arterial pressure; anuria; deep narcosis and other toxic symptoms as well as a certain degree of immunity toward subsequent injections."

Manwaring [106] and Coworkers demonstrated by perfusion experiments that the resistance was increased in the liver and lungs following introduction of peptone, while the resistance was decreased in the intestines, skin and skeletal muscles under the same conditions. They explained the increase of perfusion pressure in the liver by an increase of permeability of sinusoidal endothelium, which produced an explosive edema increasing the local tissue pressure sufficient to account for the constriction. Apparently this theory was also held by Peterson [107] and Coworkers. However Simonds [108] felt the train of symptoms characteristic of peptone shock was induced by a contraction of the smooth muscle in the wall of hepatic veins, thus producing an anatomical obstruction to the venous outflow.

Geiling and Kolls [109] called attention to the dilation of the capillaries and venules in the unanesthetized dog, and also to the fact that the pulse rate was increased. They thought the reduction in cardiac size and output was the direct result of reduced venous return caused by capillary dilatation. Abel and Geiling • [110] discovered that the second intravenous injection of peptone into a dog, recovered from a large initial dose, failed to lower the blood pressure or to render the blood non-coagulable. Howell [111] concluded, "when a peptone solution is injected into a dog intravenously it causes an output of herparin in the

blood, thus explaining the incoagulability of so-called peptone blood."

It has been suggested then, that there are four possible causes of the

fall of blood pressure in peptone shock of the dog; (1) peripheral

vasodilatation 100-102 (2)-reduced blood volume, 106-107 (3) obstruction

at some strategic point in the circulation, (4) diminished heart action. 108 109

Underhill 105 in 1903 stated "the rabbit is extremely resistant, fail-

ing to respond in so far as phenomena involving blood are concerned", in

respect to peptone injections in that animal. However, Nolf has report-

ed that it was possible to produce a noticeable retardation of blood

coagulation in rabbits when sufficiently large doses of peptone were

injected rapidly. Olivercrona 112 studied the effect of peptone on excised

intestinal strips of the rabbit and found that peptone produced a brief

increase of tone followed by loss of tone and rythmic contractions.

Larger doses produced only the inhibitory effect. Dale and Laidlaw 87

showed that 0.1% Wittes peptone produced a powerful stimulant action

on the isolated uterus of the guinea pig. Baehr and Pick 113 found that

peptone acted as a broncho-constrictor of the perfused lungs of the

guinea pig. Schultz 114 demonstrated that 0.05% peptone stimulated the

isolated gut of the guinea pig. Hanzlik and Karsner 29 reported that

peptone injections in the guinea pig was promptly fatal. It produced

typical symptoms of respiratory distress, marked pulmonary inflation

and delayed coagulation of the blood. The same authors found that

0.01% stimulated the intestines of the rabbits and 0.03% stimulated the

rabbit uterus. However, Persano found that blood from the guinea pig

in peptone shock was rendered non-coagulable only when the animal was

in a fasting state.

115
In 1929 Bally carried out a systematic physiological study of peptone shock in the rabbit. He confirmed previous reports that peptone produced a relaxation of intestinal smooth muscle. He also described a characteristic blood pressure curve and "blanching reaction" following intravenous peptone injection in that animal. Bally reported an increase of coagulation time of peptone shock blood from the rabbit.

The description of peptone shock in the cat is less readily found and is not complete. Several authors report it is very similar to that of the dog but cite no evidence to support their statement.

Underhill compared the response of the cat to that of the dog as follows: "In the cat the characteristic symptoms are evoked somewhat less readily, larger doses being necessary to produce comparable results." He also stated, "incidentally we have again learned the differences in the susceptibility of different animal species to the toxic action of injected proteoses, by comparing the response in the dog with that in the cat." But he included no description or further information concerning the response of the cat in his report.
112
Olivecrona found that dilutions of from 1-250 to 1-760000 of peptone readily increased the tone of excised intestinal strips of the cat. Dilutions of peptone less than 1-200 produced a marked relaxation and complete loss of rythmatic contractions. Emery and Griffith[98] found the effects of peptone in the cat to be a decrease in liver volume and a fall of blood pressure. They said "these changes are usually more gradual and complete return to normal of either liver volume or blood pressure are less likely to occur with peptone than with histamine."

