SCIENCE

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A CURE FOR TETANUS AND DIPHTHERIA.[1]

THE greatest interest has been aroused in scientific circles in Berlin by a paper in the *Deutsche medicinische Wochenschrift*[2] by Behring and Kitasato. These well-known bacteriologists, who for a long time past have been working in Dr. Koch's Hygienisches Institut, have not only succeeded in producing immunity against diphtheria and tetanus, but also in curing animals already infected by these diseases. Their results are to a great extent self-explanatory, and there is every reason to expect that the same method will be found to be applicable to other infectious diseases. The most remarkable part of their discovery is the fact that the blood of an animal that has been made immune against diphtheria possesses the extraordinary power of destroying the poison formed by the microbe of this disease. This power is also possessed by the serum of such an immune animal, which serum can therefore be used as a curative means on other animals that are suffering from this disease. The same statement holds good for tetanus.

Before describing in detail these interesting results, it will be well to give a short historical review of some recent bacteriological work which can be regarded as having led up to this discovery.

Towards the end of 1888, Nuttall,[3] working in Flugge's laboratory at Breslau, discovered that various bacteria are destroyed when mixed with fresh blood or blood-serum, and, further, that this destruction cannot be ascribed to the action of cellular elements, but rather to the fluid part of the blood. This discovery (which really arose from the German criticism of Metschnikoff's phagocyte theory) was soon followed by the work of Buchner[4] and Nissen[5] on the bacteria-killing power of the cell-free blood-serum. These authors considered that their work necessitated a limitation of the phagocyte theory, and suggested a new view of the nature of immunity, whether natural or acquired. In other words, they suggested that immunity was conditioned by the bacteria-killing power of the various body fluids rather than by that of any particular kind of cell. These opinions were rather severely criticised in a paper by Lubarsch[6] that was published towards the end of last year. Lubarsch emphasized the fact that while the serum of the rabbit — an animal extremely sensitive to anthrax — has a great power of destroying anthrax bacilli, horses' serum has no such power, although this animal is comparatively refractory to the disease. Again, while on the one hand such eminently pathogenic microbes as the anthrax and cholera bacilli are capable of being destroyed by serum from various animals, several perfectly harmless microbes find blood-serum to be an excellent food-medium. Further, though the serum of the rabbit kills anthrax bacilli in a pre-eminent degree, the living blood-plasma of this animal can only do so to an infinitesimal extent. Such considerations suggested to Lubarsch that the bacteria-killing power of the blood-serum was a fact rather of the nature of an epi-phenomenon than an essential factor in the conflict between the organism and the microbe. In May of this year appeared my own work on "Defensive Proteids."[1] I gave this name to a new class of proteid bodies, which I found to possess a bacteria-killing power, and which I have obtained from the spleens and lymphatic glands of various animals. This work has a distinct bearing on the foregoing, in that it suggests that the bacteria-killing power of blood-serum is due to minute traces of these substances liberated for the breaking-down of lymphatic cells. The absence of a bacteria-killing power from certain kinds of serum (e.g., horse) and from living blood-plasma (as has been shown for that of the rabbit in regard to anthrax) appears to be connected with the intactness of the leucocytes in these special cases. Further, the fact that I obtained these substances from cells which either are or can become phagocytes, may be taken as an additional proof of Metschnikoff's well-known theory. These substances appear to be absent from the normal blood-plasma, or, at any rate, only present in such small quantities that they cannot be separated from it. With blood of febrile animals, however, the case is different, and from such blood I have been able to isolate a bacteria-killing substance.[2] This fact appears to indicate that these substances are actually used by the organism in its re-action against the attack of pathogenic microbes.

During last summer, while I have been engaged in this work, various other papers have appeared, which tend to show still more clearly that the bacteria-killing power of the blood-serum (or, if my work be accepted, of defensive proteids) is of real importance in the production of immunity. Bouchard[3] was, I think, the first of many authors who have succeeded in showing that the bacteria-destroying power of blood-serum from immune animals is greater than that of normal serum. Bouchard proved this in the case of bacillus

[1] From Nature, Dec. 11, 1890.

[2] No. 49. Dec. 4, 1890, p. 1113, "Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren."

[3] "Experimente über die bakterienfeindlichen Einflüsse des thierischen Körpers" (Zeitschrift für Hygiene, vol. iv. p. 353).

