GOULSTONIAN LECTURES

ON THE
CHEMICAL PATHOLOGY OF DIPHTHERIA,
COMPARED WITH THAT OF ANTHRAX,
INFECTIVE ENDOCARDITIS, AND
TETANUS.

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LECTURE I.

Introductory.—Comparison of Peptic, Tryptic, and Anthrax Digestion of Proteids.—Chemical Changes Produced in the Tissues by Anthrax.—Diphtheria: Mode of Investigation.—Nature and Amount of Products in Blood and Tissues.—Physiological Action of Diphtheria.—Albumoses.—Production of Paralysis.

MR. PRESIDENT,—I must in the first place express my sense of the honour which has been conferred on me by my appointment as Goulstonian Lecturer, and I trust that what I shall bring forward will be deemed worthy of the traditions of this distinguished College.

The subject I have chosen is the chemical pathology of diphtheria compared with that of anthrax, infective endocarditis, and tetanus; that is, of two diseases, anthrax and infective endocarditis eminently febrile, and of two, diphtheria and tetanus, with symptoms specially referable to the nervous system. They are all disorders in which the symptoms are due to a primary infective agent or living contagium. A mere study of the morphology of this primary infective agent does not explain the symptoms of the diseases, still less is this so when we consider that in diphtheria and acute traumatic tetanus the infective agent has been found only at the point of inoculation of the disease, and does not diffuse itself throughout the body. Besides the morphological characters of the infective agent and a histological examination, a chemical investigation is necessary, and to this we shall probably in the future have to look, not only for an explanation of the symptoms of infective disorders, but for a scientifically grounded method of treatment. The direction of the research which I shall bring before you is the investigation in these specific disorders of the presence of specific poisons, the product of the primary infective agent. I will, as an explanatory introduction, state quite briefly what I have already published on the chemical pathology of anthrax, a disease which serves as an excellent example, since its microscopical anatomy and bacteriology have been very completely worked out. It is characterised, in its anatomy, by the presence of the bacillus anthracis at the seat of inoculation and in different organs of the body, especially the spleen; and in its symptoms, by the onset of fever, by the presence of great prostration, and by the occurrence of stupor ending in coma and death.

Anthrax.—1. If the bacillus anthracis is grown in a medium which resembles the fluids of the body (in containing an animal proteid and a certain proportion of mineral salts), it digests the proteid with the formation of products resembling, chemically, those found in peptic and in tryptic digestions, with the exception, however, that the final product is a base, an organic body forming salts with acids.

Primary Agent or Primary Infective Agent.	Ferment.	Digestive Products.
Living cell	Pepsin	Tyntonin; hetero-albumose; proto-albumose; deuto-albumose; peptone.
Living cell	Trypsin	Globulin-like body; tryptone (peptone), leucin; tyrosin; a bitter body.
Bacillus anthracis (Anthrax digestion)		Hetero-albumose; proto-albumose; deuto-albumose; peptone; leucin; tyrosin; alkaloid (base).

A glance at this table will show you the relation between

anthrax digestion and those by trypsin and pepsin. It is similar to the peptic digestion of proteids in the formation of albumoses and peptone, and it is like tryptic digestion in the fact that the proteid molecule is split up into non-proteid organic bodies, the chief of which is the anthrax base. The two chief proteid digestive products which concern us at present are proto-albumose and deuto-albumose. They have, in common with peptone, the following reactions: They are soluble in water, cold or boiling, forming a yellow solution; (2) they give a pink colour (biuret reaction) with copper sulphate and potash solution; (3) they are precipitated by alcohol, but not coagulated by it. In these reactions they differ from hetero-albumose and ordinary globulins and albumins. They are distinguished from each other by the following reactions: Proto-albumose is precipitated in the cold by nitric acid, the precipitate being soluble on heating, reappearing on cooling, etc.; it is also precipitated by saturation with sodium chloride. Deuto-albumose is not precipitated by nitric acid unless a certain percentage of sodium chloride be added, and is not precipitated by saturation with this salt if the liquid be only slightly acid. Peptone is not precipitated by nitric acid, and therefore the mode of precipitation by this reagent is a distinguishing reaction between the two chief albumoses and peptone.