The dearth of information concerning the response of the cat to intravenous peptone injection together with a desire to compare these phenomena with those of histamine and anaphylactic shock lead us to undertake a series of physiological studies of the response of the cat to intravenous peptone injection.

Experimental.

This series was made up of 12 normal cats, ranging in weight from 1650 to 4600 grams with an average weight of 3090 grams. Of this number seven were males and five were females. In these experiments the various physiological records were obtained simulataneously for each of the twelve animals.

The twelve cats received 22 injections of peptone. Witte's peptone was used throughout and the solution was made fresh for each day's experiments. A boiled 10% solution of peptone in physiological saline, was cooled and centrifuged to remove the precipitate. The clear supernatent fluid was then used for injection.

The dosage for the first ten animal was 0.25 gram of peptone per kilogram of body weight. Four tenths grams per kilo was injected in the last two cats of the series.

All injections were made intravenously by means of a cannula tied into the right femoral vein. Each injection was washed in with sufficient warm Ringer's solution to make the total volume injected equal ten cubic centimeters.

Six of the animals were anesthetized by an intravenous injection of 55 mgm sodium amytal per kilo. The remaining six were anesthetized with ether.

Table #4: Results of the physiological studies of peptone injection in cats.

Serial number	Sex	Weight	Anesthetic	Injection number	Dose
22	Female	3000 Grs.	Sodium amytal	1	0.25 Gr. per. Kilo.
23	Male	2900 "	Sodium	1	"
				2	"
				3	"
24	Male	3200 "	Ether	1	"
				2	"
25	Female	3000 "	Ether	1	"
				2	"
26	Male	3400 "	Ether	1	"
				2	"
				3	"
27	Female	2850 "	Sodium amytal	1	"
28	Male	4600 "	Sodium amytal	1	"
				2	"
29	Male	3600 "	Ether	1	"
				2	"
30	Male	3000 "	Ether	1	"
				2	"
31	Female	3400 "	Sodium amytal	1	"
				2	"
48	Female	2500 "	Sodium amytal	1	0.40 Gr. per Kilo.
49	Male	1650 "	Ether	1	"

Table #4: Results of the physiological studies of peptone
injection in cats. (continued)

Serial number	inj no.	Coagulation time Before	After	Temperature Before	After	Heart Before	rates After
22	1	4' 20''	2' 30''	99.6°F.	0	210	218
23	1	6'	2' 30''	100°F	100.4°F	259	250
	2	2' 10''	1' 50''	100.8°F	100°F	To weak	To weak
	3	0	0	0	0	''	''
24	1	5'	6' 30''	99.2°F	99.1°F	226	220
	2	3'	5' 30''	99°F	99.8°F	207	207
25	1	8' 10''	1' 30''	96.7°F	96.6°F	210	210
	2	1'	2	95.4°F	95°F	210	212
26	1	15'+	4' 50''	96.8°F	96.8°F	162	142
	2	1' 30''	1'	0	0	150	150
	3	2' 30''	3' 30''	96°F	95.5°F	156	156
27	1	1' 30''	50	97°F	96.5°F	208	200
28	1	7'	3' 30''	99.6°F	98.5°F	228	210
	2	1' 30''	1' 50''	97.8°F	97.1°F	204	201
29	1	11'	1' 30''	102.2°F	101.4°F	258	260
	2	4'	1' 30''	101°F	100.8°F	258	256
30.	1	7'	6'	98.9°F	98.2°F	198	189
	2	2' 30''	3' 30''	97.4°F	96.8°F	189	192
31	1	6' 15''	10' 45''	99.8°F	99.4°F	216	216
	2	8'	11'	99.2°F	0	0	0
48	1	10'	10' 30''	97.4°F	96.6°F	207	207
49	1	4' 15''	2' 30''	96.6°F	95.8°F	203	208

Table #4: Results of the physiological studies of peptone
injection in cats. (continued)

