EXPERIMENTAL INTRADERMAL PNEUMOCOCCUS INFECTION IN RABBITS.

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PLATES 1 AND 2.

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The work to be described in this paper is the outgrowth of an observation (1) made in this laboratory a few years ago to the effect that the intradermal inoculation of rabbits with Type I pneumococci produces a characteristic and gradually extending lesion which, representing a sort of "dermal pneumonia," permits direct observation of changes, progressive or healing, under various experimental conditions.

Preliminary experiments showed that this lesion and the various occurrences as nearly resemble the sequences in human lobar pneumonia as do those of any other experimental method (except possibly experimental pneumonia in monkeys). Furthermore, the advantages of a visible lesion and the reliability in its production have led us to believe the technic to be a valuable one.

The production in animals of lesions comparable to lobar pneumonia has been attempted by many investigators. Wadsworth (2) produced typical lobar pneumonia by introducing pneumococci into the respiratory passages of partially immunized rabbits. Many others have employed this technic and modifications of it but such methods are not altogether reliable. Stillman and Branch (3) have produced inhalation pneumonias in mice and rabbits, but these pneumonias are not lobar and the results are not regular. Bull and McKee (4) have produced pneumonias in rabbits by intranasal inoculation. Lobar pneumonia in monkeys, such as that studied by Blake and Cecil (5), has some of the same disadvantages as the rabbit pneumonia and the expense of animals precludes their routine use.

The status of the pneumonia problem has not been materially changed since it was reviewed (1) in 1925. Human pneumococcus

lobar pneumonia is regarded as a symptom-complex arising from a local infection, complicated in many cases by the entrance of bacteria into the blood stream. Symptoms described clinically as those of toxemia are produced, although the exact cause of this condition is not known and no convincing demonstration of a pneumococcus toxin has been given. The therapeutic use of antisera as now prepared, even in concentrated form, has not proven satisfactory unless employed early in the course of the disease.

We have undertaken to resurvey the subject of pneumococcic infection, using the intradermal rabbit lesion as a basis for experimentation. In this paper we purpose to describe the lesion in detail and give a preliminary report on certain experiments bearing on immunity and serum therapy.

Experimental Methods.

Pneumococcus Cultures.—The Type I pneumococcus used in these experiments was grown in beef heart hormone broth (pH 7.5) to which small amounts of sterile defibrinated rabbit blood had been added. The virulence of this strain for mice was such that 0.000,000,01 to 0.000,000,001 cc. of an 18 hour culture, given intraperitoneally, sufficed to kill within 96 hours. This virulence was usually checked for each new experiment, the tests being made at the time of infecting the rabbits.

Rabbits.—Healthy, light colored female rabbits of 1300 to 2000 gm. were selected. The entire abdominal area of each animal was shaved, care being taken not to injure the skin in any way. The size, sex, or breed of the rabbit is unimportant but it must be of healthy stock. Because of the large amount of technical work involved, the largest convenient number of rabbits for a single experiment is six.

Infection.—After taking the necessary normal readings, the rabbit is given an intradermal inoculation of 0.2 cc. of the desired dilution of 18 hour broth culture. The site of infection is well up on the side of the shaved area, 6–7 cm. lateral to the rabbit's ventral midline.

Observations.—At regular intervals the appearance of the focal skin lesion is described, particularly as to its extent, the color of the various parts, the amount of swelling and the location of the excessively swollen areas, the consistency of the exudate, the amount of wrinkling and contraction of the skin, and the changes in these features from time to time.

Blood Cultures.—Using an accurately graduated tuberculin syringe a definite amount of blood is withdrawn from the rabbit's marginal ear vein. This blood and dilutions of it are plated immediately in cooled hormone agar. Small quantities of fresh, sterile, defibrinated horse blood are added in the case of dilutions. Plate counts obtained in this fashion represent approximately the number of

aggregations of pneumococci per cc. of circulating blood and give a rather accurate comparison of the septic processes at various times in different individuals. If carefully carried out, an almost indefinite number of such blood samples may be taken from the same animal.

Blood Samples Other Than for Cultures.—Since it is important to leave the marginal ear veins intact for obtaining blood for cultures it is necessary to obtain blood samples for other purposes from the smaller vessels of the ear. An area is carefully shaved and cleaned, and a small amount of xylol applied to the tip of the ear. When sufficient dilatation has been brought about, one of the smaller vessels is severed with a sharp razor, gross tissue injury being avoided. The blood flowing from the wound is collected and the serum used for the determination of content of protective substances, agglutinins, precipitins, etc.

Lesion Cultures.—The presence of pneumococci in the primary lesion is determined by culturing fluid aspirated from it. A fine gauge needle is inserted at a point previously treated with alcohol and a small amount of fluid is aspirated into a syringe and transferred to a blood agar plate. Positive results are regarded as more significant than negative for late in the disease, when the animal has lost considerable weight, it is often difficult to obtain fluid from the lesion.

The Focal Lesion Arising after Intradermal Infection.

The lesion usually makes its first appearance at 8 to 12 hours as an inflamed, swollen area 1 cm. in diameter. It progresses ventrally until at 24 hours it occupies a strip 2–3 cm. wide extending from the point of inoculation to, and across, the midline. The area at the midline is especially swollen by the accumulation of serous or serofibrinous exudate. Any further progression is along the ventral midline and the entire midabdominal area may become involved. Fig. 1 shows a drawing of a lesion at 30 hours. In the following paragraphs a detailed description is given.

The time of appearance of the initial lesion is dependent upon the number of organisms injected. With the intradermal inoculation of about 0.001 cc. of an 18 hour broth culture, the injection bleb completely disappears within the first half hour. In 8–10 hours the blood vessels on the infected side show congestion, then in the immediate vicinity of the inoculation the congested vessels lose their sharp outlines and the skin over a 1–2 cm. area takes on a highly inflamed color and becomes swollen. As this development continues the edema is most prominent on the ventral border. The lesion then spreads ventrally, the heightened color being usually preceded by the accumulation of fluid. The amount of swelling and the actual or apparent movement of the serous exudate give the impression that a viscous, unorganized fluid is seeping or flowing ventrally from the force of gravity. At 14–16 hours the edematous area usually has extended to

the midline. More serous material accumulates in the subepidermal tissues until the entire area is puffy. At 24 hours the lesion usually has a width of not over 3 cm. (as measured along the midline) but in length it extends from the point of inoculation ventrally to the midline and passes this by 2–3 cm. Within the next 24 hours the lesion usually extends along the midline in both directions, although the zone of greatest swelling is still located at the midline ventral to the point of inoculation.