The anthrax albumoses have the same chemical characteristics as those formed in peptic digestion. The anthrax alkaloid is an amorphous yellow body with an alkaline reaction, soluble in alcohol and in amyl-alcohol, and precipitated by many reagents which throw down alkaloids, but not by Mayer's solution.

Chemical Products of Tissues of Anthrax Animals.—The results of the investigation of the artificial chemical products of the bacillus anthracis indicated the chemical bodies to look for in the blood and other tissues of animals suffering from the disease. In guinea-pigs and a sheep, which were inoculated with anthrax and died from it, it was found that both classes of products were present in the œdema produced at the site of inoculation, in the blood and in the spleen; and in a man who died of anthrax in Guy's Hospital from the natural disease the same results were obtained; and in this case it was also found that both classes of products were excreted in the urine. An approximate estimation of the amount of anthrax products present in the body at death is seen in the following table, in which the amount in the local lesion, the spleen, and the blood is shown:—

In Full-grown Sheep Dead of Anthrax:

	Albumoses.	Alkaloid.
	Gramme.	Gramme.
From local lesion	0.187	0.1346
„ spleen	0.191	1.2080
„ blood—(chiefly deuto-albumose)	0.455	0.6430
	0.813	1.9856

It will thus be seen that in the natural disease the two classes of products are both present, but that the amount of the alkaloid is much greater than that of the albumoses, and the results of the investigation of the physiological action of the products show that the alkaloid is the chief agent in producing death. In mice so small a quantity of the mixed products as 18 milligrammes of the albumoses and 28 milligrammes of the alkaloid will produce death in nineteen hours. In guinea-pigs in which the mixed products are injected subcutaneously there is at first fever, which may pass off. If a large dose of the alkaloid is given in proportion to the albumoses coma ensues, which may last as long as fifty hours, and at the same time at the seat of inoculation there is a spreading œdema. During this coma there is no high fever, and there may actually be a depression of temperature.

The rôle which these products individually play is seen by injecting them separately into animals. The albumoses are the fever producers, the alkaloid is the coma producer.

The chart exhibited shows the fever produced in guinea-pigs by a subcutaneous inoculation of anthrax albumoses compared with that produced by peptic albumoses; the dose in all is the same—namely, 0.2 g. per kilo. of body weight. The upper line shows a rise of temperature two hours after inoculation, and lasting over twenty-four hours; this is of anthrax albumoses unheated. The second thin line shows the fever produced after boiling for thirty seconds; it is slightly less than the first. The third dotted line shows the fever pro-

duced by peptic albumoses, which is not so well marked as that of the unheated anthrax albumoses. These animals showed no other symptoms but fever. The prolonged effect of the anthrax albumoses is best seen when they are injected directly into the circulation. The effect of the injection of a dose of 0.122 g. per kilo. of body weight into the marginal vein of the ear of a rabbit is a rise of temperature of over 4° in four hours after inoculation, and a continuance of the fever during the second and third day of experiment, the temperature being normal on the fourth day. Three times this dose produces a very moderate rise of temperature and then a fall, ending in death in a few hours. The alkaloid produces either no rise of temperature or a very slight one; it is a local irritant producing oedema, and is the cause of the coma.

The investigation of the chemical pathology of anthrax gives us, therefore, a clear idea as to the means by which the bacillus anthracis, the primary infective agent, acts. When introduced into the body the bacillus begins to digest the proteids, the products of digestion cause a local oedema containing in solution (like other pathological effusions) a large quantity of proteids, which are outside the metabolism of the body, and which, therefore, serve as a suitable food for the bacillus.

