

THE CHARACTERISTICS OF SYNOVIAL FLUID IN GONOCOCCAL ARTHRITIS

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To anyone who has studied a group of cases of gonococcal arthritis, it is plain that some patients recover entirely without any permanent disability. In a large number, however, the disease is progressive and results in a chronic arthritis with resulting restriction of motion or ankylosis. The reasons for the variations observed are not clear in every case, although the type and severity of the reaction in the joints are of the highest importance. Keefer, Parker and Myers (1) have shown that the pathologic process, as determined by the histological examination of the joints of patients with gonococcal arthritis, varies tremendously in its severity and extent. When there is pain, periarticular swelling and slight exudation of fluid into the joint cavity, the process is confined for the most part to the subsynovial connective tissue where there are collections of polymorphonuclear leukocytes, lymphocytes and plasma cells, about the blood vessels and between the strands of connective tissue. The surface synovial cells are intact. In other cases in which the synovial fluid is excessive and contains many cells, there develops a much more extensive inflammatory reaction of the synovial membrane and underlying connective tissue. In such cases the superficial synovial cells are entirely destroyed leaving only a layer of granulation tissue with newly formed blood vessels, many polymorphonuclear leukocytes and numerous micro-organisms. The deeper parts of the synovial membrane are not extensively involved. In such instances, there may be destruction of the cartilage and underlying bone with a resulting fibrous or bony ankylosis.

In view of the varied pathologic picture and the uncertainty of the outcome in a given case, we studied the synovial fluid from forty cases of gonococcal arthritis in an effort to gather more exact information regarding the alterations that occur and to determine if any correlations could be made between the type of reaction and the subsequent outcome of the joint disorder.

METHODS

Fluid was withdrawn from the affected joints with a needle and syringe, using the usual aseptic precautions. The fluid was obtained from the knee joints

in thirty-seven cases and from the wrist, ankle, and olecranon bursae respectively in the remaining three. In all, seventy-seven specimens from forty patients were studied. The amounts removed varied from three to 250 cc. with each aspiration. The total and differential cell counts were made immediately. Most of the differential counts were done using the supravital method described by Forkner. A few were made following the staining of a smear with Wright's stain. The former method proved to be the more satisfactory. All specimens were cultured for gonococci and smears of the exudate were stained, according to the Gram technique, for organisms. Chemical examinations were made on oxalated fluid, and included total protein, nonprotein nitrogen and sugar. In some cases the results of the determinations were compared with those for the nonprotein nitrogen and sugar in the blood at the time the joints were aspirated. Gonococcal complement fixation tests were done upon both the blood sera and the synovial fluids.

The diagnosis of gonococcal arthritis was made from: 1. the history of a recent attack of gonorrhoea; 2. the presence of a localized gonococcal infection as proven by symptoms, signs and bacteriologic examination; 3. the presence of gonococci in the synovial fluid or a positive gonococcal complement fixation test in the blood serum or synovial fluid. In the cases in which gonococci were not demonstrated in the synovial fluid, care was taken to exclude other types of arthritis, including rheumatic fever and tuberculous arthritis. In no case, however, was the diagnosis of gonococcal arthritis accepted without *at least* finding a localized gonococcal infection or a positive gonococcal complement fixation test in the blood or synovial fluid.

General characteristics of fluid

The fluid varied in color and clarity from pale yellow to yellow and from slight turbidity to a definite cloudiness. It clotted upon standing, but in many cases the clot was not complete for a period of several days. Mucin was frequently abundant and it was found that unless the fluids were studied immediately, the presence of mucin interfered with the examinations.

From the cultures of sixteen fluids from ten patients gonococci were readily grown in pure culture. These organisms were identified by their morphological and fermentation characteristics and, in some instances, by agglutination to known antisera. No organisms were grown from the remaining fluids.