In untreated animals the color of the lesion varies from a pale to a moderately bright orange red. In treated animals the lesion becomes uniformly red after treatment and then the color fades completely.

Depending upon local trauma and upon factors affecting the cutaneous circulation, parts of the surface of the lesion may become necrotic. This necrosis is preceded by petechial hemorrhages, and the area then takes on a greenish hue. Seepage from such areas tends to deplete the total amount of fluid and in such cases secondary infection may occur.

TABLE I.

Distribution of Deaths by Days in a Series of Fifty-Six Untreated Cases.

	Day of death						Recovered
	2nd	3rd	4th	5th	6th	7th	
No. of rabbits	12	16	6	7	4	3	8
Percentage distribution	21.4	28.7	10.7	12.5	7.1	5.3	14.3

Within 30–40 hours, even in fatal infections, the skin contracts and folds, large with serofibrinous exudate, develop. The mechanism of this process of contraction probably represents the involvement of the underlying muscles. In one typical case the shaved area had an original length of 13 cm. At 24 hours after infection this was 8 cm., while by 48 hours it was only 5 cm. Owing to the shortening of the abdominal surface the rabbit usually assumes an abnormal posture, with the hind legs drawn up closely under the body.

There is no change in the local lesion before or at death, but with recovery a process of resolution is instituted which is characterized by epidermal desquamation and fading of color. In the course of several days the lesion then disappears completely, and except in the case of previous necrosis no scar remains.

The Disease Other Than in the Focus.

The development of the focal lesion is accompanied by an abrupt rise in temperature and this temperature persists at a high level until

death or recovery. Organisms enter the blood stream within 12 to 24 hours.

The majority of untreated animals die with severe pneumococcus bacteriemia, the distribution of deaths by days being shown in Table I. At autopsy virulent organisms are found in all parts of the body. Save for the skin lesion and a slight enlargement of the spleen there is no significant pathology.

About 14 per cent of untreated cases recover spontaneously on the 5th, 6th, or 7th days. This recovery is preceded by the disappearance of organisms except from the focal lesion and is associated with an abrupt fall in temperature, changes in circulating cellular elements, the appearance in the blood stream of "protective substances," and with changes in the local lesion.

The relationship of these various occurrences to each other is described below.

The Bacteriemia.

In most instances, shortly after the appearance of the local lesion, organisms may be detected in small number in the circulating blood. This number tends to increase so that at 24 hours the aggregations of pneumococci per cc. of circulating blood in the average animal is about 50. In exceptional cases the number is so high as to grossly distort any arithmetical average of the entire series. The number of circulating organisms tends to increase gradually; this rate is not in strict geometrical progression such as would be expected if the bacteria were multiplying in the blood stream. In the typical case the number increases up to a certain point (near 100,000 per cc.) that appears to constitute a lethal level. The time necessary for arriving at this level may be as short as 30 hours but it is more often 60 to 70 hours after infection. In some animals there occur fluctuations in the bacteriemia such that at times no organisms may be isolated. These individuals are apt to ultimately recover. If the lethal level has not been reached in the characteristic period, recovery is associated with or preceded by the disappearance of the organisms from the blood stream.

Charts showing the development of the bacteriemia will be found below.

The Temperature Reaction.

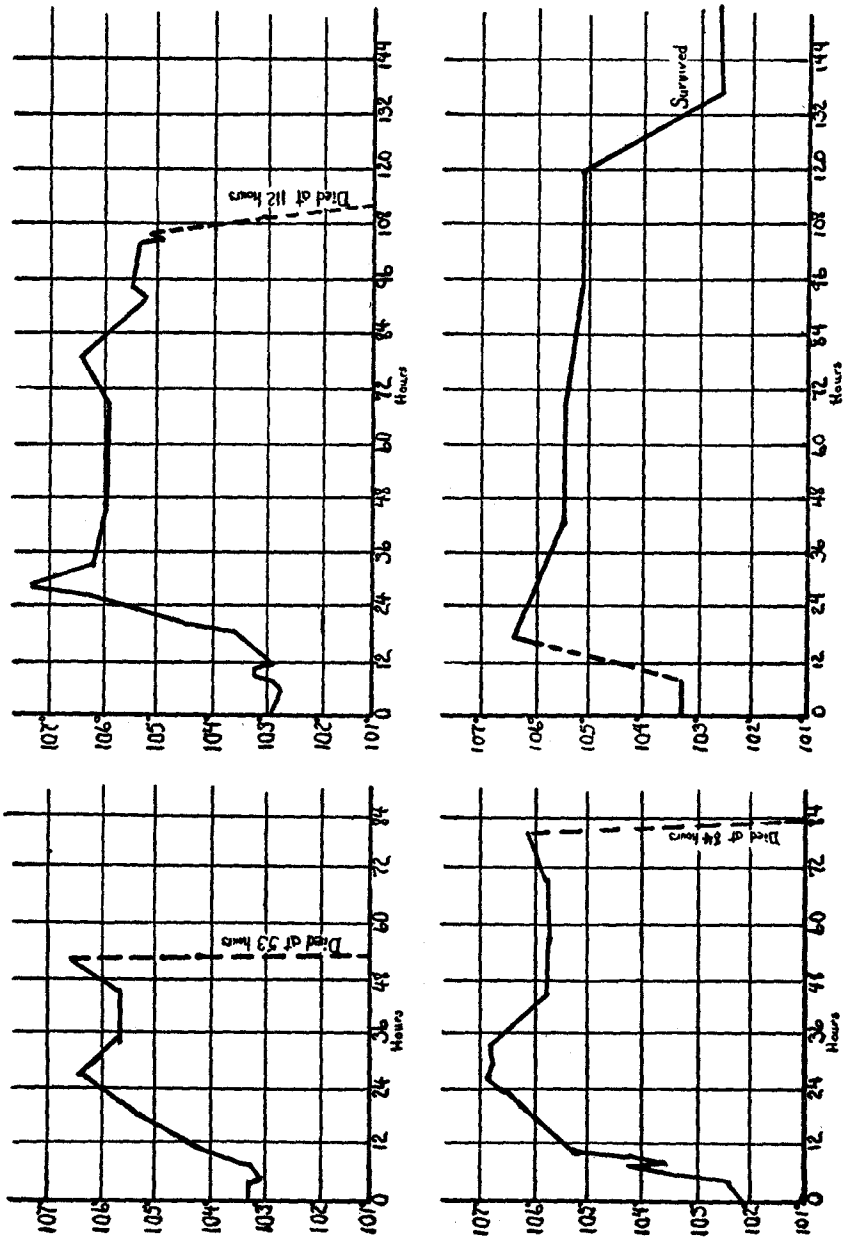
The temperature of the normal rabbit is variable and easily influenced by environment. In a series of 120 rabbits we find temperatures distributed over a range from 101.9° to 103.5°F., with an average of 102.8°F. The temperature of an acutely diseased rabbit undergoes less fluctuation due to environment and is of some significance when correlated with other data. Temperatures over 104.0°F. are regarded as definitely above normal levels.

