Original Articles.

EXPERIENCE WITH OPSONINS AND BACTERIAL VACCINES IN THE TREATMENT OF TUBERCULOUS AND NONTUBERCULOUS ARTHRITIS.*

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OBSERVERS of new phenomena lay themselves open to errors both of observation and interpretation. Particularly is this true when the phenomena concern problems, the solution of which has been sought long and diligently. There has never been a time when so many well trained men were working upon the problems of physiological chemistry and bacteriology as there are at the present day. At this time, also, great popular as well as professional and scientific interest has been aroused in the subject of tuberculosis, and, to a lesser degree, in chronic nontuberculous joint disease. Witness the money being advanced for the anti-tuberculosis crusade, and the attention devoted by all classes of society to attempts made to wipe out this curse. In the midst of all this popular enthusiasm and highly specialized scientific attainment, has come a new method which has much to recommend it from the theoretical and laboratory points of view. The questions at issue are, Do the clinical results correspond with the laboratory findings? Are the limits of error in methods of laboratory investigation so wide that the conclusions which seem legitimate from such observations may be erroneous? To the first of these questions only will the writer devote his attention.

The literature on opsonins and bacterial vaccines is getting to be quite voluminous, but the greater part of it is concerned with laboratory technic and theoretical considerations of the processes by which immunity may be brought about. A very few reports of clinical experience are on record, and many of these are valueless because of the paucity of data recorded, or because of the obvious inaccuracies of the observations.

Clinical experience must be the court of last resort in matters of this sort for many years to come. The human being is not a chemical retort into which reagents may be injected and results obtained which are identical with those we look for when experimenting in the laboratory upon the lower orders of animal life. Wonderful as have been the advances made, rational conservatism must be the prevailing state of mind of those who would not be carried away by their enthusiasm.

Attempting to put ourselves in this mental attitude, it is proper to review the facts. The laboratory side of the question has been thoroughly presented in the previous paper, and even though clinical experience cannot wholly bear out the brilliant results obtained along purely scientific lines, this does not in any way vitiate the results of such inquiry.

Successes obtained by some observers in the

treatment of septic wounds, boils, acne, and similar localized infections, encourage the clinician to hope that there are as yet some ill-understood obstacles in the way of the application of the method to those conditions where it has failed. The good results in some other fields, notably in the treatment of diphtheria, by an analogous method, also offer much encouragement. One cannot read the literature covering the clinical experience of the writers without considerable misgiving as to the practical value of bacterial vaccination. Neither can he be particularly encouraged in the hope that the opsonic index is to be of advantage as a guide to the dosage or the repetition of inoculation. The consideration of its value as a diagnostic aid has not been extensively considered in the literature. Its value from this point of view, in the writer's experience, will appear in the course of this paper.

A few citations from current literature to show the character of the reports of clinical observers may not be amiss. These are cited because in most cases the writer believes acceptance of the findings at their face value would lead the uninitiated reader to improper conclusions regarding the efficacy of the method. French,¹ in the *British Medical Journal*, reports a case of tuberculous dactylitis and tuberculous disease of the os calcis, both having fistulæ. The child had a low opsonic index to the tubercle bacillus. One five thousandth mgm. of tuberculin "R" was given. A negative phase lasting nearly four weeks was the result. A second inoculation, again followed by a prolonged negative phase, was accompanied by some improvement. A third inoculation was given and the sinuses then promptly healed, and at the end of four months the writer says the patient was practically well. Such a case as this, even though it represents an observer's personal experience with bacterial vaccines in the treatment of tuberculous arthritis, should not be given much weight in determining the value of tuberculin in the treatment of bone disease.

Ohlmacher,² writing in the *Journal of the American Medical Association*, reports a remarkable series of cases of various sorts treated by bacterial vaccines. In determining the dosage and frequency of inoculation he was admittedly lax in the observation of the opsonic index, without which Wright himself, and Ross, the principal exponent of his technic on this side of the water, claim satisfactory results cannot be obtained. In spite of this failure the results were so uniformly good in all cases, he concludes that, with the possible exception of diphtheria antitoxin in the treatment of diphtheria, there is no more valuable reagent than bacterial vaccines for the treatment of many surgical infections.