Serial number	inj. no.	% Drop	Blood Pressure Type curve		Recovery time
22	1	57.1	Three phase		Fatal
23	1	45	"	"	incomplete in 30'
	2	14.5	"	"	complete in 30'
	3	26.6	"	"	incomplete in 30'
24	1	35	"	"	incomplete " 20'
	2	5.5	"	"	little recovery
25	1	52	Single phase		incomplete in 50'
	2	20	"	"	" " 15'
26	1	42.3	"	"	complete " 36'
	2	22.2	"	"	" " 10'
	3	14.3	"	"	Fatal in 10'
27	1	40.7	"	"	Fatal in 9'
28	1	45	Three phase		incomplete in 31'
	2	33.3	"	"	complete in 7' 40''
29	1	36.9	"	"	incomplete in 35'
	2	8.3	Single phase		complete in 1'
30	1	50.9	Three phase		incomplete in 38'
	2	13.3	Single phase		complete in 1'
31	1	44.7	Three phase		incomplete in 40'
	2	33.3	Single phase		Fatal in 8' 30''
48	1	58.8	Three phase		" " 33'
49	1	56.4	"	"	incomplete in 54'

Table #4: Results of the physiological studies of peptone injection in cats. (continued).

Serial number	inj. no.	Kidney volume	intestinal pressure	Bladder Pressure
22	1	No change	Decrease Loss of rythm	No change
23	1	Marked Decrease	Increase	Slight slow increase
	2	Increase	"	"
	3	"	"	"
24	1	Marked decrease	No change	No change
	2	slight increase	" "	" "
25	1	Marked decrease	Decrease Loss of Rythm	increase
	2	slight decrease	"	"
26	1	Marked decrease	No change	No change
	2	Slight decrease	slight increase	" "
	3	slight increase	increase	" "
27	1	No change	Loss of rythm	" "
28	1	Marked decrease	" " "	" "
	2	slight decrease	" " "	" "
29	1	Marked decrease	" " "	No record
	2	Little change	" " "	No change
30	1	Marked decrease	slight increase	" "
	2	slight increase	Loss of rythm	" "
31	1	Marked decrease	" " "	" "
	2	increase	No change	" "
48	1	Marked decrease	" "	increase
49	1	"	Loss of rythm	No change

Methods for determining the mean arterial pressure, heart rates, coagulation time of the blood, rectal temperature, kidney volume, intestinal pressure, and intracystic pressure were the same as those described in the section of anaphylaxis.

Results.

Blood pressure: The data for the blood pressure response of cats to peptone injection was compiled from the reactions of twelve animals, which received 22 injections.

The blood pressure curves were readily separated into three groups. The first group was composed of six animals which received ten injections. This group responded with a "three phase drop" as described in the histamine section. The preliminary recovery following seven injections amounted to only a few m. m. Hg., following one injection the recovered pressure attained the level of 50 m. m. Hg overcompensation, and following two injections the pressure reached the normal value. Immediately following every preliminary recovery there was a slow decline to a low pressure level.

The second group was composed of three animals receiving six injections. They reacted with an immediate abrupt drop which shaded into a slower decline lasting for from one to three minutes.

The third group was made up of three cats which received six injections. These animals showed a three phase drop following the first injection of peptone, but responded with a single phase drop after the second. However, following the second injection the pressure drop was small and complete recovery was consumated in a short time.

The percentage drop of pressure and the time required to reach
the minimum value were surprisingly constant following the correspond-
ing injection in all animals regardless of the type curve recorded.
The percentage drop and the time required to reach the minimum value
were greater following the first injection than after the second.
The average drop following the first injection of peptone was 44.9%,
with the extreme variations being 57% maximum and 35% minimum. The
average time required for the blood pressure to reach its lowest level
after the first injection was two minutes twenty seconds. The maximum
was three minutes 40 seconds and the minimum was 45 seconds.

The average drop which followed the second injection of peptone in-
to a cat was 15%, and the average time consumed in reaching the low
point was 45 seconds.

