fever developed this spring, the exact source being unknown; but it is believed to have come from outside the city, and the isolation of the cases has put the disease in check with only three reported cases and possibly another case, which was not reported, but which was the probable source of the contagion in the city. The books were held blameless.

5. Burned Books.—Books that had been burned while they were in homes where scarlet fever developed were proved to be probably as innocent of acting as carriers, as either of the other classes. One book belonging to this class was taken out of the library by David L. November 1. His brother developed the disease Nov. 3, 1910, not having read the book. This book is not a very popular one, had few borrowers with no history of having been exposed to the disease, and therefore could not be charged with producing the disease.

At the beginning of this investigation of the public library, as fast as any suspicious book was discovered it was taken from the shelves and put in the store-room and kept there until the study had been completed. The weight of evidence indicated clearly that the books were not an important factor in the spread of the disease, and they were placed back on the shelves without being fumigated and again put in circulation, without producing the disease and no scarlet fever developed in the city proper between July, 1910, and April, 1911. The last case among the university students occurred March 16, 1911, and during this interval from March, 1911, to May 25, 1912, the students have been using the university library and also using rented books from the university bookstores, showing that these books cannot be regarded as carriers of the disease. This to my mind warrants the following conclusions:

CONCLUSIONS

1. If books act as carriers, it is only immediately after being contaminated with the discharges of the patient; yet this investigation has failed to reveal a single instance of this kind.

2. Books that have been used by scarlet fever patients do not long contain the infection in such a way as to transmit the disease to man.

3. Any book which has been handled by a scarlet fever patient should be burned or fumigated. The most practical method for general book disinfection at this time is the Beebee carbogasoline method. This consists in using gas-machine gasoline and 2 per cent. phenol crystals; the books are immersed in this mixture for twenty minutes, removed and placed before an electric fan for two minutes, and then set on end for from twenty-four to forty-eight hours.

The supplemental study books used in the Valparaiso public schools were all disinfected by this method last September. Prof. A. A. Hughart and I devised an apparatus for this consisting of a zinc tank 21 inches long, 15 inches deep and 8 inches wide, with a tight-fitting cover. A faucet in one end near the bottom drains off the gasoline. Zinc strips bent in suitable form to serve as racks facilitate the handling of the books.

ABSTRACT OF DISCUSSION

DR. C. E. FORD, Cleveland: We are sending the books from given cases of communicable disease to the appropriate ward in the hospital for contagious diseases. We find that a fairly satisfactory way of avoiding the burning of books. If we get a book in a scarlet fever case, it is sent to the scarlet fever ward, sprayed with formaldehyd and wrapped with paper for safety during transportation.

DR. JOSEPH GOLDBERGER, Washington, D. C.: We very frequently have observations of a positive nature; that is, observations showing the apparent transmission of communicable diseases by fomites, such as books. The trouble with all such observations is that it is almost impossible to exclude other modes of transmission than those alleged in the particular instance. In cases such as reported by Dr. Nesbit we have negative results; and although the observations may by some be regarded as relatively few, it is nevertheless perfectly safe to conclude, even if they were much fewer in number, that in those instances no transmission actually took place. And this is a very much better thing than to be told that in one or two instances, perhaps a dozen, or even two hundred, or a thousand, or six thousand, transmission apparently took place, but where, as a matter of fact, absolute exclusion of other sources of infection could not be made. I think the observations reported are of such high significance that one cannot emphasize their value too much.

RECENT ADVANCES IN OUR KNOWLEDGE OF SCARLET FEVER*

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In 1907, Ludvig Hektoen[1] gave a complete summary of our knowledge of scarlet fever. He took the view that the specific cause of scarlet fever was not known and that the streptococcus was a secondary invader which found an especially favorable soil in the condition of this disease. To-day, five years later, the true nature of the pathogenetic agent of scarlet fever still remains to be discovered and little progress has been made in our understanding of this disease. Yet some contributions have been added of sufficient interest to justify a connected report of them and a new review of the present status of our knowledge.