Kellogg³ finds the determination of the opsonic index of value diagnostically in the following reported case: A young woman consulted him because of a troublesome hip. There had been an injury to this joint some years previously, and she had been obliged to use crutches during all

¹ H. French: *Brit. Med. Jour.*, Feb. 2, 1907, p. 256.

² Ohlmacher: *Jour. Am. Med. Asso.*, Feb. 16, 1907.

³ Kellogg: *Northwest Med. Jour.*, vol. v, no. 1, p. 20.

*Read before The Massachusetts Medical Society, June 11, 1907.

this time. The head of the affected femur was dislocated. One observation showed the tubercular opsonic index to be .22. From this he concludes that the disease was a tuberculous one. In all probability this was true, but to have argued that it was because of one positive result in testing the phagocytic power of her leucocytes, constitutes a very insecure basis for such a conclusion. A second case is reported by the same author. A patient came under his care for a pleural effusion. The chest was aspirated, but guinea pigs inoculated with this fluid showed no signs of tuberculosis. A diagnostic dose of tuberculin was given and a typical reaction followed. Between July 12 and August 24, of the same year, she was inoculated with Koch's tuberculin, "R," not over three times (the record states at ten-day intervals). At the end of this period her physical signs had all cleared up and her weight had increased $7\frac{1}{2}$ lb. I submit that the proof of the tuberculous character of her effusion is lacking, and that to offer such a case as a striking example of the curative value of tuberculin in such conditions is improper.

Wolff⁴ reports some interesting results in the treatment of pneumonia by a pneumococcus vaccine. He feels that raising the opsonic power of the patient's serum in pneumonic cases was attended by more favorable results than attends the usual treatment of pneumonia patients, but thinks too few observations have been made to justify any positive assertion that such is the case.

Hollister⁵ reports several cases too briefly to be of any scientific value. The general impression conveyed was that there was improvement, but not such as would be inconsistent with other and general treatment, simultaneously carried out.

Ross,⁶ in a recent article, reports success in a number of cases of lupus, empyema, staphylococcus infection, endocarditis and Malta fever.

Bunch⁷ refers to two cases where bacterial vaccines were employed to reinforce surgical treatment. He believes that this method offers great possibilities in the management of surgical tuberculosis by diminishing the negative phase produced by operating upon tuberculous foci, when the resistance of the patient has not been properly fortified. He also advocates the use of vaccines after operation during long periods, for the same reason. He cites a case of extensive lupus operated upon by Mr. Godlee. The operation was an excision of the lupoid tissue, followed by skin graft. Before the operation and for some time after, injections of tuberculin were carried out, in consequence of which he believes that the entire graft was successful. One one-thousandth mgm. was used at ten-day intervals. He also reports a case of acetabular hip disease which had been treated for one and one-half years, by apparatus and bed treatment, without any appreciable progress. An abscess developed, for which

operation was performed. Just before operation 1-500 mgm. of tuberculin was injected, and this was repeated during the succeeding four months, at the end of which time the patient was reported as practically well. He also refers to an article of Turton's, in which 30 out of 34 cases of different sorts were treated with bacterial vaccines with very satisfactory results.

Fraser⁸ reports 41 observations upon the opsonic power (tubercular) of the blood in healthy individuals. In the first place she attempted to establish a mean of variation. In the second place she compiled a table of 43 indices from individuals who were suffering from other diseases than tuberculosis. She also reports observations upon the tuberculo-opsonic index in nine members of tuberculous families. Her next series of observations was upon 91 cases of tuberculous disease. She found no striking diagnostic value in the tuberculo-opsonic index. In 58 of these cases the index was higher than that seen in health, while in 33 it was within normal limits. She found she could not classify her cases according to their indices as Wright claims to be able to do. The low index did not necessarily show a localized focus; neither did a high index, within the limits of variation, indicate a generalized process.