The absorption of the digested products from the local oedema and from the other parts of the body in which the bacillus grows produces the symptoms of the disease, and it is to the gradual accumulation of the poisonous anthrax base that the stupor ending in coma and death is due. These bodies are the specific products of the bacillus, and are readily recognised either in a cultivation or when separated from the tissues of an animal dead of the disease.

Diphtheria.—The general conclusion from the study of the chemistry of anthrax was that two classes of products were formed from the proteids of the body by the bacillus, one belonging to the digested proteids—namely, albumoses—the other to the non-proteid class, a definite organic base with a specific action. With these results in mind, the work on diphtheria was begun, but a somewhat different method of investigation was adopted. The tissues of patients dead of diphtheria were, in the first instance, chemically investigated before an attempt was made to isolate the products of the bacillus diphtheriæ. In the search for specific poisons in diphtheria the aim was perhaps theoretically simpler than in the case of anthrax, for in diphtheria there is the peculiar palsy which follows the disease, and is so closely associated with it that it is more properly considered a symptom and not a sequela. All facts point to the diphtheritic membrane as the seat of origin of the disease, so that it was examined chemically as well as the blood, spleen, and kidneys.

Cases of Diphtheria Examined.—In all 8 cases of diphtheria were examined, 6 of which are shown in the following table. They all occurred in children.

No. of Post-Mortem.	Hours after Death.	Age of Patient.	Duration of Disease.	Extent of Diphtheria.	Other Lesions.
		Yrs.	Days.		
1	3½	1	6	Laryngeal	—
2	3	5	8	Nasal, pharyngeal, laryngeal	—
3	6½	4	10	Tonsillar	Small suppurating gland below jaw.
4	12	1½	9	Pharyngeal and laryngeal	—
5	4	3½	7	Pharyngeal and laryngeal	Broncho pneumonia.
6	13½	8	4	Nasal-pharyngeal.	—

Cases 2, 4, 5, and 6 showed at the *post-mortem* examination the typical diphtheritic membrane, and a microscopical examination exhibited the typical structure of the membrane with the presence of the bacillus diphtheriæ in the superficial layers. Case 6 might be classed as one of malignant diphtheria from its rapid course with high fever and great prostration. Cases 1 and 3 differed from the others in the following respects: In Case 1 there was at the *post-mortem*

examination nothing visible to the naked eye as the cause of death. There were a few small erosions on the under surface of the epiglottis and in the upper part of the larynx, but no membrane, nor had membrane been observed during life. The pharynx and fauces were normal. On a microscopical examination, a few minute flakes of membrane were found in the larynx, with the diphtheritic bacillus near the free surface of the membrane. During life the child had suffered from a croupy cough, and died in dyspnoea after tracheotomy. Case 3 showed at the *post-mortem* examination congestion and erosion of the tonsils and congestion of the pharynx; there was no membrane, and cultivations of the throat yielded only micrococci and not the bacillus diphtheriæ. Membrane was, however, present in the throat on admission into the hospital. These 6 cases, therefore, represent the different classes of cases which die; those with typical membrane in the nose, pharynx, or larynx, as Cases 2, 4, 5, 6, some of which may have broncho-pneumonia as well; those in which the disease is limited to the larynx, and in which membrane is discovered only microscopically; and lastly, cases in which the membrane, as such, has disappeared, leaving a congested condition of the throat, and in which the disease is associated with a secondary pus infection of the lymphatic glands below the jaw.