At 5 to 12 hours after intradermal pneumococcus infection an animal's temperature begins to rise slowly and then abruptly goes up to a high level, usually over 105.5°F. The time occupied in this abrupt rise is ordinarily not over 4 hours. The third phrase is again one of slowly increasing temperature, a maximum being reached in 18 to 24 hours. This maximum ranges from 105.7° to 107.5°F. Then in spite of handling, the temperature remains at a high, though not stationary, level until death or the beginning of the recovery phase. In the case of death the temperature usually remains high until a few minutes before actual death.

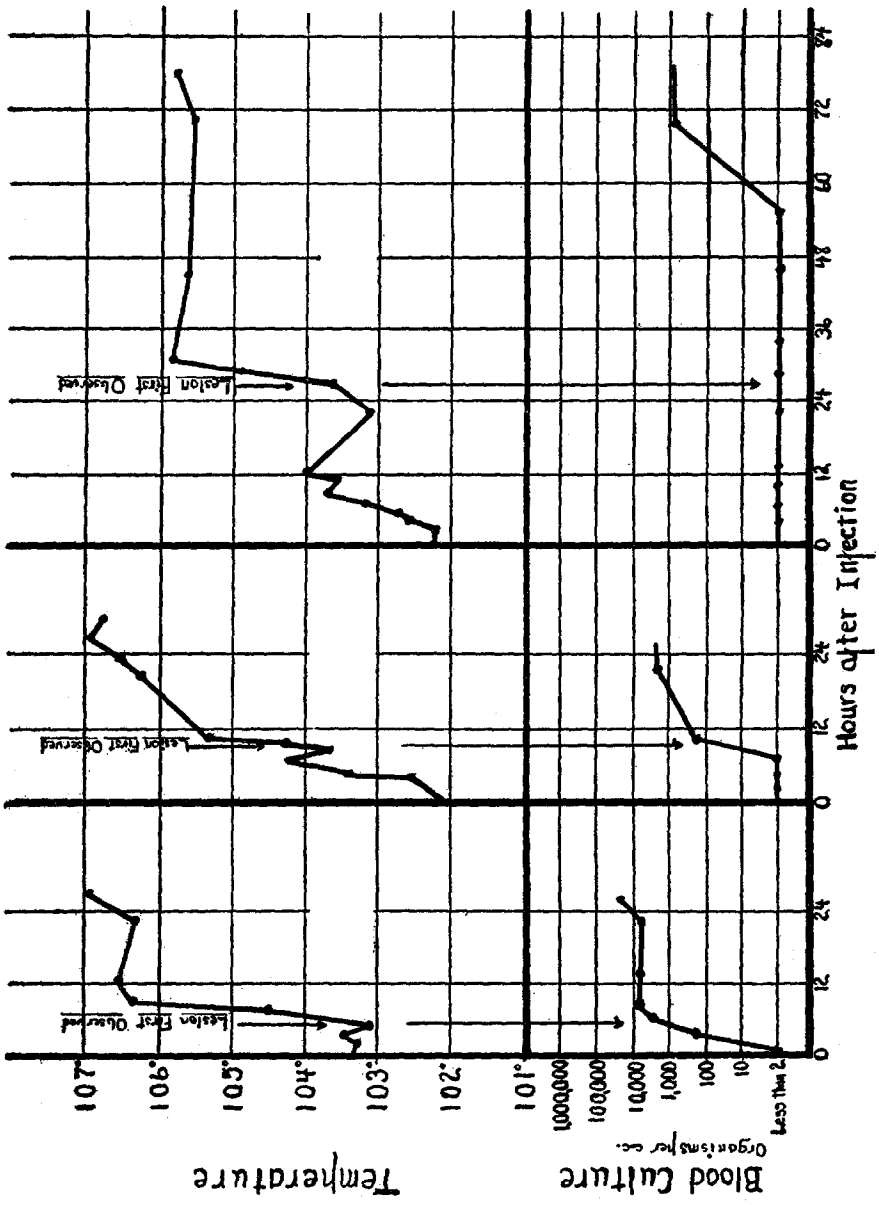
In the cases of rabbits which recover, the temperature persists at a high level for 5 to 7 days and then without warning drops to normal. This fall in temperature is rapid and is associated with other signs of recovery, in these respects not unlike what is spoken of as crisis in human pneumonia, another observation which persuades us of the close analogy of our rabbit disease with that of human pneumonia. As will be seen in a later section, again as in human disease, such a "crisis" is definitely correlated to the appearance of protective substances in the blood.

Text-fig. 1 shows charts of characteristic temperature curves in untreated cases.

It has long been believed that the temperature in lobar pneumonia is not related to the septicemia, but it seemed desirable to investigate this point in the experimental condition of the rabbit. An examination of records of a series of over fifty untreated cases shows that the temperature onset may occur (1) at the time when the organisms are first found in the blood stream, and more often this is the case; (2) it may occur as long as 36 hours before the beginning of the bacteriemia



TEXT-FIG. 1. Characteristic temperature curves in various rabbits, including one instance of survival without treatment. Infection in each case at 0 hour.



TEXT-FIG. 2. Temperature and bacteriemia determinations on three rabbits. These curves show the independence of the beginning of the bacteriemia and the onset of temperature These three cases reading from left to right represent maximal, average, and minimal intradermal dosage of pneumococci.

(as with minimal dosage); or (3) it may be delayed until several hours after the onset of septicemia (as with maximal dosage). Charts of examples of such findings are given in Text-fig. 2. The temperature onset is therefore independent of the bacteriemia.

From correlations of the appearance of the local lesion with the temperature it is apparent that the temperature rise always occurs exactly at the time that the local lesion is first observed.