Brooke⁹ refers to Bullock's remarkable series of staphylococcus infections reported in the *Practitioner* for November, 1905. Eleven cases treated with vaccines showed 9 prompt and complete cures.

There is a notable absence of clinical reports in German and French literature. This absence should have considerable more significance than does the too sanguine position of the observers to whom reference has been made. A few good results have been reported following the use of Marmorek's antituberculous serum, conspicuous among which are the cases cited by Hoffa in a recent article.¹⁰

In July, 1906, at the commencement of a four months' service at the House of the Good Samaritan, I began the treatment of tuberculous bone disease with Koch's new tuberculin. The inoculations have been kept up by my colleagues, Dr. Augustus Thorndike and Dr. J. S. Stone, during their services up to the present time. The patients upon whom this treatment had been tried were kept in the hospital in nearly every instance throughout this entire period, so that in addition to any benefit which may have accrued from these injections, they have had the benefit of sanitarium treatment. They were all advanced cases when treatment was begun, and were all children. In addition to these children I have followed the same treatment in a few cases of tuberculous bone disease in the adult, at the Carney Hospital. These patients had not the benefit of as good hygienic treatment as had the group at the Samaritan. It was not possible to keep them in the hospital for as long periods and they could not be controlled as well, because they were adults. They were all bad cases. The laboratory work

⁴ Wolff: *Jour. of Infectious Diseases*, Oct. 30, 1906.

⁵ Hollister: *Surg., Gyn. and Obstet.*, vol. iii, no. 6, p. 740.

⁶ Ross: *The Canada Lancet*, January, 1907.

⁷ Bunch: *Lancet*, London, Jan. 19, 1907, p. 145.

⁸ Fraser: *Glasgow Med. Jour.*, March, 1907, p. 194.

⁹ Brooke: *Dublin Jour. Med. Sc.*, Sept. 1, 1906.

¹⁰ Hoffa: *Berliner klin. Wochenschr.*, xliii, no. 8.

in connection with these observations was done through the courtesy of Dr. Leary at the pathological laboratory of the Tufts Medical School. In private practice I have also treated a few patients with bone tuberculosis in this way and in both private practice and at the Carney Hospital clinic we have treated several cases of chronic polyarthritis, of the rheumatoid type.

In brief detail the cases and results have been as follows (their charts have been shown in Dr. Leary's paper):

CASE I. Mrs. B., thirty years. Tuberculosis of the lumbar spine, the left ankle and the right great toe. Clinical diagnosis confirmed, so far as the ankle lesion was concerned, by histological examination of material removed at operation and by the tuberculous opsonic index. Patient had been under apparatus treatment for the Pott's lesion for two years and for the ankle one year. Ten injections of tuberculin were given, beginning with 1-10000 mgm. and going as high as 1-500 mgm. on two occasions. The Pott's lesion has made good progress; the ankle lesion was much worse than at any time for a period of three months, but has slowly been improving during the past four months; the lesion on the great toe has caused no trouble at any time during or immediately before the commencement of the injections. Rest and fixation have been enjoined throughout this entire period. The patient has gained in weight, improved in color and general condition, but no more so than has often been experienced in the same time and under the same conditions of hygiene and protective treatment.

CASE II. Mr. K., thirty-three years. Tuberculosis of mesenteric and retroperitoneal glands. Suppuration and mixed infection with the bacillus pyocyaneus. There is in all probability at this time an osseous involvement of the lumbar spine. There has been no pathological confirmation of the clinical diagnosis. The case has been under treatment for ten months and has had thirteen inoculations with tuberculin and a streptococcus and pyocyaneus vaccine. During the first five months of treatment there was considerable improvement in general condition and local signs, together with an almost complete closure of the sinus. The past six months his general condition has failed markedly; he has developed a very well defined phthisis, his sputum being loaded with tubercle bacilli, and the local signs in his spine have become much worse. His sinus is discharging very freely and death seems imminent at any time.