It was surprising that we were able to cultivate the gonococcus from the synovial fluid in only twenty-five per cent of the cases. It might be said that we were unable to cultivate them from the remaining fluids due to a lack of the proper technique, or that the gonococci were present in such small numbers that they were not detectable upon artificial cultivation. We have, however, discarded both of these objections, inasmuch as opportunities were present for two different laboratories to examine the fluid for micro-organisms; one the Bacteriological Laboratory of the Boston City Hospital, and the other our own; and in but one exception the results of cultivation were the same. It was, in addition, possible to cultivate gono-

cocci whenever they were found in stained smears made from the fluid. On the other hand, we were occasionally able to cultivate organisms from synovial fluid when we were unable to find them in stained smears. From the results of our pathologic studies of two cases, we have come to another conclusion regarding our failure to grow organisms from the synovial fluid in every case; namely, that the inflammatory reaction in the cases with non-infected fluids is chiefly below the surface of the synovial membrane, and in the periarticular tissues. In such cases, the surface layer of synovial cells is intact and no organisms can be cultivated from the fluid, but they may be present in the synovial tissues beneath the surface where they may be found on microscopic examination of the tissue.

In the cases in which organisms can be cultured with ease, the surface of the synovial membrane is destroyed, and is the site of an intense inflammatory reaction. In other words, in the cases with infected fluids the organisms have extended from the periarticular tissues into the synovial cavities and destroyed the synovial lining of the joint; in those with non-infected fluids, the inflammation is confined to the periarticular tissues beneath the surface of the synovial membrane.

This explanation is not far-fetched when one recalls the reaction in other serous membranes when infection is present in the neighborhood, for example, the sterile pleural effusions in pneumonia, the aseptic meningitis in extra-dural or brain abscess or the sterile effusions in the joint cavities in the presence of osteomyelitis.

The total cell counts of the fluids varied between 1,800 and 158,000 per cubic millimeter, varying from 7,350 to 158,000 per cubic millimeter for infected fluids and for non-infected fluids from 1,800 to 78,250 per cubic millimeter. While the variations in both groups were wide, it was true that higher cell counts were found more often in the infected than in the non-infected synovial fluids.

In all of the fluids, the polymorphonuclear leukocytes predominated and fluctuated so as to form from forty-six to 100 per cent of the cells. The other common cells were clasmatocytes and monocytes. Of the former, there were between one and sixteen per cent, and of the latter between one and thirty-three per cent. Only rarely were the lymphocytes increased above ten per cent, although the extreme variations were between one and thirty-one per cent. In the infected fluids polymorphonuclear cells were always over seventy-six per cent. The non-infected fluids more often had higher monocyte and clasmatocyte counts than infected fluids, especially when the total count was low. On the whole, then, the non-infected fluids showed a somewhat lower total cell count, and contained more monocytes and clasmatocytes than the infected fluids. The total and differential cell counts are recorded in Table I.

These findings are in agreement with the cellular reactions in other serous sacs when the fluid is infected or non-infected. Thus Scott and

TABLE I

Summary of total and differential cell counts of synovial fluids in gonococcal arthritis

Number of fluids	Total cells per cubic millimeter	Polymorphonuclear cells	Lymphocytes	Monocytes	Clasmatocytes	Eosinophils
	<i>thousands</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
<i>Infected fluids</i>						
2	7.3-10.0	76-85	6-12	5-7	2-5	0
4	10.1-40.0	86-99	3-5	1-4	0-12	1-2
5	40.1-60.0	89-98	1-6	1-4	1-3	0
3	60.1-158.0	92-99	1-6	0-2	1-2	0
<i>Non-infected fluids</i>						
20	1.8-10.0	46-100	1-31	1-33	1-19	0-2
28	10.1-40.0	82-99	1-8	1-7	1-6	
4	40.1-60.0	93-99	1-4	1-5	1-4	0-2
1	60.1-78.2	87-99	1-4	1-3	1-6	0

Finland (2) found that when the pleural fluid in pneumonia was non-infected the number of clasmatocytes, monocytes and lymphocytes was much higher than in the infected fluids. This was especially true when the effusion remained sterile. If the fluid became infected, practically all the cells were polymorphonuclears. The same type of reactions may be observed in the cerebrospinal fluid during the course of meningitis, resulting from an extra-dural abscess. The differential cell count, then provides some information regarding the presence or absence of organisms in synovial fluid in gonococcal arthritis.