The fact that no other organism has been found with any constancy in scarlet fever left the controversy as to the primary or secondary rôle of the streptococcus unsettled. Of the intimate biologic and clinical relation of the streptococcus to the disease there can be no doubt, because of (1) the constant presence of the streptococcus in large numbers in the throat and on the tonsils; (2) the frequency with which it is found in the blood during life and in most of the organs after death; (3) the fact that by far the greater majority of complications in the disease and of the deaths in scarlet fever are to be attributed to the invasion of this microbe, and (4) the evidence of systemic reaction to the streptococcus by the presence of antibodies in the blood.

STREPTOCOCCUS INFECTION AND IMMUNITY

The latter subject, the presence of specific antibodies for streptococci in scarlet fever, has been studied with great care in the last few years.[2] This applies chiefly to the opsonin and the complement-deviating antibodies, whereas in the study of agglutinins nothing new has been added.

The presence of opsonins[3] in scarlet fever was to be anticipated from the important rôle which has been con-

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*Read in the Symposium on Recent Advances in Our Knowledge of the Acute Infections in the Section on Pathology and Physiology of The American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

1. Hektoen, L.: Is Scarlet Fever a Streptococcus Disease? THE JOURNAL A. M. A., April 6, 1907, p. 1158.
2. For complete literature see Koessler, Karl K., and Jessie M.: Specific Antibodies in Scarlet Fever, Jour. Infect. Dis., 1911, ix, 306.
3. Tunnicliff, R.: Jour. Infect. Dis., 1907, iv, 304. Banks, A. G.: Jour. Path. and Bacteriol, 1907, xii, 113. McCrirck, T.: Jour. Path. and Bacteriol., 1911, xvi, 16. Anderson, J. M.: Jour. Path. and Bacteriol., 1911, xvi, 106.

ceded to phagocytosis in the mechanism of streptococcus infection and immunity, ever since Metchnikoff's[4] early researches on erysipelas.

The opsonic curve for the streptococcus shows a characteristic course during the various periods in scarlet fever. In the beginning the streptococco-opsonic index is below normal in the majority of cases.

As the acute symptoms subside the index rises above normal and usually remains so during convalescence in uncomplicated cases. In fatal cases the opsonic power may be markedly subnormal. Definite localized streptococcus complications, as secondary lymphadenitis and otitis media and arthritis, as well as nephritis, are inaugurated by a depression in the streptococcal opsonic index which rises again when improvement sets in. These regular variations of the opsonin are absent for the pneumococcus, staphylococcus and pseudodiphtheria bacillus and limited to the streptococcus, and are, in so far, specific for the streptococcus. But the opsonin is not specific for any certain streptococcus scarlatinæ for the same variations in the opsonic index can be observed with other streptococci as those cultivated from erysipelas. The parallelism of the fall and rise of the index with the acme of the acute symptoms and their abatement gives a very impressive picture of the systemic reaction of the organism to the general invasion of the streptococcus and substantiates the assumption that a good part of the clinical manifestation is directly to be ascribed to the streptococcus.

The presence of complement-deviating antibodies for streptococci in the serum of scarlet fever was first successfully demonstrated by Foix and Mallein,[5] who used a polyvalent antigen of streptococci which had been cultivated from numerous cases of scarlatinal angina. With serums of twelve scarlet fever patients they obtained deviation of the complement ten times. Controls made with serum of other streptococcus infections, as erysipelas and puerperal sepsis, showed complete hemolysis. Liverato[6] examined eighteen scarlatinal serums using as antigen extracts of streptococci, staphylococci, pneumococci, and typhus, colon and influenza bacilli. Complete inhibition of hemolysis was obtained by the streptococcus extract only and this in every case although the streptococci used were not cultivated from cases of scarlet fever. Liverato considers his findings an important contribution toward the proof of the streptococcal nature of scarlet fever.

