

mechanical effect, its velocity depending on the extensibility of the vessels as modified by any condition (muscular or otherwise) obtaining at the moment.

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On a Remarkable Bacteriolytic Element found in Tissues and Secretions.

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[PLATE 9.]

In this communication I wish to draw attention to a substance present in the tissues and secretions of the body, which is capable of rapidly dissolving certain bacteria. As this substance has properties akin to those of ferments I have called it a "Lysozyme," and shall refer to it by this name throughout the communication.

The lysozyme was first noticed during some investigations made on a patient suffering from acute coryza. The nasal secretion of this patient was cultivated daily on blood agar plates, and for the first three days of the infection there was no growth, with the exception of an occasional staphylococcus colony. The culture made from the nasal mucus on the fourth day showed in 24 hours a large number of small colonies which, on examination, proved to be large gram-positive cocci arranged irregularly but with a tendency to diplococcal and tetrad formation. It is necessary to give here a very brief description of this microbe as with it most of the experiments described below were done, and it was with it that the phenomena to be described were best manifested. The microbe has not been exactly identified, but for purposes of this communication it may be alluded to as the *Micrococcus lysodeikticus*.

The fully developed colony of the coccus may be 2 or 3 mm. in diameter; it is round, opaque, raised, and has a bright lemon yellow colour; it grows luxuriantly on all the ordinary culture media, and growth takes place well at room temperature, or in the incubator at 37° C.; it is aerobic and facultatively anaerobic; it does not liquefy gelatin or coagulated albumin.

PRELIMINARY EXPERIMENTS SHOWING THE ACTION OF THE LYSOZYME.

In the first experiment nasal mucus from the patient, with coryza, was shaken up with five times its volume of normal salt solution, and the mixture was centrifuged. A drop of the clear supernatant fluid was placed on an agar plate, which had previously been thickly planted with *M. lysodeikticus*, and the plate was incubated at 37° C. for 24 hours, when it showed a copious growth of the coccus, except in the region where the nasal mucus had been placed. Here there was complete inhibition of growth, and this inhibition extended for a distance of about 1 cm. beyond the limits of the mucus.

This striking result led to further investigations, and it was noticed that one drop of the diluted nasal mucus added to 1 c.c. of a thick suspension of the cocci caused their complete disappearance in a few minutes at 37° C.

These two preliminary experiments clearly demonstrate the very powerful inhibitory and lytic action which the nasal mucus has upon the *M. lysodeikticus*. It will be shown later that this power is shared by most of the tissues and secretions of the human body, by the tissues of other animals, by vegetable tissues, and, to a very marked degree, by egg white.

FURTHER OBSERVATIONS ON THE EFFECT OF THE LYSOZYME ON BACTERIA.

1. *Inhibitory Action.*

In the preliminary experiments it has been shown that on the surface of an agar plate the growth of the nasal coccus is completely inhibited by super-added nasal mucus. This inhibitory action can be strikingly demonstrated in another manner.

A small portion of the agar is removed from an ordinary agar plate making a cup into which some material rich in lysozyme (tears, nasal mucus, sputum, cartilage, egg white, etc.) is placed. A drop of liquid agar, at a temperature of about 50° C., is placed on the material in the cup and is allowed to solidify after which the cup is filled with the liquid agar which, in its turn, is allowed to set. Liquid agar is then poured all over the plate to make a thin layer over the original surface. The whole surface of the medium is now thickly planted with the *M. lysodeikticus* and the plate is incubated for 24 hours, when it will be seen that there is copious growth of the coccus, except in the

region of the implanted material. By the method of preparation of the plate, in which the material is covered with several distinct layers of agar, there can be no mechanical transference of the material to the surface of the plate, but the experiment shows that the inhibitory substance is able to penetrate the agar and absolutely prevent growth of the coccus for a distance of about 1 cm. Further, if the plate is kept for a few days, it is found that portions of the growth next to the inhibition zone have become almost transparent, and it is evident that the lytic substance has continued to diffuse through the agar after the microbes have completed their growth, and has dissolved the cocci for a distance of 3 or 4 mm. The area of inhibition and the partially dissolved zone of growth are shown in Plate 9, fig. 1, which is a photograph of a plate in which was imbedded 10 c.mm. of tears.