CASE III. Mr. A., twenty-nine years. Tuberculosis of left hip. Excision. Clinical diagnosis confirmed by histological examination. A very acute case of hip disease, said to be of only four months' duration at the time of admission to the Carney Hospital for excision of the head of the femur. Inoculation commenced before operation in the hope that his local and constitutional resistance might be built up. (*Vide opsonic chart.*) After operation there was a pyocyaneus infection and he was given pyocyaneus vaccine in addition to tuberculin. He was operated upon Oct. 17, 1906, and discharged Jan. 21, 1907. He improved slowly but reacted, it seemed, better than most cases of such severity, and since he left the hospital is reported to be doing well.

CASE VI. Miss M., forty-eight years. Tuberculous cervical adenitis. Phthisis. Chronic infectious polyarthritis. Glands in the neck suppured. No tubercle bacilli found in smears from this pus; pus not injected into guinea pig. Tubercle bacilli in sputum. Patient had three inoculations with Koch's old tuber-

culin, and later this was changed to the new "T. R." There was no appreciable improvement in the local condition of the glands, and her pulmonary process became worse. She had five inoculations of the new tuberculin at ten-day intervals. She was discharged from the hospital after a stay of eight months, in a worse condition than at entrance.

CASE V. M. W., five years. Tuberculosis of the lumbar and low dorsal spine. Abscess. The child has been at the House of the Good Samaritan for two years. On entrance there was a large cold abscess which was opened. Tubercle bacilli were demonstrable in a smear from the pus and were grown on culture media. A few days after the abscess was opened he developed scarlet fever and was admitted to the Boston City Hospital. On his return he was treated a year in the wards with jackets. One year ago tuberculin treatment was commenced and as he had a secondary streptococcus infection of his sinus, he was given a streptococcus vaccine, made from his own organism, in addition to his tuberculin. His opsonic chart has been shown. There has been no local improvement of a permanent character. His sinus is still discharging and he has positive signs of phthisis and a suggestion of the development of an hypertrophic pulmonary osteo-arthritis.

CASE VI. Master C., seven years. Tuberculosis of hip. Amyloid. Clinical diagnosis confirmed by histological examination after operation and by animal inoculation. In many ways this was a most remarkable case. The child came under observation at the Carney Hospital in less than a week after his first symptoms. Limp, pain and muscular spasm, accompanied by a high temperature, led to a diagnosis of acute osteomyelitis. At operation a small amount of pus was obtained coming from a necrotic focus in the neck of the femur. The process extended both up and down the femur and a secondary operation was performed for the removal of more of the dead bone. This was succeeded by an acute nephritis, which virtually became chronic. The spleen and liver were greatly enlarged and there was profuse suppuration from sinuses in the thigh. The boy was soon in such poor condition that it seemed as though he might die at any time. Inoculation with 1-1000 mgm. of tuberculin was commenced and repeated on the average of once in ten days. Improvement, though slow, has been steady since the injections were begun. There is much less discharge from the abscess, his color is better, and his abdominal distention is greatly diminished. The urine also shows less of the products of a chronic nephritis than it did some months ago. This patient had a mixed infection with staphylococcus and was given a staphylococcus vaccine along with the tuberculin. About twenty inoculations were administered. There has been a decided improvement in the general condition of this patient, a change which it seems fair to attribute to the administration of tuberculin. This case would not have been so suggestive were it not for the fact that at the same time we had another child in the hospital in almost the same condition.

CASE VII. F. S. This child is a boy of five and one-half years. He entered the House of the Good Samaritan in the fall of 1906. He had double tumor albus, both of which were suppuring. He was very pale and emaciated and had an enormous abdominal distention, part of which was caused by ascites and part by the size of his liver and spleen. There was a marked "caput medusae." He had been having treatment under the best of conditions for the two years previous in the Children's, hospitals at Lowell and Bumkin's Islands, and failed to respond at all; in fact, had steadily grown worse. In desperation we commenced the administration of tuberculin, much against my better

judgment, as it seemed as though I should be subjecting the child to an unwarrantable discomfort. He began to improve after a very few injections and under no different constitutional treatment than he had been having for at least two years. He is not now recognizable as the same child who entered the hospital seven months ago. He is fat, of good color; his sinuses are nearly healed; his abdomen is soft and very little enlarged; the area of liver dullness has diminished, and though both spleen and liver are palpable, they are greatly diminished in size. Both knees are nearly completely ankylosed, but in very good position. He has had tuberculin administered with more or less regularity since his entrance. This case seems certainly to have benefited in a most extraordinary manner by the use of tuberculin.