The stimulus which brings about the continued febrile reaction is not easily determined. During this phase there are always living organisms in the local lesion, though not necessarily in the blood stream. The level of the temperature during this period is not proportional to the severity of the bacteriemia, nor is it proportional to the intensity of local inflammation, if the latter may be judged by color and edema. During this phase of high temperature the local lesion may undergo shrinkage or necrosis and it may become somewhat solid, but it never shows the cardinal signs associated with recovery: the appearance of surface desquamation and loss of inflammatory color.

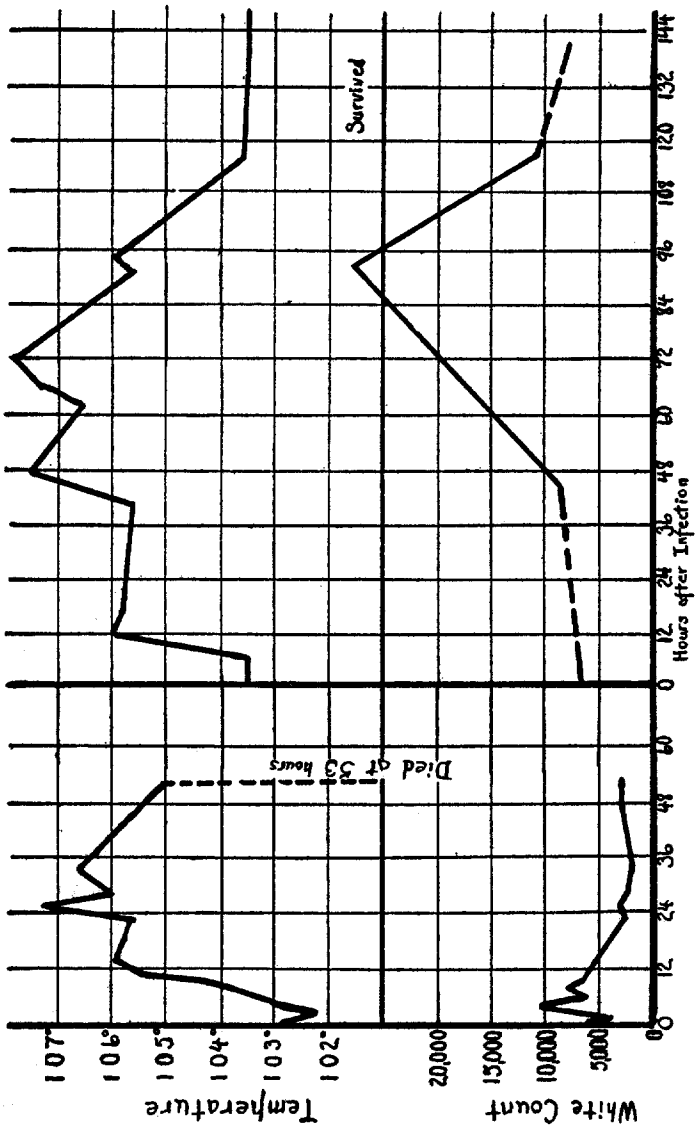
The sudden recovery, as marked by the fall in temperature, is not accompanied by the immediate disappearance of virulent organisms from the lesion, but in spite of this the lesion does show the above mentioned recessive signs.

In partially immunized rabbits, the detailed description of which will be found in a later paper, it is possible to give an intradermal injection of pneumococci and obtain a local inflammation. In this case of partial immunity there is little or no increase in temperature.

It seems therefore that the systemic effects indicated by temperature are not correlated with the presence of living organisms either in the blood stream or lesion but with the absorption from the focus, where living organisms are present, of something which either is no longer formed in the recovering or partially immune animal or which being formed is neutralized. We are led from this to believe that in the local lesion there is elaborated some toxic factor which in turn is responsible in large measure for the intensity of the general reaction.

The White Cell Count.

The white count on the rabbit is generally regarded as subject to great fluctuation. The average count in one series of fifty-four



TEXT-FIG. 3. Temperature and white count curves in two typical cases, one of which survived.

rabbits was 7280, but repeated counts on individual rabbits undergoing handling showed that it was difficult to establish a relative normal for any individual.

The first symptoms following intracutaneous infection are accompanied by a definite leucopenia, the decrease being accomplished largely by the disappearance of polymorphonuclear cells from the blood stream. In animals which recover, this leucopenia persists for 2 or 3 days and is followed by a definite leucocytosis, the number of white cells becoming normal again after the animal's recovery. In the case of animals which die during the course of the disease, the white count usually remains below normal throughout. The white count thus constitutes a definite prognostic sign, though it is by no means infallible. In Text-fig. 3 are shown examples of counts on each type of animal.

In many cases the number of white cells is roughly inversely proportional to the bacteriemia. With organisms circulating in the blood stream the white count is usually low but when the blood is freed of pneumococci the white cell count rises. There is some evidence to indicate that these inverse changes in white count do not accompany changes in the status of bacteriemia but occur only after such a change.

These findings are consistent with the favorable prognostic significance attributed in lobar pneumonia both to the absence of septicemia and to the high white count.

Lesion Cultures.

Cultures of fluids aspirated from the focal lesion in normal rabbits show large numbers of pneumococci during the active stages of the infection. Technical difficulties and late consolidation of the lesion sometimes prevent successful aspirations. At the time of recovery, as marked by various signs, there is a decrease in the number of organisms in the lesion, but virulent organisms may sometimes be isolated as long as a week and certainly for 1 or 2 days after crisis, which again is analogous to the presence of pneumococci in the lungs after crisis as demonstrated by Thomas and Parker (6).

Weight Loss.

One-fifth to one-fourth of the total body weight of the infected rabbit may be lost during the period of high temperature. A definite loss of at least 10 per cent has been an invariable finding. Some of this is undoubtedly due to the failure of the animal to take food but the emaciation initiated during the disease usually persists for several weeks after recovery, in spite of special diet and care.

Development of Protective Substances and Agglutinins.

The spontaneous recovery of untreated typical cases is associated with the appearance in the blood serum of protective substances. By this term we refer to that property of serum by which mice are passively protected against pneumococcic infection, provided that the serum is administered just prior to or at the time of infection. In such instances of critical recovery we have found that the precritical serum possesses no protective property but that serum which is immediately postcritical is protective against at least 0.1 cc. of highly virulent culture. This matter will be reported at greater length in a later paper and evidence will be presented to show that this point (immediately postcritical) may be the zone of greatest passive protective value of the serum.

