

THE TREATMENT OF GONORRHEAL INFECTIONS

BY THE INTRAVENOUS INJECTION OF KILLED GONOCOCCI, MENINGOCOCCI AND COLON BACILLI *

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After the intravenous administration of a highly polyvalent gonococcal vaccine, Bruck and Sommer,¹ in 1912-1913, observed striking therapeutic results in gonorrheal complications, especially arthritis, epididymitis and acute prostatitis. These results, within certain limits, ran parallel to the severity of the reaction following each injection. A specific temperature increase was noted which was higher in gonorrheal than in nongonorrheal patients; hence this method was suggested as a diagnostic as well as a therapeutic agent. At this time the entire process was attributed to the production of a specific immune substance, caused by the intravenous injection of the gonococcal vaccine.

It has been clearly demonstrated that, in typhoid injections, a nonspecific reaction follows the intravenous injection of colon bacilli, pyocyaneus bacilli, and secondary proteose preparations. These substances give results clinically and therapeutically quite like an injection of killed typhoid bacilli.

In order to determine the degree of specificity, if any were present, following the intravenous injection of gonococcal vaccine, three series of patients suffering from gonorrhea and some complication, such as arthritis, epididymitis or acute prostatitis, were chosen in the order in which they had entered the hospital,² no attempt having been made to classify them as to severity or complication. The first series was treated intravenously with a strongly reacting dose of gonococcal vaccine; the second series received a similar dose of meningococci, while the third series received a suitable dose of colon bacillus vaccine.

The patients, when possible, were kept in bed throughout the treatment, special care being taken to keep them quiet for two days following each injection. No local or internal treatment was given for the gonorrheal infection other than an elevation of the scrotum in all instances of acute epididymitis. The temperatures were taken and the leukocyte and differential counts were made just before each injection and at regular hours thereafter for the first forty-eight hours.

VACCINE TREATMENT

Gonococcus Vaccine.—The first thirteen patients were given intravenously 100 million killed gonococci, and the same or slightly varied dose was repeated

every fourth or fifth day until treatment was suspended. The greatest number of injections given one person was six; most of them received five, while one received but one injection.

The injection is followed by a chill of variable severity coming on in from twenty minutes to one hour and lasting from fifteen to thirty minutes. This chill may or may not be accompanied by headache, which is usually of short duration and passes away shortly after the chill is over. Exceptionally there are nausea and vomiting during the first few hours, but it is never severe and is always transient. This occurs always in patients who have disobeyed instructions, by eating heartily within a few hours of the injection.

At the onset and during the chill the patient often complains of severe pain in the affected parts. Whether this is due to some internal cause or to the unavoidable motion produced by the chill it is impossible to say. The pain, however, is variable in different patients and in the same patient at different times.

It is usual for the severity of the reaction to decrease following repeated injections, and this decrease is directly proportional to the number of injections previously given. In order to maintain a constant reaction with each succeeding injections of gonococcal gradually and cautiously increased.

In two of these patients, both of whom had had numerous subcutaneous injections of gonococcal vaccine, there appeared immediately following each intravenous injection a very transient reaction characterized by flushing of the face, cyanosis, dyspnea, and a tingling sensation over the surface of the whole body.

These reactions lasted from one to two minutes, after which the patients felt perfectly at ease until the usual reaction appeared in from twenty minutes to one hour. This anaphylactic-like reaction may have been due to a partial sensitization from the previous subcutaneous injections. Three other patients in this series developed a mild type of a very similar condition on their third intravenous injection, but had none following the first two, or after the fourth and fifth injections.

The typical temperature curve following these injections reveals a slight fall during the first part of the chill, followed by a gradual rise, which reaches its maximum in from one to four hours and gradually falls to normal in twenty-four hours. The average maximum temperature for the thirteen patients was 103.9 F., the highest temperature being 104.6 and the lowest a maximum temperature of only 102.8.