Gonococcal complement fixation test

This test was done forty-eight times on both the blood serum and synovial fluid from twenty-seven cases. The reaction was positive in thirty-one synovial fluids, doubtful in one, and negative in sixteen. Stating it in another manner, it was positive in seventy-one per cent of the cases of gonococcal arthritis when the synovial fluids were studied. When the results of the test in the blood sera and the synovial fluids were compared, there was disagreement in only six instances. The reaction of the synovial fluid was negative on four occasions when that of the blood was doubtful or positive. The gonococcal complement fixation was doubtful once with synovial fluid when the blood serum was negative, and the synovial fluid was positive in one instance in association with a doubtful blood serum reaction. In three cases both the blood serum and synovial fluid were negative early in the course of the disease when gonococci were

present in the synovial fluid. In three other cases, it was possible to observe the change of the reaction in the blood serum and synovial fluid from negative to positive. The blood serum always showed a positive gonococcal complement fixation reaction before the synovial fluid.

In another communication (3) we have analyzed in greater detail the results of the gonococcal complement fixation test in the blood sera and synovial fluids from cases of gonococcal arthritis as well as other types of arthritis. It may be repeated here that this test has been found to be of great value to us in the etiological diagnosis of gonococcal arthritis.

Total proteins in synovial fluid

These were determined in samples of fifty-four synovial fluids and varied between 3.6 and 6.0 grams per cent. This value included the nitrogen of the mucin, inasmuch as it was not removed by precipitation before the Kjeldahl determinations were made. The amount of protein in the infected and non-infected fluids was essentially the same, although all of the infected fluids had a protein content of five grams per cent or more. There was no correlation between the amount of total protein and the non-protein nitrogen, nor was there any relationship between the total protein and the total number of cells.

Nonprotein nitrogen in blood and synovial fluid

The nonprotein nitrogen content of both the blood and synovial fluid was determined simultaneously in thirty-seven instances. In the synovial fluid it varied between fifteen and forty milligrams per cent. In fourteen cases, the nonprotein nitrogen of the blood was somewhat higher than that in the synovial fluid, in seventeen others the values were the same or varied within a limit of two milligrams, and in four samples the synovial fluid contained slightly more nonprotein nitrogen than the blood. The differences between the two were never very great. Moreover, there was no evidence that the presence of bacteria in the synovial fluid increased the quantity of nonprotein nitrogen, and there was no correlation between the number of cells and the amount of nonprotein nitrogen.

From a comparison of the values in both the blood and synovial fluid, it appeared that the amount of nonprotein nitrogen in the latter was dependent upon the total amount in the blood, the differences between the two were never very striking and, in some cases, the values were precisely the same.

Sugar content of the synovial fluid

The sugar content of the synovial fluid varied between 38 and 131 milligrams per cent. In most cases it was lower in the synovial fluid than in the blood, and this was especially noticeable in the infected fluids. Seldom was the sugar content of the synovial fluid higher than that of the blood.

That this did occur can be explained by the fact that the joints were not aspirated after the patients had been fasted, though they were frequently collected several hours after a meal. Thus, the higher content of sugar in the synovial fluid can probably be explained upon the basis of a higher blood sugar sometime before the joint was aspirated; that is to say, the sugar content of the joint fluid remained high for a longer time than the sugar of the blood. Similar observations have been recorded by Cajorie, Crouter and Pemberton (4), Allison, Fremont-Smith, Dailey and Kennard (5). It was true then, that the level of the synovial fluid sugar depended to some extent upon the amount of sugar in the blood at the time the aspiration was performed, or the amount present in the blood several hours previously. There were, in addition, two other factors of significance; namely, the presence of organisms and the number of cells. The higher the total cell count in the synovial fluid the lower the sugar; and when there were organisms present in the fluid, even if the total cell count were low, the sugar content was reduced. This is shown in Figure 1.