Agglutinins and precipitins have never been detected in less than 2 days after recovery in the untreated animal. The agglutinins usually attain their highest titer at 12 to 18 days after infective inoculation (5 to 15 days after recovery).

The serum of convalescent rabbits is an effective therapeutic agent in the treatment of other cases. This will be reported on in detail in a later paper.

Pathological Examination.

At postmortem examination the skin at the point of greatest involvement is found to have a thickness varying from 12 to 18 mm., as contrasted to a normal thickness of 2 to 3 mm. On sectioning such a lesion one observes a subepidermal jelly-like mass from which straw colored fluid oozes. The skin at the point of original inoculation is usually slightly if at all thickened.

There is no constant gross pathology besides the skin lesion. In many cases there is a slight enlargement of the spleen but other organs are essentially negative. No perforations between lesion and peritoneum have been observed. It is possible to isolate virulent pneumococci from heart's blood, the serous cavities, and almost all tissues.

Microscopically, sections of the skin lesion show that the epidermis is not involved but that the corium is enormously swollen with serofibrinous material containing numerous cells. There is marked congestion of blood vessels and lymphatics. The subcutaneous connective tissues are usually swollen and here as well as in the muscle layers there is some cellular infiltration. In some cases there is a considerable atrophy of bundles of muscle fibers. Although fluid aspirated from the lesion during life reveals large numbers of diplococci, it is somewhat difficult to demonstrate these in sections. However it is certain that in the untreated lesion the organisms are extracellular. Fig. 2 shows a very low magnification of a cross-section of a pneumococcic skin. Fig. 3 represents a highly magnified detail from such a section. The character of the phlegmon is shown and in one portion there is an injected lymphatic.

The lungs are frequently congested but show no signs of pneumonitis. Virulent pneumococci may be isolated from the meninges post mortem but there is no meningitis.

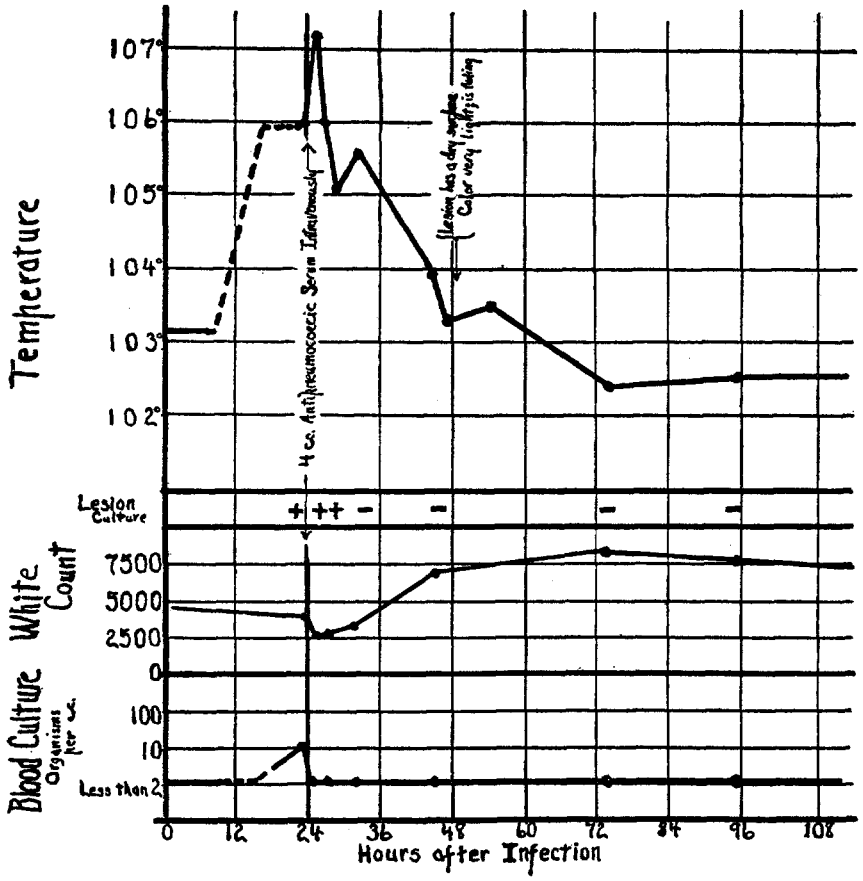
The Susceptibility of the Rabbit to Minimal Intradermal Infections.

It is generally recognized that the normal rabbit has no resistance against the pneumococcus but opinions differ as to quantitative infectivity: as to whether the necessary infective dose is a function of the weight of the animal, or of the number of virulent organisms in the culture employed.

We have found that the minimal quantity of culture necessary to infect mice intraperitoneally represents also the minimal quantity for intradermal infection of rabbits, that is to say, if a culture has a virulence for mice such that 0.000,000,1 cc. causes infection and death, the same amount constitutes the minimal intradermal dose for rabbits. This result is independent of the weight of the animal—that is, the necessary dosage is not the number of organisms per kilo of body weight but rather of organisms per individual rabbit. With smaller doses the onset of symptoms is delayed to such an extent that it is evident that the number of organisms must multiply *in vivo* to a certain level before an actual lesion is brought about. The disease resulting from a small dose, though delayed in first appearance, is in no way different from that caused by a larger infecting dose.

When undiluted virulent culture is injected intradermally there occurs as in other cases a definite latent period and then, perhaps 2 hours before the temperature rise and the actual appearance of the lesion, it is possible to isolate organisms from the blood stream. It

might be argued that the effective level was exceeded at the time of infection but that this did not hasten the termination of the latent period necessary for signs of local inflammation.