The leukocyte counts during a reaction and following it are somewhat variable. Usually there is a mild leukocytosis just before and during the first part of the chill, soon followed by a marked leukopenia, which appears toward the end of the chill. A count as low as 2,000 has been observed repeatedly during this stage of the reaction. This condition is soon fol-

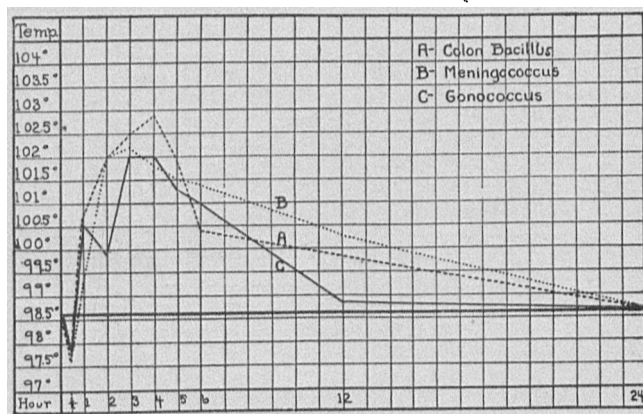


Chart 1.—Composite temperature curves following intravenous injections: fifty-four gonococcal injections in fourteen patients, twenty-three meningococcus injections in twelve patients, and eight colon bacillus injections in seven patients are represented.

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1. Bruck and Sommer: München. med. Wchnschr., 1913, 60, 1185.
2. All patients here reported were from the services of Drs. Harris, Simpson, McEwen and Stillians of the Cook County Hospital, to whom I wish to express my thanks for the privileges granted.

lowed by a gradually developing leukocytosis which reaches its maximum in from five to seven hours, and remains moderately high for from twenty-four to thirty hours. A return to normal occurs in about forty-eight hours.

The average of the highest counts made in the first thirteen patients was 33,300, the highest individual count being 55,000. The lowest count of one patient was only 22,000. This marked and sudden change in the leukocyte count is due almost entirely to an increase or decrease of the polymorphonuclear leukocytes in the peripheral circulation, their percentage being as low as 50 during the leukopenia stage and as high as 96 during the height of leukocytosis.

Meningococcus Vaccine.—The second series of fifteen patients was treated with killed meningococci in the same dose and at similar intervals as in the gonococcus series.

The reactions as far as could be determined were similar in every detail to those produced by the gonococcus vaccine. One instance of a double reaction occurred following the first injection, and one patient developed this condition after two injections. None of this series had had previous subcutaneous or intravenous injections. The average maximum temperature for this series was 103.5 F., the highest single temperature being 105.2, while the lowest reached only 102. The temperature curves were uniformly like those following injections of gonococci.

The leukocyte curve in general likewise followed those of the first series very closely, the average maximum count being 27,800; the highest single count was 46,400, while the lowest had a high count of 20,000. The

type of cell varied as in the first series. One very striking difference was observed between the two series. Over one half of the meningococcus series developed a more or less severe herpes of the lips and mucous membrane of the mouth, first appearing in forty-eight hours and remaining for from four to seven days. This condition did not occur following any but the first injection, and did not become aggravated or recur when further injections were made in a susceptible individual. No such reactions followed the gonococcus injections.

Colon Bacillus Vaccine.—This series contained but seven patients. The reactions were in every way like those produced by meningococcus and gonococcus, with the exception that the size of the dose required to produce the same results was very much less. At first a dose of 100 million organisms was given, but the reactions were so severe that 25 millions were finally used as the initial dose, this to be increased if necessary to produce the desired results.

The average maximum temperature was 104 F., while the average highest leukocyte count was 35,500.

There can be no question that the homologous curves representing the reactions produced following the injections of each organism are very similar, as

seen in the accompanying charts; however, the curves representing the colon bacillus seem to reach a higher point in both instances; this is due to the smaller number of injections represented in the curve. The crest of a curve of this kind is obviously not so high as one representing a single typical reaction, since the time of the maximum temperature and leukocytosis may vary somewhat for different individuals, or for the same individual following repeated injections.