Method of Examination of Tissues.—In the separation of poisonous products from the tissues or from a culture of a micro-organism, the same method is applicable, except that the culture has first to be freed from bacilli. With the tissues, for example, the spleen and other organs are finely minced and placed in rectified spirit, the blood is also placed in rectified spirit, and the mixtures are allowed to stand until all the ordinary proteids are coagulated. They are then filtered and the residue is extracted with cold distilled water until nothing more dissolves. All the extracts are mixed together, evaporated at 35° C. to a small bulk, and thrown into absolute alcohol. This precipitates most of the albumoses, some deuto-albumose remaining in solution. After standing the alcohol is poured off the precipitate, evaporated to dryness at a low temperature, and extracted by absolute alcohol until nothing more dissolves. The residue left is deuto-albumose with mineral salts. All the proteid is mixed together, dissolved in a small quantity of water, and precipitated by alcohol, the process being repeated several times to remove any traces of bodies soluble in alcohol and the excess of mineral salts. At the last precipitation the precipitate is allowed to stand under alcohol for six weeks to two months, after which the alcohol is poured off, and the precipitate dried *in vacuo*, so that from first to last the products are in contact with no reagent but pure alcohol, and are never heated to above 40° C. The resulting product is a light, yellowish brown powder which yields nothing to alcohol, ether, or chloroform, and which keeps indefinitely if preserved in a dry atmosphere. It is soluble in water, cold or boiling, its solution being yellowish, sometimes faintly acid, or nearly neutral. It consists almost solely of deuto-albumose, a small amount of proto-albumose being also present. There is no peptone in it. It gives all the ordinary actions of proteids and a well-marked biuret reaction. It is completely precipitated from solution by saturation with ammonium sulphate; nitric acid gives a slight precipitate, which is greatly increased if sodium chloride be added to the solution. In fact, this proteid powder is chiefly deuto-albumose, giving reactions similar to those of peptic deuto-albumose. The alcoholic extract of the tissues is strongly acid, and contains an appreciable quantity of free fatty acid, and also of another organic acid, which is separated from the first by its insolubility in chloroform. This organic acid is readily soluble in water and absolute alcohol, and quite insoluble in ether, chloroform, and benzene. It is a yellowish, amorphous body, which becomes a deep brown on being made alkaline. Its further chemical characteristics are not at present investigated. In the tissues of none of these patients was there any organic base or alkaloid present.

Amount of these Products Present.—An attempt was made in some of the cases examined to estimate the amount of albumoses and alcoholic extract (that is, organic acid) present in the blood and spleen. The weights given are only approximate, as there is such a great loss of the substances during purification.

No. of Case.	Seat of Disease.	Albumoses in Grammes.			Alcoholic Extract.
		Blood and Spleen.	Blood only.	Spleen only.	
1	Larynx	0.974	—	—	0.271
3	Tonsils	0.5955	—	—	—*
4	Pharynx and larynx	—	0.149	—	0.107 (blood only).
5	" " "	0.805	0.450	0.355	0.455
6	Naso-pharynx	—	Trace	0.715	—*

* Weighed together; 0.528 g. obtained.

From this table the following conclusions may be drawn:—
1. That the albumoses are always associated with the presence of the organic acid, and that the amount of albumoses is much greater than that of the acid. This is a fact of great importance in considering the relative physiological action of the two classes of substances. It will be noticed, too, that in Case 1, which occurred in a child only a year old, nearly a gramme of albumoses was obtained from the blood, spleen, and kidneys, which represents a much larger quantity really existing in the body, owing to the large amount lost in purification.

2. In two of the cases the greatest quantity of albumoses was present in the spleen: In Case 1, in which the organ was not enlarged; and in Case 6, in which only a trace was found in the blood, and 0.715 g. in the spleen. Similarly, from the spleen a larger amount of the organic acid was obtained than from the blood. The spleen is, in fact, the chief repository of the diphtheritic poison in the body.

3. It is also noticeable that in Cases 1 and 3, to which attention has been already drawn as differing from the typical cases of diphtheria seen on the *post-mortem* table, that the same bodies were found as in the typical cases of diphtheria, and it may be at once stated that the results of the physiological action of these bodies were the same in all the cases. Cases 1, 3, 5, and 6 were those in which the products were used for physiological experiments.