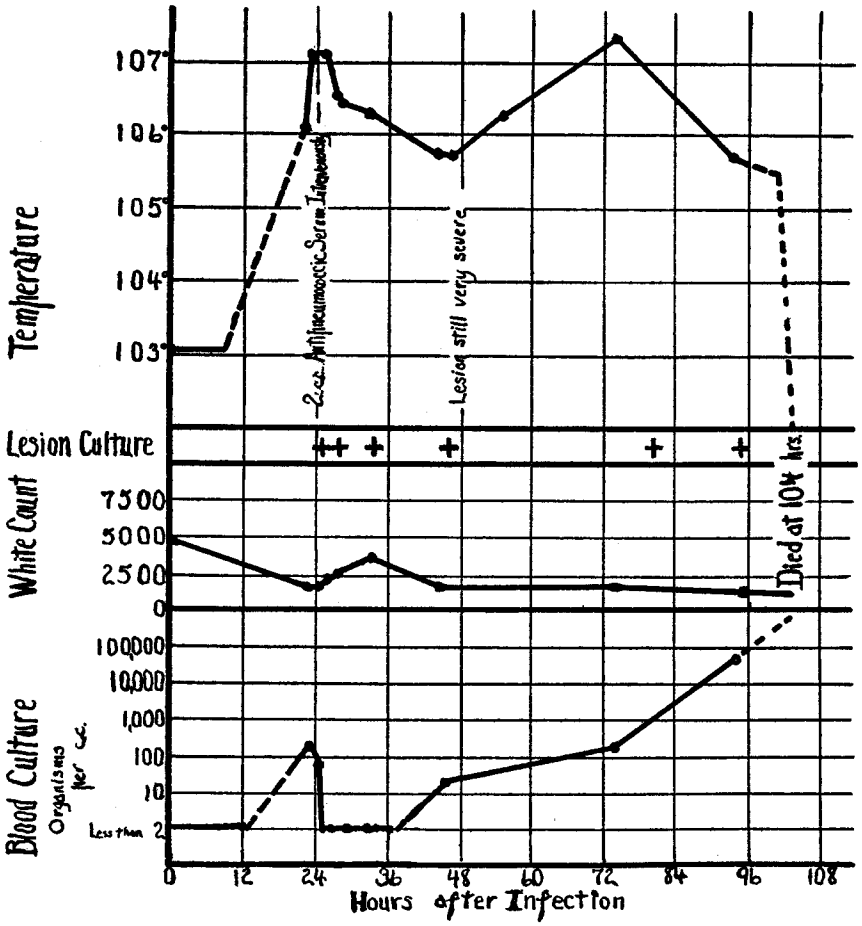


TEXT-FIG. 4. This chart shows the results obtained by treatment of a typical case with an amount of serum (4 cc.) which represents an excess over the M.E.D. (3 cc. for this serum). Weight of rabbit 1500 gm. Time of treatment, 24 hours.

Response of Infected Rabbits to Specific Serum Therapy.

Early in the course of this study, we began to experiment with various types of therapy. Since the intradermal infection of the rabbit represented a rather definite clinical symptom-complex, it was

reasoned that it might prove adaptable for (1) an analysis of the therapeutic action of specific sera, (2) for comparing the therapeutic values of various types of sera, and (3) for a method of standardization based on therapeutic value.



TEXT-FIG. 5. This chart shows the effect of treatment with an insufficient amount of serum. 2.0 cc. of a serum having a M.E.D. of 3.0 cc. were given at 24 hours. The only decided result is the temporary clearing of organisms from the blood stream.

We have not employed local therapy extensively, for, although antipneumococcic serum has a definite local protective effect in skin

areas in rabbits, it appears to have little influence if injected directly into an already active lesion.

Preliminary experiments demonstrated that prompt recovery could be brought about by the intravenous injection of a relatively large quantity of antipneumococcic serum provided that such injection be given early in the course of the disease. Further experiments were undertaken with the view of analysis of this therapeutic effect.

Text-fig. 4 shows the results obtained in a typical case by the intravenous injection at 24 hours following infection of a large amount (4 cc.) of antipneumococcic horse serum. The essential features of this therapeutic effect are: (1) the organisms immediately disappear from the blood and do not reappear, (2) the temperature begins to fall within a few hours and reaches a normal level within 24 hours, (3) organisms cannot be cultured from the local lesion after a period of a few hours following treatment, and (4) the skin lesion at first takes on a brighter color and then this color diminishes so that at 24 hours the area is very pale. At this time epidermal desquamation is also in evidence.

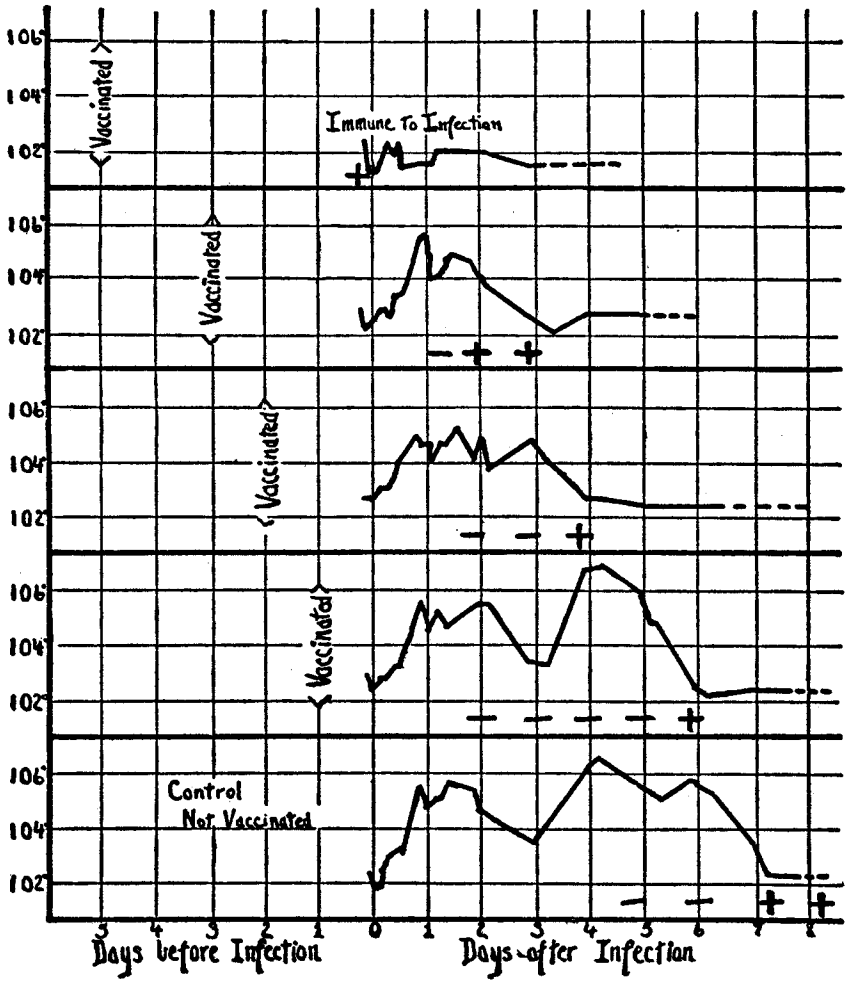
Experiments with a series of rabbits and graduated doses of serum show that beyond a certain point the excess of serum adds no value to that result which might be obtained with a definite minimum, this minimum being described as the minimal amount necessary to bring about the four decisive results given above. This definite value for any one serum is a relatively fixed quantity, other factors, such as time of treatment, being the same. This amount we designate as the minimal effective dose (M.E.D.).