As far as therapeutic results are concerned, there is no noticeable difference between the three bacterial suspensions, once the proper dosage is established. To produce results therapeutically, a reaction is necessary. That is, a chill must occur which is invariably followed by the temperature and leukocyte changes noted above. A dose insufficient to produce a definite chill is not followed by so marked a temperature and leukocytic reaction, and clinically no therapeutic benefit is derived. At times there may be some fever production and a moderate leukocytosis not preceded by a chill. The reactions and therapeutic results appear very distinctly similar for the three organisms used when gonorrhea-infected patients are considered. The reactions following injections in nongonorrheal patients are not to be distinguished from those produced in infected patients, nor is there any noticeable difference in the reactions produced here between the three organisms.

These observations were made by injecting a series of patients having chronic skin lesions but no history or indication of gonococcal infection. The size of the dose required to produce a reaction, the chill, temperature and leukocytosis were alike in every way in the infected and noninfected patients.

Twenty-four patients suffering from arthritis associated with gonorrheal urethritis were treated. Naturally most of these cases were acute or subacute, but some were of five months' duration and many were of over ten weeks' duration when the treatment was begun.

As might be expected, the most striking results were obtained in the acute and subacute cases; the most refractory cases, however, were also in the acute class. Those suffering for long periods appear to respond more slowly to the treatment, but fortunately seem to suffer from no recurrences or new joint involvements during the course of the treatment, as some of the more acute cases do. All but two of the arthritic patients were completely cured or manifested a decided improvement. The length of treatment varied from two days to one month.

Unusual effects were seen in three patients with acute arthritis so severe that sedatives were necessary to give them rest for the first two days in the hospital. After a single reacting dose in each instance they felt so well that they insisted on getting out of bed, and in three days they walked out of the hospital. Two of the patients had effusions in the knee joint, which completely disappeared before their discharge

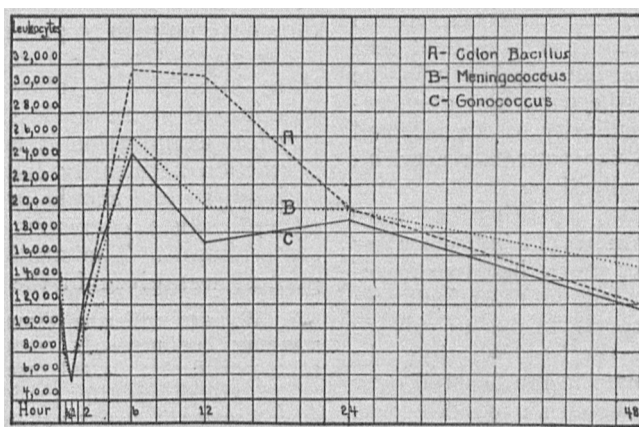


Chart 2.—Composite leukocyte curves following same intravenous injections as represented in Chart 1.

from the hospital. Unfortunately none of these men have been heard from since, so the permanency of the striking results in these instances is not known. The fact that they have not returned to the hospital suggests at least that a recurrence as severe as the original attack is not probable. Equally striking was the following instance:

J. R., a man, aged 28, had been confined to his bed for four weeks with arthritis of almost every joint of both lower extremities. These lesions had come on during the third week of gonorrhea. After the third injection he was up and walking about, and after the sixth injection he was apparently completely cured. He went back to his work as a cook and has been at work for three months with not the slightest indication of recurrence. At present he says he is gaining in strength daily.

The two refractory cases mentioned were both acute and seemed not to respond at all or very slowly to this form of treatment. One would show considerable improvement for a day or two but invariably would lapse back to the original condition; the second patient recovered completely excepting one knee joint which contained a marked effusion, and seemed not to be affected by repeated injections.