The percentage drop of blood pressure showed a direct correlation
with the size dose injected. The percentage drop was greater when
larger amounts of peptone were injected. Two animals which received
injections of 0.4 grams of peptone per Kilo body weight showed a blood
pressure drop of 58% and 56% respectively. The time required for this
loss of pressure to be manifest did not materially differ from that
following injections of only 0.25 grams per Kilo.

In no case was the recovery of blood pressure complete after the
first injection. The time allowed to elapse before administration
of the second injection varied from 30 minutes to one hour. However,
following 50% of the second injections, the blood pressure regained
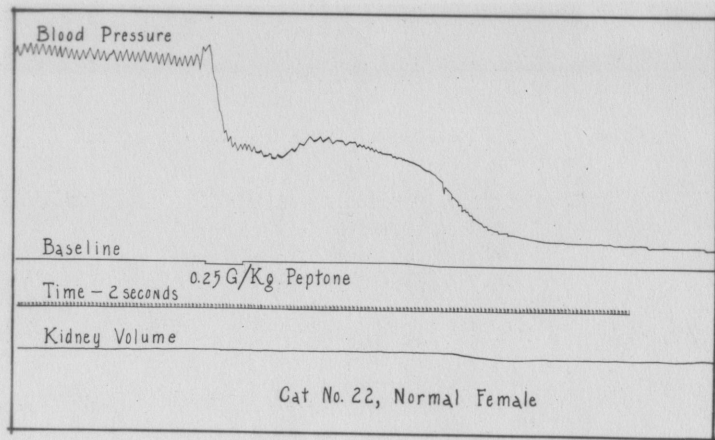the strength it displayed preceding that injection.

Figure 14: Blood pressure and kidney volume responses of a cat in fatal peptone shock.
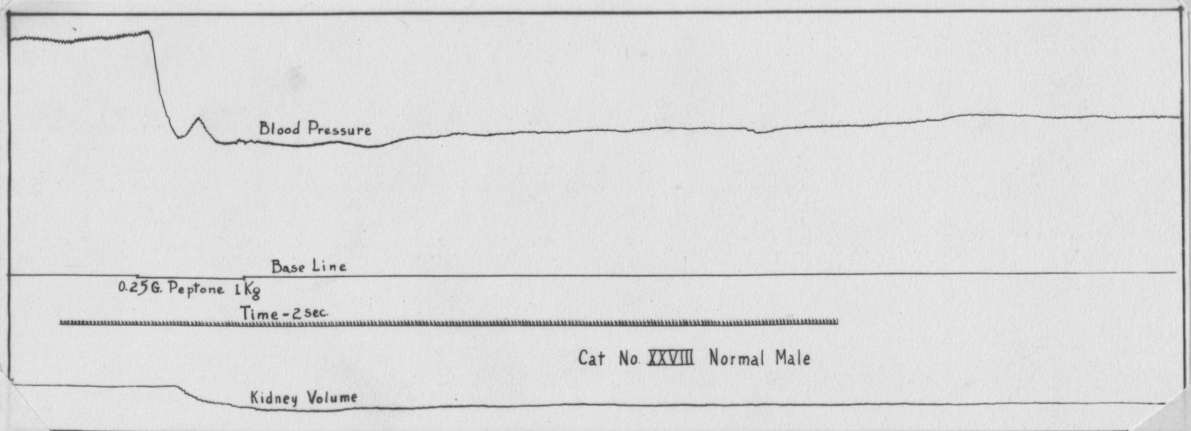

Figure 15: Blood pressure and kidney volume responses of a cat to the first injection of peptone.

Heart rate: The effect on the heart rate of the first injection of peptone into the cat was markedly different than that of the second. Following the first injection six animals showed a marked slowing of the heart. The maximum decrease in rate was 20 beats per minute. Only two animals exhibited any increase of heart rate, following the first injection. The amount of increase was eight and five beats per minute respectively. The heart rates of the remaining four animals of this series were apparently uneffected by the injection of peptone. When the rate of the heart was reduced, there was little tendency toward recovery in the duration of our experiments. The second injection of peptone consistantly produced no effect on the rate of the heart.