We might, therefore, sum up the chemistry of the tissues in diphtheria by saying that two classes of substances are present, which are abnormal to the body; one belonging to the group of digested proteids, namely albumoses; the other an organic acid. Contrasted with anthrax it is seen that whereas the bacillus anthracis produces albumoses and an organic base, in diphtheria we have albumoses and an organic acid. The albumoses of diphtheria cannot be distinguished from those of anthrax or peptic digestion by chemical means. Their physiological effect, a test more delicate than any chemical reaction, is the only method by which their specificity is made evident.

Physiological Action of the Albumoses Found in the Tissues in Diphtheria.—1. Local effect. When subcutaneously injected, the diphtheria albumoses produce a local oedema, which in one case came on in 2 hours, spread rapidly for 24 hours, and then rapidly diminished, so that in 36 hours it had practically gone and left no trace behind. It is a clear oedema unaccompanied by any naked-eye congestion of the part, and not followed by any necrosis.

2. A more important effect is that on the body temperature. The subcutaneous injection of 0.256 g. per kilo. of body weight in a guinea-pig, produced only an irregularity of the temperature and no well marked rise, a result in marked contrast to the similar experiment with anthrax and peptic albumoses which I have already demonstrated. When injected into the circulation of rabbits, however, these albumoses will produce fever.

Rabbits: Precautions.—It is necessary to premise that in all experiments on the effect of the intravenous injection of these proteid poisons certain precautions must be taken in order to ensure that the animal used for experiment is a healthy one. My usual practice is to isolate an animal and to take its weight, then to observe its temperature three or four times daily for a week or more. If during this time the animal gains in weight, and if the rectal temperature does

not at any time rise to 103°, or for one day does not keep at about 102.5°, the animal is used for experiment. If such precautions are taken both time and animals are saved, and greater accuracy in the experiments is secured. There is one disease in rabbits, namely, spinal curvature causing paraplegia, which is not excluded by the precautions I have enumerated. But this disease is a very definite one and readily recognised.

Intravenous Inoculation: Single Doses.—In one animal a dose of 0.117 g. per kilo. of body weight produced a well-marked rise of temperature on the day of inoculation and a slight degree of fever lasting four days more. Nothing further happened to this animal. It did not become paralysed, and when killed in ninety-four days it was fat and well nourished. In another animal a dose of 0.122 g. per kilo. of body weight produced a rapid fall of temperature and death in three hours. Paralysis of the hind limbs occurred in one hour and a-half, and was followed by coma. An examination made just after death showed a pinkish coloration of the lungs due to congestion, and pallor of the spleen. There were no ecchymoses and no effusion. The blood was profoundly altered; it was dark and fluid, and was slow in coagulating. A small quantity put into a watch glass did not set for over fifteen minutes. Normal rabbit's blood begins to coagulate in half to one and a-half minute. The retardation of coagulation observed in this instance is not peculiar to diphtheria products, but is observed also with the ordinary peptic albumoses.

Intravenous Inoculation: Multiple Doses.—The effects following the intravenous injection of the diphtheria albumoses in divided doses is much more important than similar experiments with single doses. With multiple doses one imitates—imperfectly it is true—the course of events in the natural disease. Moreover, as is well known, multiple small doses of a poison have a more powerful effect than a single large dose.

Intravenous Injection of Diphtheria Albumoses in Rabbits: Multiple Doses.

Weight of Rabbit in Grammes.	No. of Case of Diphtheria.	No. of Doses.	Total Dose per Kilo. of Body Weight.	Death in	Paralysis in
1,100	5	2	0.136 gramme	7 days	2 days
1,970	5	2	0.153 "	11 "	6 "
970	6	3	0.157 "	10 "	7 "
1,565	3	2	0.100 "	Killed in 24 days	20 "
1,200	6	2	0.083 "	Recovery in over 54 days	8 "

The doses were given, as a rule, on successive days; in one case on the same day. The first symptom noticed after the inoculation is fever, which in some cases is great and in some slight. In the first animal the fever lasted during the seven days the animal lived. This is the only instance of such an occurrence in any of the animals. In the second animal in which the two doses were given on the same day the fever lasted only during that day, and was very slight. In the fifth animal the fever lasted about three days after the inoculation, and was moderate in degree. The rise of temperature in these animals was between 3° and 4° F.