If smaller amounts are administered it is found, depending upon the amount of serum, that there may be a temporary clearing of pneumococci from the blood stream but that this is not a permanent disappearance. In some instances (with doses that approach the M.E.D.) there may be a slight temporary depression of temperature and a considerable reduction in the bacterial content of the focal lesion. A chart of such a case is given in Text-fig. 5.

Observations on Active Immunization.

In the course of our work we have begun to apply this method of observation to the study of active immunization. While these studies

are being extended it is interesting in connection with the work reported above to note at this time the effects of a single injection of



TEXT-FIG. 6. Temperature charts on a series of five rabbits, four of which had been vaccinated at various intervals prior to infection intradermally at 0 hour. In each case at the time of crisis the usual recessive features were noted in the local lesion. + and − indicate presence and absence of protective substances.

dead pneumococci on the development of the local lesion, the course of the disease, and especially the development of the sudden drop of

temperature which we have spoken of as the "crisis." This is illustrated in an experiment the results of which are shown in Text-fig. 6.

Text-fig. 6 indicates: (1) animals vaccinated by one injection of dead pneumococci 5 days before infection develop neither lesion nor general disease and protective substances are present on the 5th day after vaccination, (2) animals vaccinated 3 days before develop a definite, but rapidly resolving lesion and recover by crisis, again on the 5th day after vaccination. The protective bodies appeared at this time, and (3) with each day by which the interval between vaccination and infection is shortened the recovery by crisis and production of protective bodies are prolonged by 1 day (in some cases slightly more than 1 day).

It appears therefore that one injection of vaccine is followed with regularity in 5 or 6 days by a condition of immunity sufficient either to prevent infection, or, if infection precedes the lapse of this period, to bring about recovery within approximately 5 or 6 days after the administration of the dead bacteria.

Inference from this in regard to the possible usefulness of vaccine administration to cases of influenza or measles or in the early stages of pneumonia are obvious but will necessitate further study.

DISCUSSION.

The detailed discussion of these findings must await the results of experiments now being undertaken.

The chief value of this experimental condition is that it offers in a suitable laboratory animal a symptom-complex which is in many respects analogous to human lobar pneumonia and has the additional advantages of a visible and easily produced lesion. With this condition it has been possible to correlate some of the features involved in the local lesion and such more generalized factors as the febrile reaction, the bacteriemia, changes in leucocyte count, the development of protective substances, etc. While many of these correlations might have been predicted from our knowledge of lobar pneumonia, it nevertheless furnishes additional evidence of the similarity of this "dermal pneumonia" to that of true pneumonia.

Of particular interest in this condition is the temperature reaction; its features are an abrupt onset, the high level maintained during the

course of the disease, and the abrupt or critical fall. It has been shown that the febrile reaction is not primarily a factor of the bacteriemia but possibly of some unknown substance elaborated and absorbed from the active local lesion. Evidence is presented to show that the temperature onset coincides with the first appearance of the local lesion and that this temperature persists for a rather definite period of time quite independently of changes in the status of bacteriemia.

It has been shown that the critical fall in temperature is associated with the appearance of protective substances. We do not know what part such substances have in the actual recovery for it is certain that they do not appear before or during the temperature fall but do appear in maximum titer immediately after crisis. Such a crisis is preceded by a disappearance of organisms from the blood stream but not necessarily by their disappearance from the local lesion.

Changes in white cell count indicate that the leucocytes play a passive part in the disease in an untreated animal and that the polymorphonuclear elements are low in number during bacteriemia and conversely. The white count constitutes a definite prognostic sign in this respect only.

With this method it is possible to analyse carefully the result of therapy and to compare the effects from various therapeutic agencies. We have reported our observations in cases treated with the ordinary antipneumococcic horse serum. The study of passive immunization is being continued and we are now developing in detail a method for standardization of the therapeutic properties of serum, based on the observation as to the minimal effective dose for any one serum. It is hoped that such a method may offer a more satisfactory basis for measurement of therapeutic value than the present mouse protection titration.

SUMMARY.

1. The intradermal inoculation of rabbits with Type I pneumococci gives rise to a local lesion and a definite sequence of other events that offer many analogies to pneumococcus lobar pneumonia, and for this reason the condition is being employed for a resurvey of the subject of pneumococcic infection.

2. This symptom-complex has been described in detail particularly as to the development of the local lesion, the temperature reaction, the bacteriemia, the white count, the persistence of organisms in the lesion, and the development of protective substances.

3. A certain number of animals recover from this condition after a definite course and by a process spoken of as crisis. The events correlated with this crisis have been described.

4. If sufficient antipneumococcic serum is given intravenously at 24 hours, prompt recovery can be brought about. The essential points of this recovery have been established.

5. Within 5 days after a single vaccination with dead pneumococci the normal rabbit develops an immunity to infection. If the rabbit is vaccinated and then infected within the period necessary for the development of this immunity the course of the consequent disease is shortened in proportion to the interval between vaccination and infection.

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EXPLANATION OF PLATES.