Bruck noticed similar instances, which he explained by the absence of the homologous gonococcus strain from his polyvalent vaccine. It is very evident that this explanation will not suffice, but whether it is due to a special resisting power of the particular gonococcus responsible or to some peculiarity of the infected host, it is impossible to say. Such patients react with fever and leukocytosis, as do all others.

Twelve patients with acute epididymitis were treated, and invariably the pain would subside after the first injection. Usually not more than two injections were necessary, and, indeed, in most instances one, to effect a cure. The swelling begins to subside within twenty-four hours after the first injection. In no instance did the patient remain in the hospital over a week, except in one case in which an overdose was given which will be mentioned later. The patients usually left the hospital on the fifth or sixth day, or just after recovering from the reaction following the second injection.

One patient entered the hospital suffering from acute epididymitis and prostatitis and almost complete retention of urine. About four hours after an injection of meningococci, he passed urine with no apparent obstruction. After three injections he left the hospital apparently cured. No gonococci could be found in the urethra, prostate or vesicles. After he had been at work for five weeks without inconvenience, he went on an alcoholic and sexual dissipation lasting several days, at the end of which period he developed an acute epididymitis on the previous sound side. Even then gonococci could not be found in the urine or urethra.

That these injections are not prophylactic against the development of new complications is evidenced by the fact that one occasionally sees a patient, under treatment, develop an acute epididymitis or an involvement of a new joint. Again a patient may leave apparently completely cured of arthritis to return in a few weeks suffering from epididymitis.

The effect on the urethral discharge is decidedly variable. The discharge in some patients is more profuse for two or three days following the injection, and then rather suddenly subsides entirely; in others a

marked decrease in the discharge following each injection occurs, while some of the very chronic discharges seem not to be influenced at all. Regardless of the amount and type of discharge, the gonococci are noticeably decreased in number, and in most instances apparently entirely disappear after from four to six injections.

An attempt was made to follow these patients after their discharge from the hospital. Three months have now elapsed since the first were discharged, and all have been away for at least six weeks. Other than the development of acute epididymitis in three after their discharge there have been no complications or recurrences of any kind. One of the three has been previously mentioned, the second after the cure of a left epididymitis developed epididymitis on the right side one week from the day he left the hospital, while the third developed epididymitis one month after having been discharged as cured of arthritis. All three patients returned to the hospital, without sign of recurrence of the former condition. Over two thirds of all these patients have been heard from directly; some are at work and appear to be gaining in strength daily. Others feel too weak as yet to carry on the heavy work which they have to perform, although they have no pain to prevent them from doing so.

On account of the fact that the reaction following these injections is followed by a chill and general reaction of more or less severity, a very complete physical examination is necessary beforehand. Such a reaction necessarily calls for the increased cardiac activity, so one should proceed with caution when a patient with a coexisting organic heart disease presents himself. The smallest reacting dose of meningococci was given in the following case:

J. W. was suffering from mitral regurgitation of long standing but perfectly compensated, together with acute epididymitis. He passed through the chill with no distress, but in three hours after the injection he became cyanotic, his pulse became irregular and feeble, and he had marked precordial pain. This condition lasted from ten to fifteen minutes, and he had no further inconvenience.

No other cardiac irregularities were noted in the entire series. Arnold and Hölzel³ cite Lewiniski's case of acute cardiac insufficiency developing after an intravenous injection of gonococci. Heart disease was not known to be present. On the other hand, Luithlen⁴ reports a case of gonorrheal endocarditis successfully treated in this manner. There are many instances reported, however, of cardiac symptoms developing in the presence of organic heart disease following these injections, so one should exercise care and judgment in the selection of cases.

From the proper reacting dosage in this series there were noted no other symptoms attributable to the injections. Special attention was given the kidney function, particularly in three patients who had received large doses of colon bacilli. In no instance did albumin appear in the urine, nor did any indication of kidney involvement arise. One patient having a chronic diffuse nephritis with considerable albumin in the urine had two injections with no appreciable change in the kidney function.