2. *Bactericidal Action.*

If cultures are made from the inhibition zone of a plate, such as has been described in the last experiment, no growth results, showing that the bacteria implanted on this surface has been destroyed. It can also be shown that if lysozyme-containing material be added to a suspension of *M. lysodeikticus* in a test-tube these cocci are destroyed, so that cultures made from the tube remain sterile. In one experiment a suspension of *M. lysodeikticus*, of a strength of not less than 1,000 million per cubic centimetre, was exposed to the action of 1 in 100 nasal mucus and 10 c.mm. volumes were planted out after incubation for 1, 2, 5, 10, and 60 minutes. It was found that the cultures remained sterile while similar cultures made at the same time from a control tube in which the nasal mucus was replaced by normal salt solution, gave copious growth up to the end of the experiment, namely, 1 hour's incubation.

It was found that after 2 hours' incubation tears diluted 9,000 times with normal salt solution killed the whole of the cocci in a thick suspension of the *M. lysodeikticus*. In the dilutions of tears from 1 in 27,000 to 1 in 243,000 there was a very marked bactericidal power manifest.

The bactericidal action of the lysozyme may also be shown with microbes other than the nasal coccus. An example of this is illustrated in fig. 2, which is a photograph of a culture made after incubating a faecal streptococcus for 2 hours at 45° C., with tears diluted in 1 in 100 and with normal saline solution. It will be seen that from the saline tube there resulted a continuous sheet of growth, whereas, from the tube containing the tears, there were only scattered colonies, showing that the vast majority of the streptococci had been destroyed by the tears.

A similar result was obtained by acting on *Streptococcus faecalis* with the inflammatory exudation into a joint cavity.

Lytic Action.

Naked-eye Changes.—In the second of the preliminary experiments, it was shown that, if a drop of nasal mucus be added to a thick suspension of the *Micrococcus lysodeikticus* in a test-tube, there is, after a short period of incubation, a complete clearing of the opaque suspension, so that the fluid becomes perfectly clear to the naked eye. It has been noted also that other tissues and secretions have the same action. If the material used is rich in lysozyme, the action is a very rapid one. Thus, at a temperature of 45° C., a 1 in 100 dilution of tears will completely clear the suspension in about 30 seconds, or a 1 in 5 dilution of egg white in 10 seconds.

If the bacterial suspension is a very thick one, there is easily to be observed a considerable increase in the viscosity of the fluid after lysis of the bacteria has been completed, evidenced by the fact that, if the tube is shaken, the air bubbles rise much more slowly to the surface of the fluid.

The lytic action can be strikingly demonstrated by placing on the surface of a fully-grown plate culture of *M. lysodeikticus* a drop of tears, nasal mucus, or other material rich in lysozyme. In less than 1 minute at 37° C., or in about 10 minutes at room temperature, that portion of the culture on which the material was placed will have been completely dissolved, producing a clear space just as if a portion of the culture had been mechanically removed.

Microscopic Changes.—When a mixture of tears and *M. lysodeikticus* is observed with dark ground illumination, it is seen that the cocci rapidly lose their sharp outlines, become swollen and gradually disappear. At the same time, there appear a very large number of minute granules, somewhat similar in appearance to the granules of a polynuclear leucocyte.

Examined with transmitted light, it is seen that the cocci rapidly swell up and become transparent, so that, after 2 minutes at room temperature (when the cocci are suspended in undiluted tears), they become quite invisible.

When the partially dissolved cocci are examined by Burri's method, they are found to be much swollen up, and they are less indistinct, probably owing to some of the opaque material used to produce the dark background adhering to their glutinous surface (see fig. 3).

If a similar specimen is coloured with one of the ordinary bacterial stains, the stainable material is found to have diminished in size, giving the appearance of small and very irregular cocci. When the lytic action is complete, staining fails to reveal any trace of the cocci.

OBSERVATIONS ON THE PROPERTIES OF THE LYSOZYME AND ON THE
CONDITIONS GOVERNING ITS ACTION.

The lysozyme is soluble in water or normal salt solution; it is insoluble in chloroform, ether or toluol, and, as these substances do not destroy it or inhibit its action, they have been used to preserve lysozyme-containing material such as sputum for test purposes; it retains its potency undiminished after standing at room temperature for several weeks. That lysozyme of egg white is not destroyed by desiccation, and that in the dried state it can be preserved for long periods, is shown by the fact that it is present in large amounts in commercial dried egg albumin.

From albuminous fluids, protein precipitants such as alcohol, acetone, or picric acid, precipitate the whole of the lysozyme with the proteids.