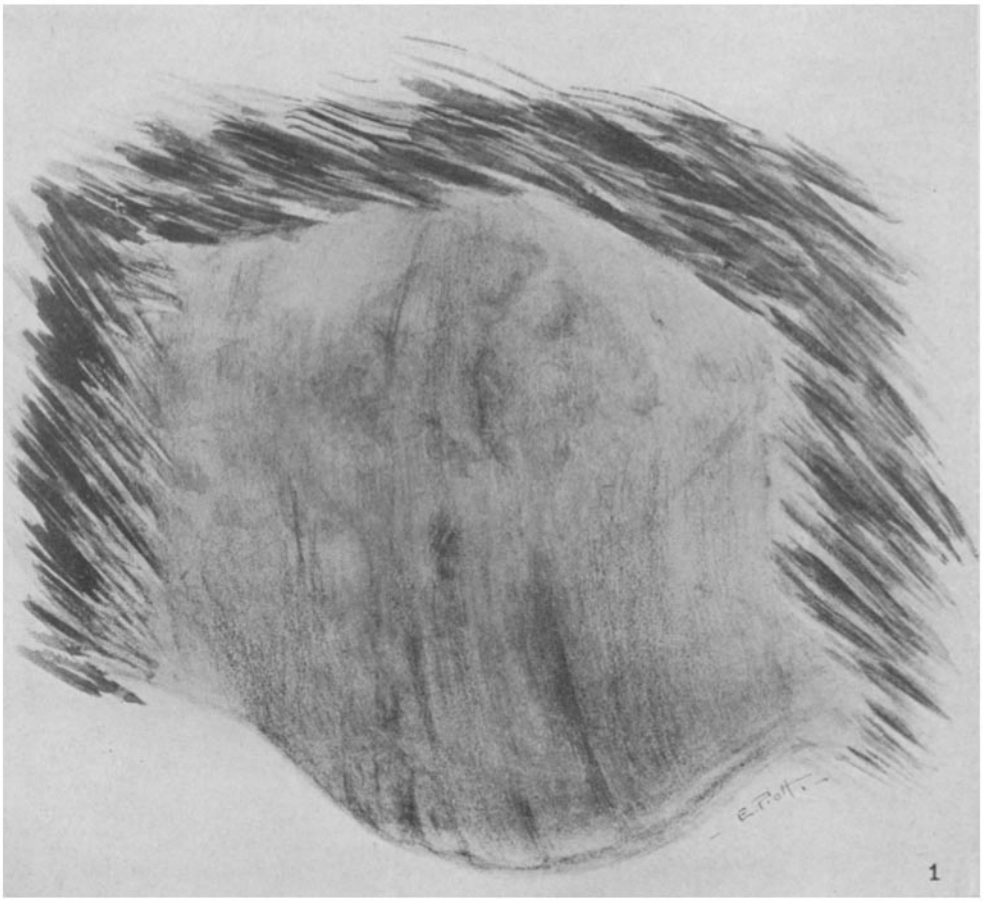
PLATE 1.

FIG. 1. Drawing of a characteristic lesion at 30 hours following intradermal infection.

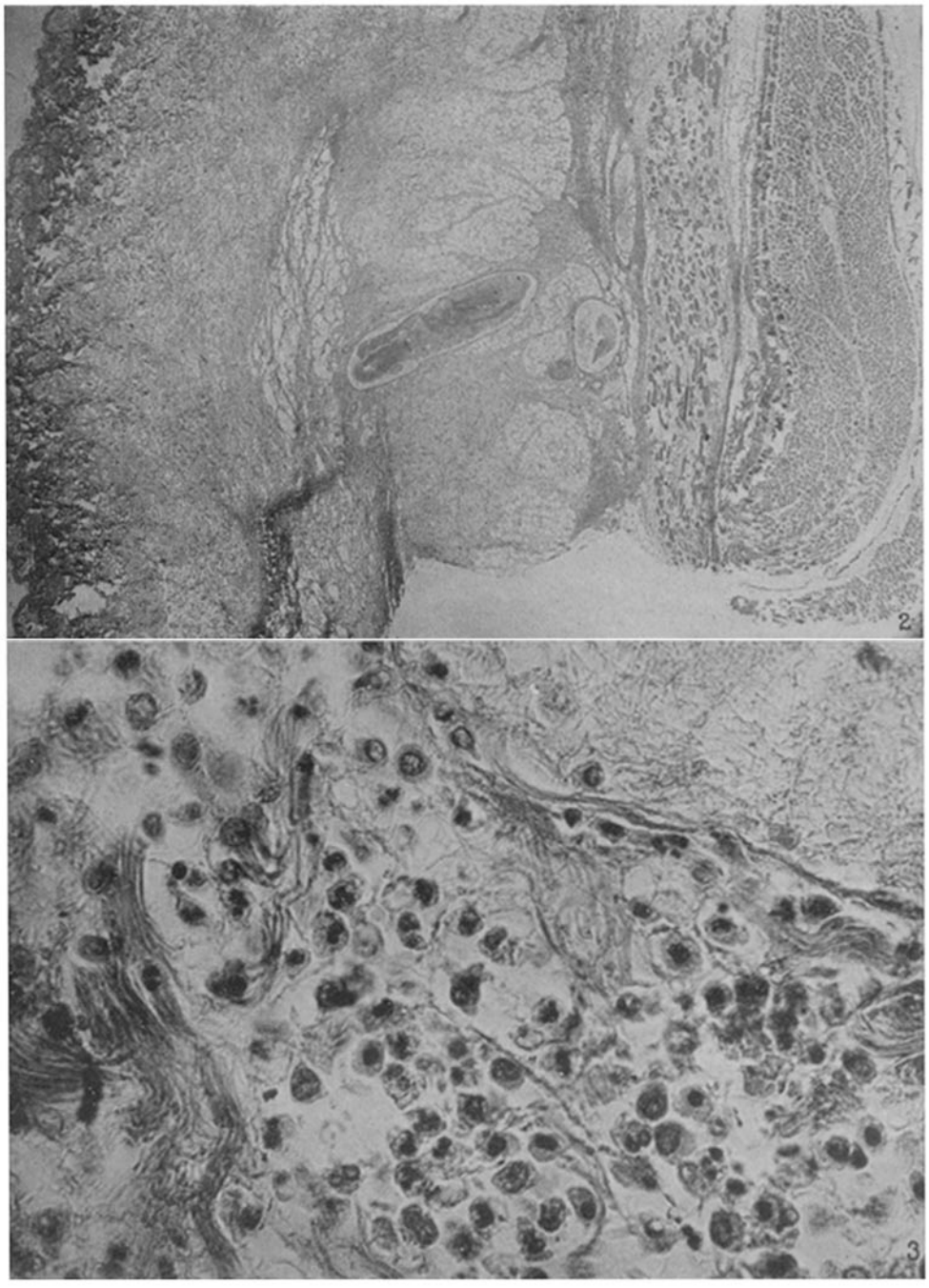
PLATE 2.

FIG. 2. A photograph of a cross-section of pneumococcic rabbit skin; low magnification. The original cross-dimension of this skin was 13.5 mm.

FIG. 3. Highly magnified detail of the section shown in Fig. 2. The structure of the phlegmon is shown, and at the upper right there is an injected lymphatic.



(Goodner: Intradermal pneumococcus infection.)



(Goodner: Intradermal pneumococcus infection.)