Foekler,⁵ however, reported epileptiform seizures after similar intravenous injections, and Fischer in

3. Arnold and Hölzel: München. med. Wchnschr., 1914, **61**, 1967.
4. Luithlen: Wien. klin. Wchnschr., 1915, **28**, 533.
5. Foekler: Med. Klin., 1914, **10**, 47.

one instance noted cerebral symptoms, which passed off in twenty-four hours.

Delirium was noted in three patients of this series, all having received a large dose of colon bacilli. This condition was of short duration and completely disappeared in twenty-four hours, leaving the patients in a weakened condition, from which they recovered slowly. All of these patients had a diarrhea of moderate severity for two or three days. One man became so weak that he was kept in bed for ten days, and left the hospital after two weeks. As far as could be determined he had completely recovered, and he appeared physically and mentally normal in every respect.

COMMENT

It is apparent that any therapeutic effect obtained by the intravenous injection of killed bacteria is not due to any specific reaction in the sense that antibody production is stimulated by specific substances contained in the organisms. Jobling and Petersen⁶ cite the work of Dunklin, who used proteose injections in typhoid immune rabbits and found a decided increase in the antibody titer, which is explained by a selective stimulation of the hematopoietic system by a non-specific substance. Walther, Hildebrand, Engelhardt, Rolly and Meltzer have reached the conclusion that high temperatures artificially produced have a favorable influence on any established infection; on the other hand, cold seems to retard the formation of immune bodies.

The optimum temperature for the growth of the gonococcus in vitro is from 97 to 98 F. Any appreciable increase in temperature has a deleterious effect on the life and growth of the organism. A sudden rise to 102 F., or over, means certain death of the culture. Boerner and Santos,⁷ using a diathermic apparatus, found that when subjected to a temperature of 102.2 F. for ten hours, the gonococci in the urethra are killed, while an exposure of six hours at 104 F., three hours at 105.8, and one hour, fifty-seven minutes at 107 is necessary to obtain the same results.

This principle has been used in various ways in the treatment of local gonorrhea, with considerable success.

When acute epididymitis develops and is recovered from, does the fever produced thereby have anything to do with the spontaneous cure of gonorrhea? Many patients with infections terminating thus have had considerable fever during the onset of the complication. On the other hand, patients are seen with infections terminating in a similar manner and having had a normal temperature throughout; this, however, does not seem to be a common occurrence.

Experimental urethritis in man by the application of a pure culture of gonococcus to the urethral meatus is known to be very constantly produced; but Finger, Ghon, and Schlagenhauser⁸ regularly failed when the experimental patient had a temperature of from 102.2 to 104 F. due to some existing disease.

A patient recently entered the hospital with acute urethritis of three days' duration. A positive gonococcus culture was obtained on entrance. The second day in the hospital he had a chill, followed by a temperature of 105 F. Malarial parasites were found in the blood, but the chills and fever were

allowed to continue for four days, at the end of which time the discharge had stopped, and no gonococci from the urethra or urine were found. He remained in the hospital for two weeks, without recurrence of the discharge, having had no local treatment whatever.

Equally noticeable is the influence of fever on those infections in the medical wards. One rarely if ever sees a gonorrheal infection coexisting with some fever-producing disease like pneumonia, typhoid or malaria, while gonorrheal infections are relatively common among the chronic, nonfever producing conditions.

By the intragluteal injection of boiled milk or sodium nucleinate, Müller and Weiss⁹ produced temperatures as high as 104.7 F. in from six to ten hours. Satisfactory results were obtained in epididymitis, prostatitis and arthritis by repeated injections. Smith,¹⁰ using normal horse serum, had results corresponding favorably with those produced by anti-gonococcic serum in gonorrheal complications. His therapeutic results ran parallel to the reaction produced, which in turn was proportional to the temperature obtained.