Its action takes place most rapidly when a small amount of salt is present in the fluid (under 0.1 per cent.), and ceases when more than 5 per cent. of salt is present. It acts both on living microbes and on those which have been killed with heat.

Influence of the Reaction of the Fluid.

It was found that when one drop of sputum extract and one drop of a thick suspension of *M. lysodeiکتicus* were added to 1 c.c. of various dilutions of hydrochloric acid or caustic soda, the lytic action was, to some extent, delayed in the tubes containing as little as 1/8,000 normal acid or 1/24,000 normal alkali, and there was complete inhibition of lysis in the tubes containing 1/800 normal acid or alkali. These figures are not strictly accurate, as alkali-free glass was not used, but they clearly indicate that the lysozyme is very sensitive to minute traces of acid or alkali.

Resistance of the Lysozyme to Heat.

Sputum extract, nasal mucus, saliva and subcutaneous fatty tissue, heated for 10 minutes at 60° C., had lost but little of their lytic power for bacteria, but 5 minutes' heat at 75° C. destroyed almost all the lysozyme. Tears, diluted 500 times with normal saline solution, were heated for 10 minutes at 75° C., and the lysozyme-content was reduced to one quarter. After boiling this dilution of tears for 30 minutes, traces of lysozyme remained active, but boiling for 1 hour apparently completely destroyed it.

In saliva, the resistance to heat of the lysozyme and of ptyalin was compared. A specimen of saliva was heated to 75° C., and specimens were taken at intervals of 1 minute, and their lysozyme and ptyalin-content were compared. It was found that these two substances disappeared from the saliva at the same time, namely, after heating for 7½ minutes.

Influence of Temperature on the Velocity of Lysozymic Action.

The lytic action takes place slowly in the ice chest and the velocity increases up to 60° C. after which it becomes slower again, probably owing to the destruction of some of the lysozyme.

If lysozyme containing material, however, is left in contact with the *Micrococcus lysodeikticus* for 24 hours the cocci are dissolved in the same dilution of the lysozyme whether the reaction takes place at room temperature, 37° C., or 50° C.

Does the Lysozyme pass through Membranes or Filters?

1. *Collodion*.—One c.c. of a saline extract of sputum was placed in a collodion sac and this was suspended in a tube containing a thick suspension of *M. lysodeikticus* and incubated for 6 hours. No lysis of the cocci took place. The sac was then punctured and the contents allowed to mix with the bacteria when complete lysis occurred within 2 minutes, showing that the sputum extract contained lysozyme, which, however, had been unable to pass through a collodion membrane.

2. *Porcelain Filter*.—Fifty c.c. of a 1 in 1,000 dilution of tears were passed through a Berkfeld filter and it was found that the filtrate was devoid of lysozyme action. As it might have been possible that some inhibitory substance (e.g., acid or alkali) had been absorbed from the filter and passed into the filtrate a small quantity of the unfiltered tears was added to the tubes containing the filtrate and the cocci when lysis promptly occurred showing that the lysozyme had actually been retained on the filter and that the absence of lysis when the filtrate and cocci were mixed, was not due to the presence of any inhibitory substance.

It was impossible to obtain human secretions, rich in lysozyme, in sufficient quantity to filter them in a strong concentration through the porcelain filters available. Egg white, however, which is very rich in lysozyme, was used for this purpose in a dilution of 1 in 10 in normal saline solution. The filtrate was collected in separate portions of about 1 c.c., and each portion was tested for the presence of lysozyme. The first 19 c.c. which passed through the filter had no lytic action on *M. lysodeikticus* but after that the lysozyme passed through and in the 30th c.c. the strength of the filtrate was practically the same as that of the unfiltered material.

These experiments show that a porcelain filter is capable of absorbing a considerable quantity of lysozyme, but when that has been absorbed the filter offers no barrier to the passage of this substance. We shall see that the same thing happens with filters of cotton wool and filter paper.

Cotton Wool.—This was tested by two methods which the author had previously used to demonstrate the gossypiotropic properties of certain aniline dyes.

The first method consists in pushing slowly to the bottom of the test-tube containing a column of about 2 inches of a lysozyme-containing material a tight plug of cotton-wool, so that the fluid percolates through the cotton-wool and collects above it. Using tears diluted 1 in 1,000 (this sample of tears showed lysis up to a dilution of 1 in 5,000,000) it was found that when this experiment was carried out the whole of the lysozyme was removed by the cotton-wool.