Schleissner[7] used suspensions of streptococci from scarlatina, erysipelas, puerperal sepsis and panophthalmia as antigen. The serum of scarlatina, especially, reacted positively with scarlatinal streptococci, whereas control serums from other infections never gave a positive reaction. Some serums, however, reacted positively with other streptococci, as those of puerperal sepsis and panophthalmia. In a later communication[8] the same author tries to bring additional proof for the specificity of the scarlet streptococcus by means of bactericidal experiments. A mixture of leukocytes, rabbit serum and scarlet fever streptococci, plated out in blood-agar, showed in most cases complete destruction of this streptococcus, while other streptococci pathogenic for man (erysipelas, puerperal fever) multiplied without restraint. Kolmer[9] obtained complement deviation of serums from scarlet fever with streptococci in only 12.2 per cent.

From all this it is plain that the serum of scarlatinal patients contains antibodies for the streptococcus. This speaks undeniably for the intimate biologic relation of this microorganism to scarlet fever. The existence of a specific scarlatinal streptococcus, however, is not demonstrated by this work, and no light has been shed on the primary etiology of the disease. The very presence of antibodies for streptococci cannot solve the problem as to whether the streptococcus is the primary agent of the disease or a secondary invader and even if it had been shown that this reaction were obtainable only with scarlatinal serum, and streptococci cultivated from scarlatina, the question of the etiology of the disease would still be unsolved. In this connection the work of DeWael and Sugg[10] may be recalled.

They found that the streptococci constantly present in small-pox are specifically and exclusively agglutinated by the serum and other serous liquids of variola patients and convalescents in a dilution up to 1:800, but not by any other immune streptococcus serums. This does not permit the conclusion that perhaps small-pox, too, is a streptococcus disease, a supposition which has been disposed of by unquestionable experimental evidence,[11] but it points to a very close relation between the primary virus and the secondary infection. That this is really a form of symbiosis has been shown[12] in the following way: If the cornea of a rabbit is treated with a mixture of variolous virus, active serum and streptococci, there results a violent reaction which, however, fails to appear if the variolous virus alone, or the streptococci alone, or the serum alone is inoculated.

SPECIFIC TREATMENT

This relation of the streptococcus to scarlet fever, together with the fact that only too often the ultimate fate of the patient depends on this secondary invader, suggests the reason for using efficacious antistreptococcus remedies and explains their eventual specific effect.

Time does not permit me to speak here of the therapeutic results obtained with the various streptococcus serums advocated as specific in the treatment of scarlet fever. But it may be emphasized that only those antistreptococcus serums should be used which have a potency in content of antibodies, or faculty to stimulate the phagocytic activity of the leukocytes, ascertained by reliable laboratory tests.[13]

One form of specific treatment I wish to mention here not so much for the practical value attributed to it but on account of a phenomenon which has direct bearing on our account of the pathogenesis of scarlet fever. This is the prophylactic treatment of Gabritschewsky,[14] by means of a streptococcus vaccine used quite extensively by Russian physicians. Langovoi, Nikitin, Vladimiroff and Tesjakoff have published detailed reports of the prophylactic use of this vaccine. Thus, in the years 1907-1909, Tesjakoff vaccinated prophylactically, 15,376 children, in eighty-six different foci of the scarlet fever epidemics at that time.[15]

Of these 15,376 children, 7,234, or 47.6 per cent., were vaccinated once; 4,060, or 27.4 per cent., were vaccinated twice, and 4,078, or 26.5 per cent., were vaccinated three times.

4. Metchnikoff: Virchows Arch. f. path. Anat., 1887, cvii, 209.
5. Foix and Mallein: Presse méd., 1907, xv, 777.
6. Liverato: Centralbl. f. Bacteriol., liv, 422.
7. Schleissner: Folia serol., 1909, iii, 271.
8. Schleissner: Jahrb. f. Kinderheilk., 1911, xxxviii, 317.
9. Kolmer: Arch. Int. Med., February, 1912, p. 220.
10. DeWael and Sugg: Arch. intern. de pharm. et de thérap., 1903, xii, 205.
11. Perkins and Pay: Jour. Med. Research, 1903, x, 195.
12. Prowazek and de Beaupaire: München. med. Wchnschr., 1908, lv, 44.
13. See in this connection the work of G. H. Weaver and Ruth Tunnicliff: Jour. Infect. Dis., 1912, ix, 130.
14. Gabritschewsky: Ztschr. f. Bacteriol., 1906, xli, 7.
15. For complete literature on vaccine prophylaxis see Smith: Boston Med. and Surg. Jour., 1910, clxii.