Coagulation time: The coagulation time of blood drawn five minutes after the intravenous injection of peptone was very inconstant. The results resemble that described for rabbits somewhat more than that for dogs. The blood of three cats following peptone injection showed an increase of coagulation time. The increase varied from one minute 30 seconds to four minutes 30 seconds. The blood of six cats displayed a progressive increase of coagulability following each injection. The blood of three cats showed a decrease of coagulation time after the first injection of peptone, but exhibited an increase of one minute following the second injection. It would appear that a refractory state in respect to coagulation time of the blood was not induced in the cat following a peptone injection. 36% of the 22 peptone injections produced an increase of coagulation time, while following 64% a decrease of coagulation time was found.

Rectal temperature: In every animal there was a slow progressive

decrease of rectal temperature throughout the duration of the experiment. This loss of temperature could not be correlated with injections of peptone so must be attributed to experimental conditions.

Kidney volume: An analysis of the kidney volume records showed that for ten cats injected with peptone there was a marked decrease in volume of the kidney after the first injection. For three animals a decrease of kidney volume was also evident following the second injection. However five of the eight cats receiving two injections, showed an increase of kidney volume after the second injection. Both cats which received three injections of peptone responded with an increase of kidney volume following the third injection. Neither of the two animals which received a simple fatal injection of peptone showed any change in the volume of the kidney.

Intestinal pressure: The reaction of the intestinal smooth muscle of nine cats receiving fifteen injections of peptone, was a loss of muscular rythm accompanied by a slight or marked relaxation of tone. One cat which received three injections responded with a slight but definite increase of intestinal pressure following each injection. For one animal a relaxation of tone was evidenced following the first injection but the second and third injections of peptone produced slight increases of the intestinal pressure, and in one cat a slight increase of intestinal pressure followed the first injection but a decrease was recorded after the second injection of peptone.

It has been shown then, that following 73% of the peptone injections in cats there was a slight or marked decrease in the tone of the intestinal musculature.
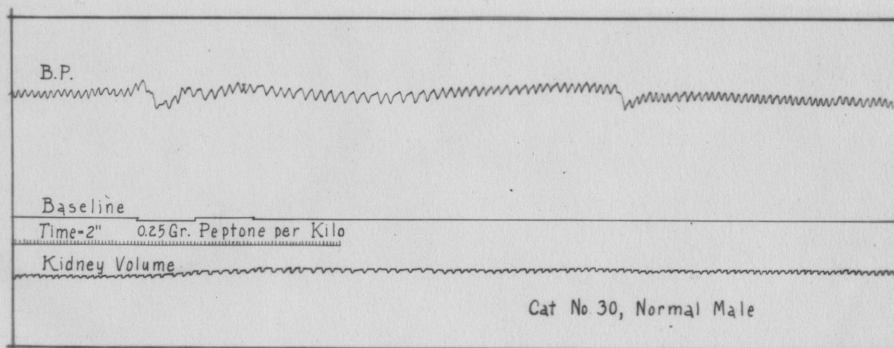
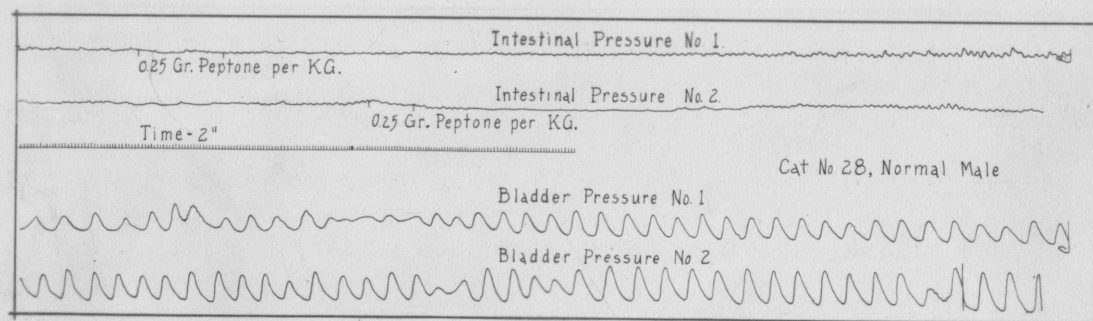**Figure 16:** Blood pressure and kidney volume responses of a cat to the second injection of peptone.