[4] "Ueber die bakterientödtende Wirkung des zellenfreien Blutserums" (Centralblatt für Bakteriologie, vol. v. p. 817, and vol. vi. p. 1).

[5] "Zur Kenntniss der bakterienvernichtenden Eigenschaft des Blutes" (Zeitschrift für Hygiene, vol. vi. p. 487).

[6] "Ueber die bakterienvernichtenden Eigenschaften des Blutes und ihre Beziehungen zur Immunität" (Centralblatt für Bakteriologie, vol. vi. p. 528).

[1] "A Bacteria-killing Globulin" (Proceedings of the Royal Society of London, vol. xlviii. p. 93), and "The Conflict between the Organism and the Microbe;" Part 2, "On Defensive Proteids" (British Medical Journal, July 12, 1890).

[2] "Indications of a Method of Curing Infectious Diseases," read at the Leeds Meeting of the British Association for the Advancement of Science, September, 1890.

[3] "Sur l'effet des produits sécrétées par les microbes pathogènes" (Paris, 1890).

pyocyaneus for rabbits. He made the animals immune by injections of sterilized culture-fluids, and found that serum from such animals exerted a far greater "bactericidal" action on the microbe in question than serum from a normal animal. Behring and Nissen,[1] in a paper published in May of this year, went a step further. They showed, that, whereas blood-serum from an animal made immune against anthrax exerted an increased bactericidal action on the anthrax bacillus, it showed no increased action on the bacillus pyocyaneus. Conversely blood-serum from an animal made immune against the latter microbe had no increased action on the anthrax bacillus, though it exerted a powerful bacteria-killing action on pyocyaneus. The authors considered that they had proved the existence of two bodies, each having a specific action on one of the two microbes in question, and, further, that these substances are present in animals made immune against the above-named diseases. These remarkable conclusions acquire a still greater interest when received in the light of a research by Gamaleia published at the beginning of last year.[2] Gamaleia found that the aqueous humor of a sheep, about three days after inoculation with attenuated anthrax, acquires bactericidal properties for this microbe. This condition lasts for nearly a month, and then gradually vanishes, though, as is well known, the sheep remains immune for a far longer period. These researches therefore suggest, first, that, when an animal has been made immune against a pathogenic microbe, its blood and other body fluids contain a substance capable of destroying the microbe in question; second, it follows that such protective substances can remain in the body undestroyed for a considerable time; and, third, that they can be present in such quantities as to be able to kill the microbes involved (even without the help of living cells) and yet produce no appreciable ill effect on the general health of the animal. If this is so, why should it not be possible to cure any infectious disease by injecting a "lymph" obtained from the blood or tissues of an animal previously made refractory to the disease in question?

Whether or not the above considerations stimulated the researches of Behring and Kitasato, their work affords a positive answer to this question, which promises to be of the greatest importance to humanity, and has led them to the most unexpected and interesting results from the scientific standpoint. The following is a summary of their paper, which is of the nature of a preliminary communication.[3] The method by which, in the first case, they produced immunity against tetanus and diphtheria, is not described. Only so much of their results is communicated as is necessary to support the following propositions: —

"The immunity of rabbits and mice against tetanus depends on the power possessed by the fluid part of their blood of rendering harmless the poisonous substances produced by the tetanus bacilli."

This proposition involves a completely new theory of the nature of acquired immunity. Hitherto it has been thought that immunity must depend either on the voracious activity of phagocytes, or on the above-mentioned bacteria-killing power of the blood, or on an acquired tolerance against a poison; and, further, that by the method of residues any one of these theories could be proved by showing the other two to be false.

Behring, however, was able to prove, by his work on diphtheria, that none of these theories would account for the natural immunity of rats or the artificially produced immunity of guinea-pigs against this disease. After disproving many speculations on this subject, the above-given explanation was arrived at, but they only obtained a satisfactory proof of its correctness when they began to test it on the tetanus microbe.

Their experiments prove,—

(1) That the blood of rabbits which have been made immune against tetanus can destroy the tetanus poison.

(2) This character can be shown to be possessed by the blood both before and after it has left the vessels, and in the cell-free blood-serum obtained from it.

(3) This character is of so permanent a nature that it is still manifested by such serum after it has been injected into other animals: consequently, by transfusion of such blood or serum, important therapeutic actions can be obtained.

(4) This power of destroying the tetanus poison is absent from the blood of such animals as are not immune against tetanus; and, after such animals have been killed by the tetanus poison, it can be shown to be present in their blood and tissues.