In the second method a tight plug of cotton-wool was introduced into a narrow tube, 1 c.c. of tears (1 in 1,000) placed above this, and with pressure exerted with a rubber teat the fluid was driven through the cotton-wool. Successive volumes of 1 c.c. were driven in this way through the cotton-wool and these were separately tested for the presence of lysozyme. It was found that a tight plug of cotton-wool 1 cm. long introduced into a piece of 6-mm. tubing absorbed the whole of the lysozyme from 12 c.c. of a 1 in 1000 dilution of tears. Further volumes of the diluted tears passed through this cotton-wool plug all contained lysozyme.

Filter Paper.—This was tested in the same way as cotton-wool and with the same results. Passage through about 0.5 cm. of compressed filter paper in 6-mm. tubing removed the whole of the lysozyme from 10 c.c. of a a thousand-fold dilution of tears.

Is the Lysozyme Removed from Solution with Substances such as Charcoal?

It was found that when a small quantity of blood charcoal was added to a thousand-fold dilution of tears and after 2 hours on the bench the mixture was centrifuged, the clear supernatant fluid contained no lysozyme. It was shown that no inhibitory substance had been absorbed into the fluid from the charcoal because, after the supernatant fluid had failed to cause lysis of the cocci, a small quantity of the diluted tears was introduced, when lysis promptly occurred. It is evident, therefore, that charcoal removed the lysozyme from the fluid.

Distribution of the Lysozyme in the Body.

In the first experiments it was found that nasal mucus contained a large amount of lysozyme, and it was later found that tears and sputum were very potent in their lytic action. It was also found that this property was possessed by a very large number of the tissues and organs of the body. The lysozyme-content of the tissues was investigated by placing small portions of tissue not larger than a split pea in tubes containing 1 c.c. of a thick suspen-

sion of the *M. lysodeikticus* incubating the tubes at 45° C., and noting whether any lysis took place as evidenced by a clearing of the opacity of the suspension. Some of these tissues were obtained from the postmortem room, others from laboratory workers or from the operating theatre. The results obtained can be summed up by saying that all the tissues and organs possessed some lytic power, even a few hairs from the head causing solution of the cocci. While in these tests no attempt was made at an exact quantitative estimation, it was noticed that lysis proceeded very much more rapidly with some tissues than with others. Briefly, it may be said that epidermal structures, the lining membrane of the respiratory tract and especially the connective tissues (whether fibrous, fatty or cartilaginous) contained large amounts of lysozyme affecting *M. lysodeikticus*. The rapidity of the lysis with cartilage was so striking that an attempt was made to estimate more accurately the amount of lysozyme in this tissue. A small portion of cartilage from the patella (deep to the articular surface) was weighed and ground up in a mortar with a measured volume of salt solution. This was allowed to extract for 6 hours when it was centrifuged and the supernatant fluid was added in various dilutions to a suspension of the *M. lysodeikticus*. It was found that with an extract corresponding to one part of the original cartilage in 1,300 parts of normal salt solution, there was complete lysis of the cocci in 5 minutes at 45° C. which shows that cartilage has approximately one-tenth the lysozyme-content of tears.

The presence of lysozyme was sought for in certain physiological and pathological fluids, and the results are set forth in Table I.

Table I.

Fluids containing lysozyme.	Fluids not containing lysozyme.
Tears. Sputum. Nasal mucus. Saliva. Blood serum. Blood plasma. Peritoneal fluid. Pleural effusion. Hydrocœle fluid. Ovarian cyst fluid. Sebum. Pus from acne pustule. Sero pus from a "cold" abscess in the popliteal space. Urine containing much albumin and pus. Semen (very weak).	Normal urine. Cerebro-spinal fluid. Sweat (one sample only tested.)

In connection with the lysozyme-content of the blood, it is to be noted that, in addition to its being present in the leucocytes, in the plasma, and in the serum, it is also present in rather large amount in the fibrin of the blood clot. It is conceivable that this is a protective mechanism for open wounds, which rapidly become covered with a layer of fibrin and leucocytes, both of which are rich in lysozyme.

The lysozyme-content of tears, sputum, nasal mucus, saliva, and blood serum of the same individual were tested. The specimens were all collected at the same time and were tested about 4 hours afterwards. The titrations were carried out by making serial dilutions of the various fluids and adding to these dilutions a measured quantity of a thick suspension of *M. lysodeikticus*, after which the tubes were incubated at 45° C., and readings were made at intervals of 15, 30, and 60 minutes. The results are set out in Table II:—

Table II.—The Lysozyme-Content of various Fluids taken from the same Individual at the same Time.