Figure 17: Intestinal and intracystic pressure responses of a cat to the first and second injection of peptone.

Intracystic pressure: The response of the bladder following intravenous peptone injections in the cat was more consistant than the response of the intestine. Three cats which received six injections reacted with an increase of intracystic pressure following each injection. The remaining nine cats of this series, showed no change in the tone of the cystic musculature following any injection.

Autopsy: Post mortem examination of the cats dying in peptone shock revealed the veins of the portal system and the inferior vena cava distended with blood. The right heart was engorged and the left heart was almost empty.

Discussion.

Reports of investigators concerning the reactions of the cat to peptone injections are few. No systematic or correlated simultaneous observations have been found describing the responses of the various organs. Most of the earlier reports seem to have been based on pure analogy to the response of the dog.

The results as recorded show that the animals even within the species react in somewhat a variable manner. Initial intravenous injections of peptone into the cat always produce a drop in blood pressure. The majority of animals respond with the "three phase drop" as described elsewhere, however, a few show only a single phase drop following peptone injection. There is never a complete recovery of blood pressure following the first injection, even one hour after injection. In contrast to the reported response of the dog, our findings usually showed a decrease in the cat's heart rate following the first peptone injection. Apparently there is also little

tendency for the normal heart rate to be regained.

It has been shown that the dog is much less susceptible to the action of the second or third injection of peptone than to the first, our experiments with the cat bear out these reports. Following the second or third injection of peptone in the cat the blood pressure drop is relatively much smaller. The average blood pressure loss following the second injection was about one third (1/3) that following the first injection. In some animals the drop amounted to only a few millimeters of mercury. In addition the blood pressure in the course of a few minutes usually returned to a value equaling that preceding the second injection. The heart rate is consistently unchanged after the second or third injection.

Some dogs do not exhibit a loss of blood coagulability following intravenous injection of peptone, however, their response is more constant than that of the cat, as judged by our findings. We have shown that following about 30% of the initial peptone injections in the cat the coagulation time of the blood is increased. Occasionally this is also true following the second injection, an observation which would indicate that the blood coagulability changes are not refractory to multiple injections of peptone.

There is also a striking differnce in the response of the kidney following the first injection in comparison to its response following the second. The first injection of peptone invariably produces a marked decrease in the kidney volume of the cat, however, following the second injection of peptone the kidney usually shows an increase of volume. This might suggest that the initial peptone injection had altered the reactivity or permeability of the renal blood vessels.

The typical response of the intestinal musculature to peptone is a/decrease in tone and a loss of rythmic contractions. In a majority of the animals no response of the bladder is recorded following peptone injection. Nevertheless, a small percentage of animals in this series shows a slight increase of both intestinal, and intracystic pressure. These findings are in direct contrast to those of histamine.

It is shown that the rectal temperature is unaffected by peptone injections. This is in accord with previous reports concerning the reaction following peptone injection in other species.

A perusal of the results shows no correlation in the response manifest and the anesthetic employed. It appears that sodium amytel may be used in the study of experimental peptone shock without fear of depressing or masking some part of the reaction.

Conclusions.

From the foregoing correlated physiological studies of peptone shock in the cat we feel warranted in drawing the following conclusions:

1. That following an initial injection of peptone in the cat, there is a characteristic drop of arterial blood pressure from which recovery is not complete in one hour, with an apparent lessening of susceptibility to further injections.

2. That the heart rate is usually decreased following the initial injection of peptone, and that it does not regain its normal value in the duration of our experiments.

3. That following the second injection the blood pressure drop is relatively small, and that the heart rate is unchanged.

4. That a decrease in the coagulability of the blood can not be used as a criterion of peptone shock in the cat.

5. That the typical response of the intestinal smooth musculature to peptone injections is a decrease in tone and loss of rythmic contractions.

6. That following 75% of the peptone injections there is no change in intracystic pressure.

7. That there is a consistent decrease of kidney volume following the initial peptone injection, and usually an increase of volume following the second injection.