The effect on the body temperature is therefore a very varying one; but whether these animals have slight or great fever, they all show a more definite symptom—that is, a paresis of the muscles. In the first animal, for example, which had high fever, paresis of the left leg appeared on the second day; it was not used so much as the right leg in jumping. The paresis was more marked on the fourth day, both legs were affected on the fifth day, and on the seventh day there was paresis of all the limbs. There was no complete paralysis, for just before death the animal could still move when touched, although it only hobbled a few paces. The second animal showed paresis of the right fore leg on the sixth day, and on the ninth day this extended to the other fore leg. There was a general weakness of the muscles until death on the eleventh day. In the third animal, with a moderate

degree of fever lasting six days, a general weakness of the animal appeared on the fifth day, and a definite paresis in the hind limbs on the seventh day. This increased till death. The fourth animal also with moderate fever, but with a smaller dose than the three just mentioned, showed only a slight general weakness for twenty days. On the twentieth day the paresis was definite in the hind legs: the animal was indisposed to move, and could not jump vigorously; the respiration was extremely rapid. The animal, however, recovered from the respiratory symptoms, and was killed on the twenty-fourth day.

The fifth animal showed a slight continued fever after the second dose, which passed off in five days. Weakness in the hind legs appeared on the second day. On the eighth day the hind legs were much weaker, especially the left one, which was held slightly abducted. It continued in this state till the nineteenth day, when almost suddenly it became much worse. Attempts at walking and jumping resulted in an irregular movement which carried the animal some distance forward, when it stopped with limbs outstretched. The breathing was extremely rapid, and there were occasionally slight convulsive movements of all the limbs, which were possibly of respiratory origin. This serious condition of the animal passed off, and it regained a great deal of power in its limbs till after the fifty-fourth day. The condition just described as passing off in this animal which had the smallest dose is the mode in which the other animals, which had the larger doses, died. It is, so to speak, the culminating point of the paresis which, although more marked in certain limbs, is always general, affecting the trunk muscles as well as those of the limbs. When it comes on with the larger doses it usually lasts 24 hours before the animal dies. It is, as shown by the *post-mortem* examination, partly respiratory and partly cardiac in origin.

From the injection, therefore, of the diphtheria albumoses, a paresis of the muscles is produced which may be most marked in one limb, but is always general and progressive. It is associated with an affection of the respiration, as shown in the rapidity, or in some cases slowness, of breathing during the attacks described, which may pass off if the dose be small enough. With this paresis there is no special wasting of the muscles; even when the limb of one side is more paretic than that of the other, it does not waste to a greater extent. As regards loss of sensation, I did not attempt to estimate it as the animals were rabbits. No affection of the pupil was noted in any of the animals. With the large doses the knee-jerks were found diminished after some days, but they never completely disappeared. When one hind limb was more paretic than the other, the knee-jerk on that side was diminished.

Loss of Weight.—Although the muscles do not specially waste, there is a general loss of weight, which is the more marked the larger the dose.

Table of Loss of Weight.

Original Weight in Grammes.	Weight at Death.	Proportional Loss of Weight.	Death in	Fever Period.	Dose of Albumoses per Kilo.
1,100	970	$\frac{1}{3}$ th	7 days	7 days	0.136
1,970	1,520	$\frac{1}{4}$	11 "	1 day	0.153
970	530	$\frac{1}{2}$	10 "	6 days	0.157