Of all the children vaccinated 746, or 4.8 per cent., were taken sick with scarlet fever.

Of those vaccinated once, 478, or 6.6 per cent., were taken sick; of those vaccinated twice, 182, or 4.5 per cent.; of those vaccinated three times, eighty-six, or 1.9 per cent.

From these figures Tesjakoff concludes that whereas one vaccination alone offers a very inefficient protection, three vaccinations produce an undoubted but not an absolute protective immunity.[16]

So far the figures of the Russian author certainly justify his conclusion, but the whole question assumes a widely different aspect if we compare these results with our conditions. Tesjakoff obtained in the children which he vaccinated three times such a percentage of morbidity as to reach 1.9 per cent. The morbidity in Chicago in the four years 1907-1910 shows an average of only 0.3 per cent. of the whole population, without prophylactic treatment. This does not infringe on the value of the prophylactic vaccination as such but emphasizes how important it would be to know intimately the character of the severity of scarlet fever at every period of the year in the various countries of the world before we could apply such statistics directly to our own conditions.

Gabritschewsky as well as Langowoi and Vladimiroff, later observed in about 10 per cent. of the children vaccinated a very startling manifestation. The place of the injection of the vaccine showed not only the usual signs of local reaction but the lymph-vessels and lymph-nodes of this region became involved, swollen and painful. A small macular exanthem appeared round the point of injection and developed soon into a general scarlatiniform eruption. The general condition of the patient grew worse, an angina and strawberry tongue developed and as early as the second and third day a desquamation appeared, in some cases even going to hematuria. This whole picture resembles so closely that of scarlet fever that Vladimiroff concludes that this phenomenon demonstrates the primary etiologic rôle of the streptococcus. In regard to this idea, it must first be said that in a study of the prophylactic use of the streptococcus vaccine in Boston, not one such phenomenon has been observed.[17] Further, in this age of extensive vaccine therapy streptococcus vaccine has been used in the last year in many thousand cases without one report of a single case in which similar symptoms developed.

LATEST RESEARCHES INTO ETIOLOGY

It is obvious that it would be of value in our understanding of the pathogenesis of scarlet fever if it could be demonstrated that other antibodies than those for streptococci are present in the blood with some constancy. The attempt has been made unsuccessfully by several investigators with the complement-deviation method. The failure seems to have been due to the choice of an unsuitable antigen from too close an adherence to the Wassermann method. In the search for antibodies in a disease the germ of which is unknown or not capable of cultivation such organs should necessarily be used as antigen which clinically as well as anatomically appear to be involved principally. In scarlet fever this was found to be not the liver but the lymph-nodes. The condition which an appropriate antigen must fulfil for use in the search for a specific scarlatinal virus seemed to my associates and myself to be the following: (1) The organs must come from an acute toxic case of scarlet fever in which the patient succumbed rapidly and without secondary reaction and complications; (2) the blood of the patient examined in the last stage before death should contain no streptococci; (3) the blood-serum ought, further, on being tested with an active scarlatinal streptococcal emulsion, to show no deviation of the complement and the activity of the streptococcus antigen used should be tested with the corresponding immune serum; (4) the extracts must show by culture experiments that they contain no streptococci; (5) the watery organ extract tested with antistreptococcus immune serum should show no deviation of complement. From the especially mild character of scarlet fever in Chicago, it was not easy to find such foudroyant and toxic cases as answered to these five conditions. My associates and I succeeded after long preliminary tests in finding three cases the conditions in which corresponded to all the demands which we had placed on a suitable antigen. We employed only inactivated serums which were obtained on the day of the experiment. As amboceptor the serum of rabbits immunized against sheep's blood was used. In order to know whether normal amboceptor for sheep's blood was contained in the human serum we tested this each time without the addition of antigen and amboceptor. If by this control test we obtained hemolysis we removed the natural chief amboceptor by absorption and then repeated the experiment. Besides the normal serums, serums of measles, diphtheria, erysipelas, malignant tumor, tuberculosis and nephritis were used as controls. None of these control serums prevented hemolysis with the extracts. In 118 cases of scarlet fever the serums were tested in this way for antibodies against the extract described, eighty-one, or 68.6 per cent. showing a complete binding of complement. It is interesting that of the serums from cases of scarlatinal nephritis examined, every one gave a positive reaction. In respect to the time of the first appearance of these antibodies it may be said that they do not seem to be present in the blood in demonstrable quantities before the onset of the second week, the eighth day being the earliest in which positive reaction was obtained. So far as the duration of the action is concerned the serum was found to be active in the twelfth week and in one case of scarlatinal nephritis even in the sixteenth week. The following conclusions were suggested by the results obtained:

1. The serum of scarlet fever patients contains specific antibodies for an unknown virus.

2. This unknown virus seems to be present especially in the cervical lymph-nodes.

These conclusions lead necessarily to the inference that the streptococcus is to be discarded as the etiologic factor of scarlet fever.

EXPERIMENTAL SCARLET FEVER

The great difficulty in determining the specific properties of material containing the supposed virus lies in the fact that scarlet fever is not communicable to animals. Recently, however, several investigators have reported encouraging results in experimental scarlet fever. The successful work of Metchnikoff and Roux in experimental syphilis in apes suggested the use of these animals for the transmission of scarlet fever also.

Cantacuzene[18] reports that he has produced typical scarlet fever in monkeys (*Macacus cercopithecus*). From

16. Tesjakoff: Westnik. Obschestvenst Gigient, September and October, 1910; from Folia Serologica, 1910, vii, 76.

17. Watters, W. H.: The Journal A. M. A., Feb. 24, 1912, p. 546.

18. Cantacuzene: Compt. rend. Soc. de biol., 1911, lxx, 403.

nine animals injected, four showed after thirty-seven, nineteen, twelve and five days, respectively, fever of 40 C. and a purple-red eruption of the face, followed by a marked desquamation. Two of the positive results were obtained through the subcutaneous injection of the blood of one patient sick with scarlet fever, who had shown the eruption for only a few hours. Of the remaining two monkeys that developed symptoms, the first was injected subcutaneously with pericardial exudate, the other with an emulsion of the tracheobronchial glands. The blood and exudate were free from any demonstrable microorganisms.

About two months later Bernhardt[19] gave an account of experiments in the same direction. He injected an emulsion of the coatings from the tongue in the early stages of scarlet fever into the groin of his monkeys. Some of this material he rubbed over their tonsils and tongue. This inoculation was followed by a rise in temperature and swelling of the lymph-nodes in the inguinal region and on the fifth day the animals were quite sick. The inguinal glands were now extirpated and an emulsion of them injected into the groins of another series of monkeys. After three such passages this material was free from streptococci, yet it was still virulent for the animals. The symptoms developed were similar to those of scarlatinal fever, a punctiform exanthem on face, neck, shoulders and chest, and the characteristic strawberry tongue. This was followed by a lamellate desquamation. These symptoms appeared whether the material injected was freed from streptococci by filtration through a Berkefeld filter or not. But streptococci alone did not produce the characteristic symptom-complex.