8. That there is no correlation in changes of rectal temperature with peptone injections.

9. That in fatal peptone shock there is engorgement of the visceral veins together with the large trunk veins of the body.

10. That sodium amytal anesthesia can be used in the study of experimental peptone shock.

Table #5: A table in which the physiological responses of the cat in histamine, peptone, and anaphylactic shock are compared.

Physiological Responses		Histamine	Peptone	Anaphylaxis
Blood	Percentage Drop	46.9%	44.9%	42.7%
Pressure	Percentage Showing "Three Phase" curve	67%	59%	50%
	Average Time required for recovery	20 mins.	more than 1 hr.	12 1/2 mins.
Reducation of heart rate (Average)		10 beats per min.	4.75 beats per min.	35 beats per min.
Changes of blood coagulability		Progressive decrease	Slight increase in 36% of animals	Progressive decrease
Changes of rectal temperature		"	Progressive decrease	"
Changes of kidney volume		initial incr. 100% Marked Dec.	100% Marked decrease	100% Marked decrease
Changes of intestinal pressure		100% increase	73% loss of tone 27% increase	33% No change 67% increase
Changes of intracystic Pressure		33% No change 67% increase	73% No change 27% increase	67% No change 33% increase

Physiological comparison of histamine, peptone and anaphylactic shock.

An analysis of the data obtained from the various physiological studies herein described permits a comparative summary of the feline responses in histamine, peptone, and anaphylactic shock.

The arterial blood pressure response is very similar in all. The average percentage drop in pressure is surprisingly constant. Undoubtedly the size dose chosen for histamine and peptone study explains this consistency of results. The type curve resulting is likewise very similar in appearance as well as in the percentage exhibiting the "three phase" drop. It appears that the "three phase" curve is peculiar to the cat, but is induced by the injection of other substances than histamine for which it was originally described.

The cat usually fails to recover completely from peptone shock in one hour, while recovery is consumated in 20 minutes and in twelve to fifteen minutes from histamine and anaphylactic shock respectively.

The heart rate of anaphylactic shock stands apart but is somewhat more closely simulated by histamine than by peptone shock. The marked reduction of heart rate in anaphylaxis of the cat strengthens the evidence that the mechanism of this phenomenon is of nervous character.

Although histamine injection produces a profound drop of blood pressure in all laboratory animals, it does not cause a change in the coagulability of the blood. The results of our studies in the cat are in accord with these observations.

Thompson, Underhill, Manwaring, Simonds and numerous other investigators have pointed out the loss of blood coagulability following rapid peptone injection in the dog. Bally showed that the coagulation time of rabbit blood was increased following peptone injection.

Arthus, Pearce and Eisenbrey, Biedl and Kraus, Sherwood and Stoland as well as others have observed the loss of blood coagulability in canine anaphylaxis. However, the last named authors found that approximately 10% of the dogs which exhibited a drop in blood pressure did not show coagulability changes of the blood. Analogous observations have been reported of anaphylaxis in the rabbit by Bally. Likewise, the blood of anaphylactic guinea pigs is rendered less coagulable. Manwaring, and Edmuns have reported that the blood of anaphylactic cats had lost its ability to coagulate.

Weil[116] in 1917 suggested that the mechanism of blood coagulability changes in peptone and anaphylactic shock was the same. He thought that perhaps the liver was the responsible organ. Manwarings work on hepatic anaphylatoxins was based on the same principle. Howell[111] in 1925 from his experiments concluded, "when a peptone solution is injected into a dog intravenously it causes an output of heparin in the blood, thus explaining the incoagulability of the so-called peptone blood."

Haughey and Stoland[117] found that in canine anaphylaxis, "the inability of the blood to coagulate after a typical anaphylactic shock is due to an increase of heparin or heparin-like substance in the blood" and that, "following anaphylactic shock, the amount of heparin or heparin-like substance to be found in the blood seems to be roughly proportional to the severity of the shock." Thus the evidence points to the liver as the origin of blood coagulability changes.