On the other hand, Jobling and Petersen⁶ assert that intravenous injections cause a fluctuation in the ferment-antiferment balance of the serum as well as changes in the coagulation mechanism and the opsonic complement properties. "No single factor can be identified as responsible for all the changes" resulting from this fluctuation, but "a whole train of events is inaugurated, . . . all of which tend toward a condition favorable for recovery from infection." That there are factors at work other than fever seems probable. Miller and Lusk¹¹ have found striking therapeutic results in arthritis due to other infections than gonorrheal, as well as in gonorrheal patients, by the intravenous injection of typhoid vaccine. These results, obtained in patients with nongonorrheal infectious arthritis, could not consistently be attributed to fever alone, as the streptococcus and other organisms commonly associated with this condition are known not to be especially heat sensitive. Again, why should a patient completely recover from arthritis by this treatment and occasionally still harbor live, cultivable gonococci in the posterior urethra? The temperature and leukocytes presumably being equally distributed, why should the organisms in a joint disappear and those in the urethra remain? Numbers and arrangement in clumps may be of some importance, while a less resistant organism may be developed by its growth on a new type of tissue. Possibly a continuance of the treatment after recovery from the complication would be sufficient to eradicate the urethral gonococci in all instances.¹²

The therapeutic results in the group which forms the basis of this report noticeably correspond to the temperature increase and to hyperleukocytosis. Considering the facts that the gonococcus is heat sensitive both in vitro and in vivo, that fever patients cannot

9. Müller and Weiss: *Wien. klin. Wchnschr.*, 1916, **29**, 249; abstr., *THE JOURNAL A. M. A.*, April 15, 1916, p. 1281.

10. Smith, L. D.: *The Value of Anaphylaxis in the Treatment of Gonorrheal Complications*, *THE JOURNAL A. M. A.*, June 3, 1916, p. 1758.

11. Miller, J. L., and Lusk, F. B.: *The Treatment of Arthritis by the Intravenous Injection of Foreign Protein*, *THE JOURNAL A. M. A.*, June 3, 1916, p. 1756.

12. This question is now under investigation, as is also the question of finding a substance which may be given safely in standard doses at certain intervals. The difference in reaction caused by two supposedly equal bacterial suspensions may be very variable, and thus almost necessitates some standard substance if this treatment is to be used by persons other than those familiar with the dangers of a too severe reaction.

6. Jobling, J. W., and Petersen, William: *The Nonspecific Factors in the Treatment of Disease*, *THE JOURNAL A. M. A.*, June 3, 1916, p. 1753.

7. Boerner and Santos: *Med. Klin.*, 1914, **10**, 1062.

8. Cited by Kyaw: *Med. Klin.*, 1912, **8**, 1829.

be experimentally infected with the gonococcus, and that a fever-producing disease spontaneously cures previously existing gonorrheal infections, there can be but little question that fever artificially produced plays some part in the recovery from these infections.

It cannot easily be determined how much influence, if any, the leukocyte increase in the peripheral circulation has, for when artificially produced in the manner employed here, the fever and hyperleukocytosis are invariably present together.

It is apparent that the usual treatment of gonorrheal arthritis is not satisfactory in all instances when almost daily one can see an ankylosed joint and atrophied muscles following this condition. Should this treatment by intravenous protein injections prove to give permanent results in these conditions, as present data seem to indicate, are we justified in using such measures?

In view of the chronicity of the disease and the destructive complications which commonly arise, it would appear to be a rational procedure when properly used and controlled. Until some substance is obtained, however, whose dosage can be more definitely standardized, it seems that this form of treatment should not be used generally by those not thoroughly familiar with the reaction and the manner of regulating the size and interval of dosage of such as used in the work here reported.

SUMMARY AND CONCLUSIONS

Intravenous gonococcal vaccines have no specific action either as a diagnostic or a therapeutic agent. A similar reaction is secured by suitable injections of meningococci and colon bacilli. There is no noticeable difference in the temperature or leukocyte curves produced after the intravenous injection of the foregoing bacterial suspensions.