Material examined.	Time of incubation at 45° C.	Dilution of fluid, 1 in:—						
		10	30	90	270	810	2430	
Blood serum.....	mins.							
	15	+	+	±	0	0	0	
	30	+	+	+	±	trace	0	
	60	+	+	+	+	±	0	
Saliva		100	300	900	2,700			
	15	+	±	0	0			
	30	+	+	±	0			
	60	+	+	±	0			
Nasal mucus.....		500	1,500	4,500	13,500	40,500	121,500	
	15	+	+	+	±	±	0	
	30	+	+	+	+	±	0	
	60	+	+	+	+	±	0	
Sputum	15	+	+	+	±	±	0	
	30	+	+	+	+	±	0	
	60	+	+	+	+	±	0	
Tears	15	+	+	+	+	0	0	
	30	+	+	+	+	±	0	
	60	+	+	+	+	+	±	

+ signifies complete clearing of the fluid.

± „ partial „ „

0 „ no „ „

It will be seen from the above Table that tears, sputum, and nasal mucus are very rich in lysozyme to the *M. lysodeikticus*, while saliva and blood serum are relatively weak. Fluids from a number of different individuals have

been tested and the relative amounts of lysozyme contained in these have been found to be comparatively constant, except in the case of saliva, which seems to vary considerably, although it never approaches in lysozyme-content tears, sputum, or nasal mucus.

The Question as to whether Lysozyme exists in Tissues other than Human Tissues.

Only a limited amount of work has been done in this direction, but it is sufficient to show that lysozyme is very widespread in nature. Rabbit and guinea-pig tissues were examined and it was found that nearly all of these contained some lysozyme for the *M. lysodeikticus*, but in general the lysis was not nearly so marked as it was with the corresponding human tissues. It may be noted that the lachrymal secretion of both these animals contained no lysozyme for the *M. lysodeikticus*, against which the human tears are so powerful. The tissues of a dog were much more lytic than those of the rabbit and guinea-pig, but even they were not so active as human tissues.

It was found that egg-white was very rich in lysozyme for the *M. lysodeikticus*, there being, after incubation for 24 hours, lysis visible to the naked eye when a dilution as great as 1 in 50,000,000 was employed. Egg-white also contains lytic substances for many other bacteria. It was found also that commercial dried egg albumin was very rich in lysozyme.

In the vegetable kingdom it was found that turnip had a very definite, though not very strong lytic action on *M. lysodeikticus*. Several of the other common table vegetables were tested, but they appeared to be devoid of lytic activity.

Does the Lysozyme act on Bacteria other than the M. lysodeikticus?

In the investigation of this problem the method adopted was to make a suspension of the bacteria of such a strength that it gave a very decided opacity when diluted with an equal amount of saline; $\frac{1}{2}$ c.c. of this suspension was mixed with the same quantity of a 1-in-50 sputum extract or a dilution of tears from 1 in 100 to 1 in 1,000. As a control, a twofold dilution of the original suspension was made with normal salt solution. The tubes were incubated at 45° C. and observations were made at intervals up to 24 hours, the opacity of the tube containing sputum or tears being compared with that of the control tube.

Three groups of microbes were tested: the first group consisted of 104 strains of bacteria derived from the air of the laboratory, and of these 75 per cent. were dissolved, more or less readily, by a 1 in 100 dilution of sputum. These air-borne bacteria consisted mainly of cocci of various sorts, but there were also bacilli, yeasts, and two species of mould.

The second group consisted of a series of cultures of bacilli which are pathogenic for some animals, but not, so far as is known, for man. These were kindly supplied by Dr. St. John Brooks from the National Collection. They were tested with tears (1 in 100) and nasal mucus (1 in 100), in addition to the sputum extract, and seven out of eight cultures showed some lysis after incubation with one or other of these fluids. These cultures included *B. abortus* of Bang, and *B. pseudotuberculosis* rodentium, to both of which there was some lytic power and which will be referred to later.

The third group consisted of bacteria which had been isolated from the human body, and it was found that, whereas most of these were not acted on by the lysozyme contained in sputum or tears, some were completely, and others partially dissolved. Not one of the various members of the coli typhoid group showed the slightest signs of lysis, while sixteen out of nineteen strains of intestinal streptococci were dissolved to a greater or less extent.