CASE VIII. F. K., six years. Tuberculosis of both hip joints. Abscess. Erysipelas. Child was under treatment at various places for a fairly active tuberculous process in both hips. The left one suppurated, and during the course of the treatment the sinus became infected with streptococci, and she had quite a virulent erysipelas. A culture from her own sinus gave us the opportunity to make a streptococcus vaccine from her own organism, and this was administered along with her tuberculin injections. In this case the pus burrowed out below Poupert's ligament on the anterior surface of the thigh, and though opened freely, two or three times, under ether, refused to cease discharging. After the commencement of vaccine injections there was a very rapid diminution in the discharge until it finally ceased altogether. She was in the hospital about five and one-half months. Her chart has been shown. The progress of the tuberculous phase of her trouble was not affected by the use of tuberculin in any way.

CASE IX. A. McD., four and one-half years. Tumor albus. Abscess. Flexion and subluxation deformity of the knees. This child was transferred from the Convalescent Home of the Children's Hospital, where he had been under treatment for a year or more. His general condition was excellent. The knee itself had six or eight sinuses, from which there was moderate discharge. The joint was very much swollen, caused chiefly by bony thickening. A culture from his sinuses gave a pure culture of the staphylococcus. From this a vaccine was prepared and administered along with tuberculin during the fall and winter of 1906-7. During the past three months he has been at the seashore hospital at Marblehead, and his sinuses are reported closed. During this time he has not been having tuberculin. I could not observe any unusual response to treatment in this case.

CASE X. Miss P., twelve years. Tuberculosis of left hip. Abscess. This child entered the hospital with a very acute hip. She came from poor home surroundings and had had no adequate care. The thigh was flexed to a right angle with the body and traction would not overcome the spasm. Ether was given and the position corrected. Later a deep seated abscess appeared and was opened. From the time that I manipulated her in October, 1906, she commenced to fail. Tuberculin was administered before the manipulation and was continued through the fall and early winter without any effect; the patient became generally infected and died in March, 1907, of tuberculous meningitis. In this case I made the mistake of manipulating the hip-joint and precipitating into the child's general circulation more tuberculous toxins than she could neutralize. I very much question, in view of that fact, if it was proper to have given tuberculin. This catastrophe should not be cited as an argument against the employment of tuberculin, except in cases of a similar character.

CASE XI. Mr. B., forty-five years. Tuberculosis of left hip. Operation. Clinical diagnosis was confirmed by histological examination. Patient was a longshoreman, who had a rapidly developing ankylosis of his left hip, without shortening. An x-ray showed nothing suggestive of tuberculosis and it was regarded as a non-tuberculous, infectious process. Under ether the hip was manipulated. The motion gained was not preserved. Suspicion of tuberculosis again being aroused, he was given a diagnostic dose of tuberculin and had a sharp constitutional reaction but no exaggeration of local symptoms. An open operation was performed upon the hip later, and a number of spurs removed from the superior lip of the acetabulum and a small abscess was exposed in the region of the gluteal bursa. The pathological report from this was tuberculosis. Injections of tuberculin were commenced and continued through the summer, fall and early winter of 1906-7. The patient gradually failed, developed signs of phthisis, and died in the early spring of 1907. Again, in a case of this sort, the lesson it seems to me is that tuberculin is not to be administered, whatever other indications there may be upon estimates of the opsonic power of the patient's serum. Both this case and Case X were treated according to their opsonic indices.