In support of these assertions the following experimental results are brought forward.

A rabbit was made immune against tetanus by a method which will be described in a forthcoming paper by Kitasato in the *Zeitschrift für Hygiene*. To prove the completeness of its immunity, 10 cubic centimetres of a virulent culture was injected into it. Half a cubic centimetre of the same culture was quite sufficient to produce tetanus in a normal rabbit. The treated rabbit, however, remained immune, and it showed immunity not only against the tetanus bacillus, but also against the poison produced by this microbe, for it remained unharmed by an injection of twenty times the quantity of tetanus poison which will kill with certainty a normal rabbit. Blood was taken from the carotid artery of this rabbit. Before clotting occurred .2 of a cubic centimetre of this blood was injected into the body-cavity of a mouse, and .5 of a cubic centimetre into that of another. Twenty-four hours later, these mice, together with two control-mice, were inoculated with tetanus of such virulence that the latter showed the symptoms of tetanus after twenty hours, and were dead in thirty-six hours. Both of the treated mice, on the contrary, remained healthy.

The greater quantity of the blood of this rabbit was allowed to stand, and its serum collected.

Six mice each received 2 cubic centimetres of this serum in the abdominal cavity, and all withstood a subsequent inoculation with tetanus. Control-mice died of tetanus within forty-eight hours.

With this serum the authors succeeded in curing animals that had been previously infected with tetanus. They have also been able to show that this serum possesses an intense power of destroying the tetanus-poison.

Of a ten-days-old tetanus culture which had been sterilized by filtering, .00005 of a cubic centimetre was enough to kill a mouse after four to six days, and .0001 would always produce the same result in less than two days.

Five cubic centimetres of the serum of a tetanus-immune rabbit was mixed with 1 cubic centimetre of this filtered culture, and kept for twenty-four hours. Of this mixture, four mice each received .2 of a cubic centimetre (that is to say, .033 of the original culture, or more than 300 times the quantity which would otherwise be capable of killing a mouse).

[1] "Ueber den bakterienfeindlichen Einfluss von verschiedenen Serumarten" (Zeitschrift für Hygiene, vol. viii. p. 412).

[2] "Sur la destruction des microbes dans les corps des animaux fébricitants" (Annales de l' Institut Pasteur, 1889, p. 229).

[3] A fuller account will shortly appear in the Zeitschrift für Hygiene.

All these four mice remained in good health. Control-mice, on the contrary, which were at the same time inoculated with .0001 of a cubic centimetre of the original culture, succumbed within thirty-six hours.

All the mice mentioned in each of the above series of experiments have been subjected to repeated injections with the tetanus bacilli, and have shown themselves to be permanently and completely immune.

This result is the more remarkable in that up till now, in spite of innumerable attempts, no one has ever succeeded in making any animal whatever immune against tetanus. A theory of the nature of acquired immunity which at once led to a method of treating the disease which is easy to understand, harmless to the animal, and certain in its effect, must surely possess some basis in fact.

Naturally every kind of control experiment with serum of normal rabbits has been carried out with uniformly negative results. Serum of cattle, horses, and sheep has also been found to have no action on the tetanus poison. The living blood and tissues of an animal which has not been made immune, likewise show no power of destroying the tetanus poison, as appears from the following experiment, which has been many times repeated: —

Rabbits into which .5 of a cubic centimetre of a germ-free tetanus culture is injected subcutaneously, succumb after showing typical tetanus symptoms. Almost always a serous transudation is to be found in the thoracic cavity. Of this transudation .3 of a cubic centimetre is, on the average, enough to kill a mouse with typical tetanus symptoms. The same is true for the blood.

The authors close their paper by pointing out the possibility that their method of curing tetanus and diphtheria which they have used with such brilliant results on animals so highly susceptible to these diseases as mice and rabbits, may also be used for the far less susceptible hospital patient. They also note the possible influence of their work on the practice of blood-transfusion. E. H. HANKIN.

HEALTH MATTERS.

Risks to Health in East Africa.