The results obtained with this group of microbes are set forth in Table III, but of necessity, considering the multiplicity of strains involved, this Table is incomplete, and it may well be that by altering the conditions of the experiment somewhat, a much higher percentage of the bacteria will be dissolved.

Table III.—Effect of the Lysozyme contained in Sputum or Tears on Bacteria isolated from the Human Body,

Type of microbe.	Number tested.	Number showing some lysis.	Number showing no lysis.
<i>Streptococci</i>	22	16	6
<i>Staphylococci</i>	4	2	2
<i>B. coli</i>	12	0	12
<i>B. typhosus</i>	1	0	1
<i>B. paratyphosus</i>	2	0	2
<i>B. proteus</i>	2	0	2
<i>B. pyocyaneus</i>	3	0	3
<i>B. pestis</i>	1	0	1
<i>M. melitensis</i>	1	0	1
<i>Diphtheroid Bacilli</i>	3	0	3
<i>Pneumococci</i>	2	0	2

It was noticed that with different microbes, different fluids in their lysozyme-content did not always bear the same ratio to one another. Thus, while tears were apparently the most powerfully lytic to the *M. lysodeikticus*, they had a less powerful lytic effect on some other cocci than had sputum or synovial fluid. This may be the explanation of the immunity of



FIG. 1.



FIG. 2.

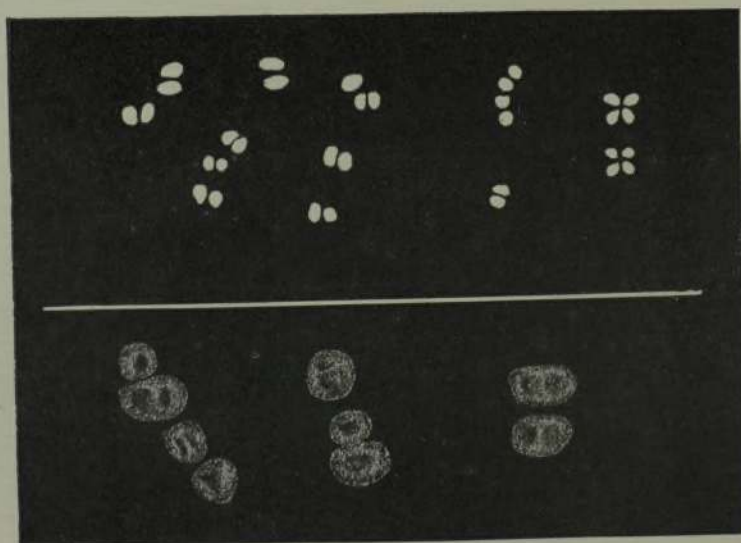


FIG. 3.

certain tissues to certain infections, or conversely the well-known predilection of certain infections for certain tissues.

The view has been generally held that the function of tears, saliva and sputum, so far as infections are concerned, was to rid the body of microbes by mechanically washing them away. Metchnikoff in his treatise on "Immunity and Infectious Disease," expresses himself very clearly and precisely on this point. From the experiments detailed above, however, it is quite clear that these secretions, together with most of the tissues of the body, have the property of destroying microbes to a very high degree.

It has not been possible to test extracts of all the different tissues to each of many microbes, but it has been shown that human tears and sputum can dissolve the majority of the microbes (presumably non-pathogenic) recovered from the air of the laboratory. Most of these air-borne bacteria are non-pathogenic, and it seems extremely unlikely that they could become pathogenic when the human secretions show such a destructive action towards them.

Again, the human secretions showed lytic power to most of the microbes tested which, although pathogenic to some animals are harmless to man. Notably there was a certain amount of lysis evident with the bacillus abortus of Bang and *B. pseudotuberculosis rodentium*, which are culturally and serologically identical with *M. melitensis* and *B. pestis* respectively, both of which latter organisms are very pathogenic for man, and for which there is apparently no lysozyme in the human secretions. It may be that it is in this sensitiveness to a human lysozyme that the difference between these microbes lies.

DESCRIPTION OF PLATE.

Fig. 1.—Photograph of agar plate with imbedded tears.

Fig. 2.—Bactericidal power of tears on streptococci. Upper half—culture from streptococci in salt solution. Lower half—culture from same number of streptococci in tears (1 in 100).

Fig. 3.—Upper half—*Micrococcus lysodeikticus* before being acted on by tears. Lower half—same partially dissolved by tears. Examined by Burri's method.