In this series of 11 cases, therefore, we find 4 who were not benefited at all. Two were apparently most extraordinarily improved, and still another (case III) experienced an improvement which, considering the gravity of the symptoms, may fairly be classed as attributable, in large measure, to his vaccines. Two have died and a third is dying. It is an open question if another (case V) has not been made temporarily worse by the treatment. If we take out the 2 cases who have died, and it is fair to do this because they were cases in which the surgical measures employed may have imposed more of an infection upon the patients than it was reasonable to suppose any vaccination could take care of, there are only 2 cases left to speak positively in favor of the employment of tuberculin in the treatment of bone and joint disease. My experience, however, leads me to wish to give the method a longer trial, and with a more judicious selection of cases, I believe better results may be forthcoming.

If the outcome of vaccine treatment has not been brilliant in tuberculous lesions it has been even less so in the case of non-tuberculous lesions.

In chronic polyarthritis it would be the greatest possible boon if the opsonic test could be employed to discriminate between types of infection. If this could be accomplished with any degree of certainty, the next step, that of making a bacterial vaccine for purposes of treatment, should be a comparatively easy one.

In the earlier part of our experience with opsonic work there seemed to be considerable to suggest the possibility of a solution of the problems in the diagnosis and treatment of chronic polyarthritis. When, however, one regards the cases through a long perspective, there is not much to give encouragement at the present time. In acute infectious lesions of joints, such as gonorrheal arthritis, encouraging reports are coming from such reliable sources as the Johns Hopkins

Hospital and the Loomis Laboratory in New York, but the chronic problem seems to be a very different one.

Schüler, in Germany, has isolated from a very large proportion of the cases upon which he has been privileged to operate a bacillus which he regards as the specific organism of chronic progressive polyarthritis. Three years ago Fayerweather isolated from the knee-joint of a patient, upon whom I had operated at the Carney Hospital, an organism which he has described¹¹ and which Schüler¹² has declared from the description in Fayerweather's article to be identical with his bacillus.

The cultures of this organism had been preserved in the Tufts Pathological Laboratory, and we have been working with a vaccine which Dr. Leary has prepared from these cultures, in an attempt to diagnose and treat the type of polyarthritis with which, according to Schüler, this bacillus is constantly identified. All that can be said as a result of practically a year's experience with the application of the opsonic test for this bacillus is that we have been able to obtain a characteristic serum reaction in the blood of nearly all the patients who were possessed of the clinical signs of this type of polyarthritis. When it has come to treatment I think it is fair to say that there has been no considerable degree of improvement in any case, at least none which is not frequently seen in cases treated by other methods.

The fact that there has been such a uniformity in the opsonic findings in cases that are clinically of one type, together with this further observed fact, that when inoculated with a vaccine made from this organism they reacted locally, just as tubercular joints will react locally to too large an injection of tuberculin, it would seem that a lead had been given which it is worth while to follow.

The following cases are reported to show the kind of problems which have been attacked rather than to record favorable results of treatment:

CASE XII. Mrs. L., forty years. Infectious polyarthritis. For five or six years the patient has been gradually becoming crippled in all of her principal joints and has been a great sufferer. With it all has come a considerable degree of neurasthenia. The joints are swollen, only slightly deformed, and possess very little motion. There is occasionally some redness over the phalangeal joints. Patient has been able to sit up in a chair, but walking has been impossible, except with the assistance of two persons to support her. All the possible sources of infection were investigated to make sure that there was no present infective focus. A blood culture was made and found to be negative. Cultures from the stools were also made, but the investigation along this line was not completed. The opsonic index to the staphylococcus aureus, the streptococcus, and Schüler's bacillus of villous arthritis was determined. The reports showed that the index was low, at various times, to each of these organisms, and vaccines were given for considerable periods, being graduated according to the response of the patient's serum to the inoculations. After approximately five months of such treatment there has been no appreciable improvement in the patient's local condition, which could

be attributed to the vaccines. I think it is fair to assume, therefore, that the inoculation treatment in her case has been a failure.