The reactions produced in nongonorrheal patients in every way resembled the reactions in gonorrheal patients, there being no noticeable difference in the temperature and hyperleukocytosis produced.

Twenty-four patients with gonorrheal arthritis were treated. Complete recovery or marked rapid improvement was observed in all but two instances. Eleven patients were treated with gonococci with one failure, and eleven patients with meningococci with one failure, while but two were treated with colon bacilli, and both recovered.

Twelve patients with acute gonorrheal epididymitis were treated, and all were apparently completely and permanently cured within a week. There was no difference in results produced with the gonococcus, meningococcus and colon bacillus.

This mode of treatment in gonorrheal arthritis and epididymitis and at least in some instances of acute prostatitis possesses a decided therapeutic value. The results appear to be permanent in character. It possesses, however, little or no prophylactic value against the development of new complications.

Great care must be exercised in the selection of cases, and patients with organic heart disease should not be treated in this manner. No other definite contraindications have been observed.

Clinically the benefit to the patient runs parallel with the fever and hyperleukocytosis produced. It would seem that these factors play an important rôle in the treatment.

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SYPHILITIC BONE AND JOINT LESIONS SIMULATING TUBERCULOSIS*

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Every paper should present its special points in the beginning so that the attention of those really interested may be fixed. This paper aims to give two special points: first, that there is a considerable number of syphilitic cases simulating tuberculosis and other bone and joint lesions that escape recognition; second, that there is a considerable number of cases of bone and joint syphilis that do not give a Wassermann reaction.

In the past year or two I have seen at least eighteen cases of bone and joint syphilis that have given negative Wassermann reactions. Some of these were unmistakable syphilis, as revealed by Roentgen-ray examination. In others the nature of the process could not be told in this manner. In these two groups of cases the clinical histories are strikingly similar in the individual cases in each group. In those frankly syphilitic on Roentgen-ray examination the histories are all the same, pain in the affected part, frequently more marked at night, and little or nothing else. They have each been in the hands of one or more physicians, some of whom have suspected syphilis, but on account of the negative Wassermann they have been regarded as something else. In this group there were four patients, all of whom promptly improved on the administration of mercury and iodids.

In the second group, the larger numerically, the lesions were in and about the joints, rather than in the shafts of the bone as in Group 1, and in these cases, too, there was great similarity in the histories. Each of these cases had been treated by one or more doctors, many of these patients had been in institutions, teaching institutions or hospitals, and their trouble had been regarded as tuberculosis and they were treated accordingly by immobilization or operation.

As case histories are exceedingly boring, I will cite but a few and make these as short as possible.

CASE 1.—L. L., Chinese boy, aged 5 years, came to the Stanford University children's clinic with a sore on the back of his hand. He was sent to the surgical clinic, where, after a little time, the diagnosis of tuberculosis of the carpal bones was made and confirmed by the Roentgen ray. He was kept under observation in the surgical department for about a month; then, as the lesion was regarded as tuberculous, the child was transferred to the orthopedic clinic. It was then ascertained that he had had this sore on the back of his hand for about ten months. At this time he had the hand in plaster of Paris, and through a window in the plaster it could be seen that there was some swelling and two sinuses. The sinuses did not seem to be tuberculous, so the boy was put on mercurial ointment and iodids and improved rapidly in spite of the fact that the Wassermann had been negative shortly before the treatment was begun. All plaster was removed, and the boy made a rapid recovery. A guinea-pig injected with some of the material from the sinus remained perfectly well.

CASE 2.—F. M., white man, aged 42 years, sustained a fracture of the lower end of the radius in December, 1913, which healed without any trouble. Oct. 7, 1914, the man returned to the surgical clinic, complaining of pain and swelling of the right wrist. There was diffuse swelling, pain and limitation of motion. Roentgen-ray examination at that time showed probable tuberculosis of the wrist, with a possibility of

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