THE colonizing wave setting steadily from Europe to East Africa gives peculiar interest to Dr. Kohlstock's experience of the risks to health and the chances of longevity among his compatriots in that region. As director of the sanitary arrangements at the German headquarters, says the *Lancet*, he has had excellent opportunity of forming his opinions, and the sense of responsibility with which he gives them to the world is in some measure a guaranty of the care with which he has collected his facts and drawn his conclusions. The first note he strikes is one of warning. Let no one, in any stage of phthisis, even the pre-tubercular, think of settling in East Africa, if he does not want to leave his bones in its soil. At first this danger was not appreciated in the Fatherland, and the inspection of officers setting out with colonizing parties was carried out in somewhat perfunctory fashion. But the climatic conditions of the region soon made their effects apparent, and nine subalterns had to be sent home, —precisely those in whose families pulmonary phthisis had prevailed. For a man of thoroughly sound constitution the two diseases to be dreaded are dysentery and malaria. The former, in Dr. Kohlstock's experience, responds satisfactorily to the measures usually taken in European centres in the East, the disease among the German troops running generally as favorable a course as in French or English garrisons. The latter is dangerous only when the patient is precluded from taking rest, and compelled to continue at work; as, for instance, on necessarily forced marches. Even so, but three fatal cases have as yet been recorded among the German troops in East Africa as due to malaria. As a rule, under conditions of rest the malaria patient soon gets well. In stubborn cases he has to be transferred to the sanatorium; the transferrence hitherto being effected on shipboard, in the absence of railways. Very often the change of locality, coming after the voyage, has sufficed to restore the patient's health. A liberal allowance of fresh butcher's meat has proved the most efficacious diet in malaria: indeed, the risks arising from the disease have been greatly reduced by the excellent nursing and accommodation now enjoyed by the patient. Dr. Kohlstock holds it to be a mistaken practice to completely cut off alcohol as a prophylactic against malaria: he would rather, within the limits of temperance, that the German in East Africa should live, as far as possible, as he did at home. The necessary upturning of the soil for purposes of tillage is, in such virgin territories as that of German Africa, the most prolific source of malaria; and, at that inevitable stage of colonizing operations, the sanatoria must be in constant requisition, and their treatment supplemented by change of locality for the convalescent. So well, however, have these measures been understood and carried out, that Dr. Kohlstock can point to a steady diminution in the statistical returns of malaria cases; the places where the disease has been most pronounced being, naturally enough, those like Mpwapwa, where the earth exhalations from the disturbance of long inert soil have been the most extensive, while no good water-supply has been obtained by boring. Soon, however, a marked reduction of the malaria returns will, it is hoped, be effected even in that locality.

LETTERS TO THE EDITOR.

*** Correspondents are requested to be as brief as possible. The writer's name is in all cases required as proof of good faith.*

The editor will be glad to publish any queries consonant with the character of the journal.

On request, twenty copies of the number containing his communication will be furnished free to any correspondent.

A New Kansas Meteorite.

THE year 1890 has brought to scientific knowledge a larger number of tangible celestial visitants than all preceding years combined. Up to this year the Waconda meteorite was the only representative from Kansas on the list of authentic meteoric falls. In March of this year the now famous group of irons from Kiowa County was made known to science; and on June 25, 1890, the Washington County aerolite was heard and seen to fall at midday by thousands of Kansas citizens; and now, just at the close of the year, I have the pleasure of announcing a third fall of unknown date. This may be called the Tonganoxie meteorite. So far as now known, this fall consists of a single specimen, weighing 26½ pounds. It is an iron of the ordinary character (not a pallasite). It is of an irregular shape, and is thought by the owner to resemble a lion couchant. It is 9¾ inches long, 6½ inches wide, and 3½ inches deep.

This meteorite is the property of Mr. H. C. Fellow, principal, 1887–90, of the Friends' Academy at Tonganoxie, in Leavenworth County, now pursuing a post-graduate course of study in the University of Kansas. Mr. Fellow bought it in the spring of 1889 of Mr. Quincy Baldwin, who found it upon his farm, one mile west of Tonganoxie town, in 1886. Mr. Baldwin was not aware of its true character, although he had manufactured a fish-hook from a small fragment of the iron. He considered it to be a piece of iron ore, and proposed to start an iron-mine upon his farm; but this fragment proved to be the only "indication," and the mining project was reluctantly abandoned. This meteorite is now deposited in the museum of the University of Kansas, but is still the property of Mr. Fellow. A preliminary analysis shows the presence of iron, nickel, and cobalt. Professor E. H. S. Bailey will soon publish a complete analysis.

A small portion of the surface has been polished, and exhibits very distinctly the Wiedmanstaaten figures. Careful search has recently been made for other fragments of this meteorite on the Baldwin farm and vicinity, but without success.

F. H. SNOW.

Lawrence, Kan., Dec. 27.