CASE XIII. Mr. F., forty-eight years. Chronic, progressive, infectious polyarthritis. Three years' duration. No present source of infection made out. Eighteen years ago had gonorrhea. Nearly all the joints in the body have become involved. No redness or other signs of acute inflammation. Marked deformities of the knees and limitation of motion in all the joints which have been involved. A blood culture was sterile. The patient's index was low to Schüler's organism and also to the streptococcus. No improvement attended the administration of vaccines from either of these organisms. During the treatment the patient has developed an iritis which has pretty completely impaired the vision in one of his eyes.

CASE XIV. Mr. S., twenty-one years. Chronic infectious polyarthritis. After an exposure to dampness and cold one year before entrance to the Orthopedic Clinic of the Carney Hospital, the patient began to have swelling, stiffness and pain in both knees. This was rapidly succeeded by similar conditions in the wrists, fingers and feet. His index was low to Schüler's organism, but neither local nor constitutional condition was benefited at all by a few inoculations with a vaccine made from this organism.

CASE XV. Mrs. S., thirty-eight years. Chronic infectious polyarthritis. Patient has had a chronic suppurating ear for several years. Following the birth of a child five years before, coming under vaccine treatment, she began to have trouble in several joints. The knees have become so badly flexed that she cannot straighten them completely. Her index was low to the streptococcus. The injection of a vaccine made from three strains of streptococci produced no alteration in the local condition, except that the pain was worse and there was greater stiffness immediately after the injections. The discharge from the ear practically ceased, but this may have been in consequence of careful treatment at the hands of an aurist.

CASE XVI. Miss L., thirty-five years. Chronic progressive polyarthritis. The patient has been more or less constantly afflicted for five years with painful, stiff joints, particularly the knees, wrists, elbows and ankles. The symptoms were not very acute at the time she came under observation. She had had two very badly infected tonsils, and they were both removed; she had also had acute sinus inflammation. Her index was determined to be low to the streptococcus and also to Schüler's organism, and she was given faithfully for several months a vaccine made from a triple streptococcus culture. She also received a number of inoculations with a vaccine made from Schüler's organism. Neither of these produced any permanent effect. At times she, as well as several other patients, seemed to receive some temporary benefit from the inoculation.

CASE XVII. Mr. W., forty-five years. Infectious polyarthritis. For four or five years he has been gradually becoming stiffened in the joints of his knees and hands. One year ago he had an attack of pneumonia, during which the swelling disappeared entirely from his joints, and when he commenced to get about during convalescence, he felt that his arthritis had entirely disappeared. This immunity from former joint symptoms was only temporary, for within a few weeks all his old troubles had recurred, and since that time the knees had flexed to such a degree that walking was painful and difficult. The patient's index was taken for the staphylococcus, streptococcus, pneumococcus, colon bacillus, and Schüler's bacillus. His index was low to the pneumococcus and Schüler's bacillus. Vaccines

¹¹ R. Fayerweather: *Am. Jour. Med. Sc.*, Dec., 1905.

¹² Schüler: *Am. Jour. Med. Sc.*, Aug., 1906.

from these two organisms were repeatedly given, guided by the opsonic index, and no material improvement occurred, which could not be attributed to local and constitutional treatment coincidentally carried out.

CASE XVIII. Mr. S., fifty-two years. Subacute phlegmon. Two years ago, while in Egypt, had a very acute phlegmon of the cheek, for which he was operated upon in Cairo, and had at the same time very large and often repeated inoculations of antistreptococcic serum. Since then, in various parts of his body, never in any joint, but usually in close proximity to some large articulation, he has had more or less subacute phlegmons. One of these, close to the elbow joint, was incised and a pure culture of the staphylococcus aureus was obtained. From this culture a vaccine was made and the patient was given several inoculations of this vaccine without any appreciable benefit.

The next 2 patients had intermittent hydrops.