While Bernhardt used for his experiments the lower monkeys (*Macacus cercopithecus*), Landsteiner and Levaditi[20] used chimpanzees, the same species as Metchnikoff and Roux had first used successfully in the experimental transmission of syphilis. They took the coating of the tonsil and the blood of children sick with scarlet fever as material. By introducing this into the throat and by inoculation under the skin, they produced a disease in one chimpanzee, characterized by fever, an angina, with redness and swelling of the mucous membranes of pharynx and tonsils, and the formation of a grayish-yellow deposit on the latter, and swelling of the papillæ of the tongue. A general eruption followed resembling closely the scarlet fever rash in children. This ape died and the post-mortem findings showed lesions in the kidneys and the skin and a tumefaction of the lymph-nodes which Landsteiner and Levaditi consider as identical with the changes found in human beings. With streptococci isolated from scarlet fever patients they were unable to produce the disease picture.

Hektoen and Weaver[21] reported some experiments made during the time from December, 1909, to September, 1910, in which they fed monkeys with milk which was infected with material from the throat and mouths of children sick with scarlet fever. From thirteen monkeys (*Macacus*) fed in this way, ten remained well and three died. No streptococci or other microorganisms could be demonstrated by microscopic or cultural methods. The sterile blood taken from the heart of the third monkey immediately after death was mixed with sterile milk and fed to a healthy monkey for three days. This one became sick four days after the milk was first fed, and refused food, the temperature rising to 104.1 F.; the leukocyte count was 52,000. The leukocytosis persisted for five days and disappeared as the temperature subsided and the appetite returned. This sickness was suggestive, as it came on four days after feeding and ran a short course with fever and leukocytosis; but there was no cutaneous eruption.

These are, in brief, the advances made in the last five years in our knowledge of scarlet fever. Though the etiologic agent has not been found and is yet to be discovered, the place to be attributed to the streptococcus has been more clearly recognized. The streptococcus almost constantly present leads to a systemic reaction of the organism which finds its expression in the presence of antibodies against it. The streptococcus, however, can no longer be identified with the virus of scarlet fever, whose existence and presence in the lymph-nodes in a high concentration must be assumed from the presence of specific antibodies in the blood. The experimental transmission of scarlet fever to apes and monkeys substantiates this statement and points to new possibilities for the closer study of the nature of this virus.

32 North State Street.

19. Bernhardt: Deutsch. med. Wchnschr. 1911, xxxvii, 792.
20. Landsteiner and Levaditi: Compt. rend. Soc. de Biol., 1911, lxx, 641; Gaz. d. hôp., 1911, p. 784. Landsteiner, Levaditi and Pracek: Ann. de l'Inst. Pasteur, 1911.
21. Hektoen, L., and Weaver, G. H.: THE JOURNAL A. M. A., June 17, 1911, p. 1795.

THE ARTIFICIAL CULTURE OF FILARIAL EMBRYOS

A PRELIMINARY NOTE *

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NEW ORLEANS

The earliest success of Bass[1] in the cultivation of certain parasitic protozoa (plasmodia) *in vitro* led one of us (Wellman) to attempt the nurture in artificial mediums of the embryos of *Filaria immitis* Leidy. At that time a considerable number of positive cultures was obtained, using defibrinated dog's blood inactivated for long periods of time at comparatively low temperatures. Since the return of the malarial expedition of the Tulane University Department of Tropical Medicine from Central America additional work has been completed, employing their technic[2] and comparing results with ordinary blood-cultures. A fuller statement of the work thus far accomplished and the details of future progress will be presented later.

Experiments were devised to determine the influence of various whole bloods, serums and diverse mediums, and also the effects of temperature, air, etc., on the cultures.

The embryos live for ten or twelve days in some specimens of sterile defibrinated dog's blood at room temperature (28 C.), and considerable increase in size occurs, the parasites growing to 1⅔ their former

* Study 24, from the Laboratories of Hygiene and Tropical Medicine under the direction of Creighton Wellman, Medical Department, Tulane University of Louisiana.

1. Bass, C. C.: THE JOURNAL A. M. A., Nov. 4, 1911, p. 1534.
2. Bass, C. C., and Johns, Foster M.: The Cultivation of Malarial Plasmodia (Plasmodium Vivax and Plasmodium Falciparum) in Vitro, Jour. Exper. Med., October, 1912, p. 567.