It will be noticed that the larger the total dose the greater the wasting which is produced. With the largest dose given the wasting was enormous, being nearly one-half of the original body weight. This wasting is not proportional to the fever, as it goes on after the fever has subsided. This is seen in animals 2 and 3, in one of which, with fever lasting only one day, one-quarter of the body weight was lost, and in the other, with fever lasting six days, one-half of the body weight was lost. With the smaller doses given, although the paresis was well marked and the respiratory troubles very manifest, the loss of weight was much less than in the animals shown in the table. Thus the animal with the total dose of 0.1 g. per kilo. of body weight showed on the eleventh day a loss of

one-tenth of its body weight, after which it rapidly increased in size until it was killed (on the twenty-fourth day), while the animal with the total dose of 0.083 g. per kilo. of body weight showed in eighteen days a loss of only one-sixtieth of its body weight, after which it rapidly surpassed its original weight by 100 g., and subsequently showed only slight fluctuations in its weight. In these cases also the loss of weight is proportional to the dose of albumoses, and not to the fever.

Diarrhoea, watery and non-sanguineous, is also a symptom shown by these animals. It is more marked the larger the dose, and may last several days. With the smaller dose it is absent, although the fever and paresis are both present.

One of the most striking features of the action of these albumoses is their prolonged effect. The fever may last a long time, the paresis produced may be rapid in onset, but is slow in progress, and the general wasting produced is slow and prolonged.

Post-mortem Examination.—That the symptoms described are really due to the action of these diphtheritic albumoses is evidenced by the *post-mortem* examination. That the animals did not die from the accidental introduction of a pathogenous micro-organism is shown by the fact that neither a microscopical examination of the organs of the body, nor cultivations of the blood and spleen on agar and gelatine, showed the presence of any such micro-organisms. The liver, spleen, and kidneys were, to the naked eye and to microscopical examination, normal. The lungs, lymph glands, and suprarenals were normal. In only one instance was subcutaneous oedema found; that was in the first animal, in which there was a large amount of oedema over the abdomen. As this was absent in the other animals, it was looked upon as an accidental effect of the poison. The albumoses used in inoculation were free from micro-organisms; the mode of preparation ensures this, since from their removal from the body until they are dried they are always in contact with an excess of pure alcohol, and when dried they are not touched, except with sterile instruments, and are preserved in a sterile bottle in a dry atmosphere. All instruments used in the experiments are also sterilised, so that the effect of bacteria in producing the symptoms described is definitely excluded; but that the albumoses were acting in the body while the animal was alive is shown by the condition of the blood after death. It has already been mentioned that the blood was slow in coagulating in the animal which died in three hours after a single dose. In the animal which had the largest dose of the albumoses in three doses, the blood was found in a similar condition. The animal died during the night, and blood drawn from the right ventricle at 10 A.M. was liquid, and of a lighter red than venous blood. In twenty-five minutes (at the temperature of the laboratory) a small amount placed in the watch glass began to coagulate, and was completely set in two hours. This slow coagulability of the blood, which is a well-known feature of the action of albumoses on the blood, showed that the diphtheria-albumoses were actually present in the circulation in this case ten days after inoculation; but even in the animal which was killed twenty-four days after inoculation the blood was found slow to coagulate, commencing to set in about fifteen minutes, when removed one hour after death. This condition, however, was not found in another animal which died in eleven days after the inoculation of two doses of 0.153 g. per kilo. of body weight, but in this instance the two doses were given on the same day, and this fact, together with a difference in the rate of excretion in different animals may show that in this case the albumoses were not in sufficient quantity in the blood to retard coagulation, but were present in sufficient amount to produce the other symptoms of diphtheria-albumoses—namely, the paresis and loss of weight. The condition of the blood in these animals appears to me to be extremely important, as it helps to explain why diphtheritic paralysis in man can occur some time after the acute disease is past.

THE municipal authorities of Nuremberg have decided to erect a new hospital in that ancient city. Accommodation is to be provided for 700 patients, but arrangements are to be made whereby the number of beds can at any time be increased to 1,000. The estimated cost is 2,900,000 marks (£145,000).