We found only a moderate increase of coagulation time of feline peptone shock blood. This increase was present following only 36%

of the peptone injections. We observed no loss of blood coagulability in anaphylactic shock of the cat. However, the experimental shock was not severe as judged by the recovery time. It is shown then that the blood responses of the cat in anaphylactic and peptone shock are different from those of other experimental animals. This fact might suggest that the mechanism of feline shock is somewhat different from that of the dog, and that possibly the liver is not the principal organ involved in peptone and anaphylactic shock of the cat.

The reaction of the kidney volume in histamine shock is unique in that there is a fleeting increase of volume which is not observed in peptone and anaphylactic shock. The ultimate marked decrease in kidney volume is a constant observation in all.

In respect to changes of intestinal pressure, those of anaphylaxis assume an intermediate position, being almost exactly midway between histamine and peptone in the percentage of increased pressure exhibited.

The response of the bladder in anaphylaxis of the cat is very similar to that of peptone shock. Histamine alone demonstrates what appears to be a fairly consistent stimulatory action.

In the preceding physiological experiments and summary it is pointed out that histamine shock bears a somewhat closer resemblance to anaphylaxis in the cat than does peptone shock. However, the desensitization of the hypersensitive cat by the shock dose, the more pronounced reduction of heart rate together with the specific contractions of sensitized smooth muscle of the intestine and uterine horn make it improbable that anaphylaxis is the result of either

histamine or peptone action.

General Conclusions

From the results of the foregoing physiological studies the following conclusions were drawn.

1. That in the light of our results, it appears that the so-called anaphylactic phenomena in cats as reported by earlier investigators were exaggerated "Brodie Reactions".

2. That active sensitization does not occur in cats, or is so rare that it was not observed in the series of this study.

3. That this refractory characteristic noted in cats, cannot be attributed to faulty or inadequate absorption, lack of phagocytic action or the non-antigenic nature of the sensitizer employed.

4. That the refractory character of cats is due to an inability to generate sufficient antibodies, since only slight antibody formation was demonstrated following the injection of vastly different antigens such as sheep cells, crystalline egg albumin and suspensions of bacteria.

5. That the intravenous injection of as large amounts as 2 c.c. of 4% crystalline egg albumin per kilogram body weight does not induce the "Brodie Reaction" in cats.

6. That the crystalline egg albumin employed was antigenic as shown by its power to stimulate the production of readily demonstrable precipitins in rabbits, and to induce specific contractions of uterine horns from sensitized virgin guinea pigs.

7. That cats can be passively sensitized by injecting intra-peritoneally adequate amounts of high titered rabbit antisera.

8. That the anaphylactic responses of such passively sensitized cats are specific, and that the cats show complete desensitization upon reinjection of the specific antigen.

9. That the anaphylactic symptoms are principally the result of smooth muscle responses as shown by specific contractions of excised intestinal strips and uterine horns.

10. That the coagulation time of blood drawn from cats in anaphylactic shock is not prolonged. This observation is in direct contrast to those of dogs, rabbits, and guinea pigs in which the blood drawn from a high percentage of individuals in shock exhibits a prolongation of the clotting time.

11. That the symptoms of experimental anaphylaxis in the anesthetized cat are:

    i. Profound drop in blood pressure.

    ii. Marked decrease in heart rate.

    iii. Decided decrease in kidney volume.

    iv. Increase of intestinal pressure in the majority of animals.

    v. Specific contractions of excised smooth muscle such as intestinal strips and uterine horns.

    vi. Desensitization upon reinjection.

12. That the responses to histamine injection in the cat as previously reported have been confirmed with a single exception. The exception being that we have found a fleeting definite

increase of kidney volume, which is immediately replaced by a marked decrease of volume. Apparently this preliminary increase has previously escaped observation.

13. That the blood pressure response of the cat in peptone shock as previously reported has been confirmed. In addition a number of new responses have been described.

14. That several of the current theories as to the mechanism of anaphylactic shock hold that the symptoms of this phenomenon are due to the action of protein cleavage products such as peptone or histamine. From a critical comparison of our physiological results, we conclude: that the symptoms of anaphylactic shock in the cat, while being similar to the responses produced by the injection of peptone or histamine, cannot be attributed to the action of either of these substances.

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