CASE XIX. Mr. R., thirty-six years. Intermittent hydrops. Psoriasis. For seven years has had at irregular intervals an intermittent swelling in both knees and both ankles. Associated with this condition has been a very general psoriasis. When, as has happened on several occasions, he has had freedom from joint symptoms for six months at a time, he has also been entirely free from psoriasis. The knees have caused him the greatest inconvenience. The right one has been the more swollen and has had a five-day interval between attacks. The cycle for the ankles was not as clearly defined and he had never taken the trouble to determine it. The capsular swelling in the knees wholly disappeared. The right knee-joint was subjected to an arthrotomy with the hope that the cycle might be broken up. A culture taken from the interior of the joint gave the staphylococcus, which seemed a peculiar bacteriologic finding, but a vaccine was made from the culture and was regularly administered. For three months the operated knee showed no signs of an intermittent swelling. The left knee during this period was less inclined to swell, but did so to some extent. At the end of this interval the right (operated) knee returned to its cyclic distention, though the enlargement has not been as great as before. Observations upon the opsonic index at first showed that it was low to the staphylococcus, but later on the streptococcus seemed to be the organism which showed a low index, and accordingly a streptococcus vaccine was substituted, but without any alteration in progress of the trouble.

CASE XX. Miss S., thirty years. Intermittent hydrops. Both knees have swollen alternately every seven days for over two years. Two days were required for the swelling to attain its maximum and recede. The swelling caused a little pain for a few hours, but chiefly inconvenience from the enlargement. Her serum was tested and found to be low to the streptococcus. A vaccine was injected regularly for some time, but not carefully watched with opsonic tests. The patient has been taking Fowler's solution alternating with quinine during this entire period. There have been two intervals of two weeks each when there was no appreciable swelling in either joint, but this has occurred before under other treatment and no treatment. The amount of swelling is decidedly less, though except for the two intervals cited, there has been no intermission of the regular cycle.

Discouraging as these cases are, looked at from the clinical point of view, it must be remembered that we have been applying a new method, the shortcomings of which are not at present wholly understood. Circumstances have sometimes ex-

isted making it impossible that some of the conditions imposed by laboratory investigators could be carried out. It may be that cases have been treated with vaccines made from organisms having no possible kinship to the organisms originally present in the patient, though the opsonic findings have pointed that way. Again it may be possible that some of the conditions treated were not originally caused by an infective agent. These and many other obstacles stand in the way of drawing conclusions from the results of the first year's clinical experience. A good many more cases were treated and tested than have been recorded here, but those selected for report were chosen because they covered the types of cases most satisfactorily. It would have been possible to select a group, perhaps an equally large one, where the conformity of the opsonic and clinical findings would have been entirely favorable to this new method of study. So in the matter of treatment, typical opsonic charts might have been exhibited corresponding to remarkable degrees of clinical improvement. The writer believes the danger of expecting too much from an untried method is greater than that of expecting too little, and is desirous of encouraging the continuance of trials now going on in the laboratory provided they can be checked by unbiased clinical observation.

DISCUSSION.

Dr. L. S. MEDALIA, of Boston: I wish to say that some of the cases that Dr. Painter has mentioned have not been under treatment since the first of February. There are a few cases at the Good Samaritan which have been treated up to date, but those at the Carney Hospital have not been followed up since February 1.

I would emphasize the fact that this treatment has to be carefully and energetically carried out, for the conclusions drawn from those not followed up properly have been unsatisfactory.

THE SERUM TREATMENT OF EXOPHTHALMIC GOITER. A REVIEW OF THE LITERATURE.

BY FRANK S. HULKELEY, M.D., AYER, MASS.

Upon looking over the available literature on exophthalmic goiter, one is at once struck by the fact that drugs having very different actions are, or have been said to be, of benefit. Much of the treatment has been purely symptomatic, perhaps necessarily so. It is hard to see how many of the drugs used could have any influence on the causative factor in the trouble, and their main, if not only, value seems to have been in palliating certain symptoms. This leads us to ascribe the reported cures to general hygiene and the tendency to spontaneous recovery that certain cases show. In a general way such drugs may be divided into four classes: "Nerve sedatives," "vascular sedatives" and cardiac stimulants,