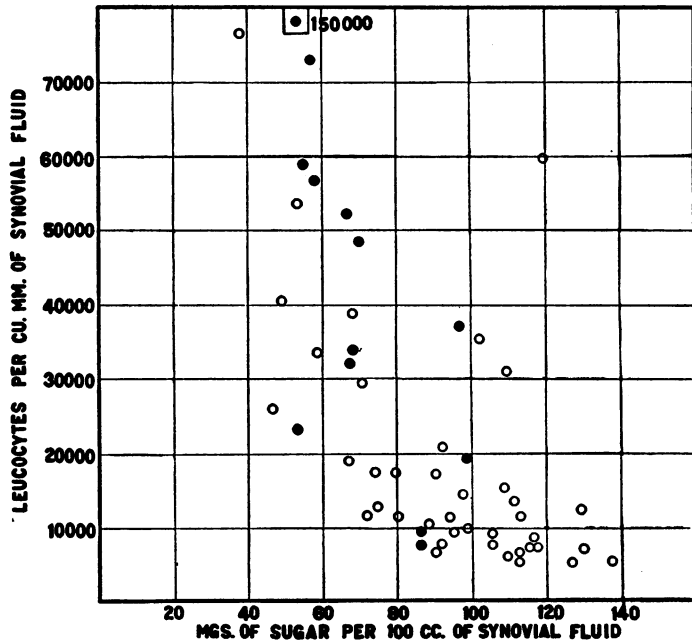


FIG. 1. CHART SHOWING VARIATION IN THE SUGAR CONTENT OF THE SYNOVIAL FLUID AND THE TOTAL LEUCOCYTE COUNT

The solid dots indicate infected fluids and the circles, non-infected fluids.

The results of the determinations of the total proteins of the synovial fluids together with the nonprotein nitrogen and sugar content of both the blood plasma and synovial fluids are summarized in Table II.

TABLE II

Summary of the non-protein nitrogen and sugar content of blood and synovial fluid in twenty cases

Number of fluids	Total protein joint fluid	Blood plasma nonprotein nitrogen	Synovial fluid nonprotein nitrogen	Blood sugar	Synovial fluid sugar
	<i>grams per cent</i>	<i>mgm. per cent</i>	<i>mgm. per cent</i>	<i>mgm. per cent</i>	<i>mgm. per cent</i>
<i>Infected fluids</i>					
10	5.4-5.9	17-34	20-37	82-108	52-86
<i>Non-infected fluids</i>					
25	3.8-6.0	19-41	21-33	82-175	52-131

Briefly, then, the sugar content of the synovial fluid depended upon three factors: the level in the blood, the number of leukocytes and the presence of organisms.

Relation between type of reaction in the synovial fluid and the outcome of the arthritis

In view of the fact that gonococcal infections of the joints frequently lead to a crippling disease and, in some cases, to death, we were interested in analyzing the outcome of the patient's illness in the light of the various characteristics of the synovial fluid. In a number of cases, this is a task of no small difficulty in view of the chronic nature of the pathological process and the relapses that occur, especially following a reinfection of the genital tract. We have records of the outcome of thirty-three cases. The results are summarized in Table III.

TABLE III

The outcome of thirty-three cases of gonococcal arthritis

	Patients with infected synovial fluid	Patients with non-infected synovial fluid	Per cent
Died.....	2	0	6
Well.....	2	6	25
Chronic joint disease.....	5	18	69

From this table, it is obvious that gonococcal arthritis is a serious disease, whether the synovial fluid is infected or non-infected at the time of the examination. Thus, sixty-nine per cent of the patients had some evidence of chronic changes in their joints following the infection. This disability varied from slight impairment of function to considerable limita-

tion of motion. In order to gain further information we studied the cell count of the synovial fluid of the patients in the different groups to determine whether this response gave any indication of the possible outcome in a given case. It was found that in no instance was recovery complete when the synovial fluid cell count was above 40,000 per cubic millimeter. This was true whether the fluid was infected or non-infected. On the other hand, of the patients with synovial fluid cell counts below 40,000 only thirty-seven per cent recovered completely. In other words, from this small series of cases, a synovial fluid cell count over 40,000 was invariably followed by some permanent change in the joints, and complete recovery occurred in only thirty-seven per cent of the cases with counts below 40,000 per cubic millimeter. These facts would seem to indicate that the cell count of the synovial fluid may serve as a very crude index in determining the outcome in a given case. There is another factor of some importance, namely, the presence of organisms in the fluid. Complete recovery was observed in only two of the nine patients with infected fluids. Briefly, it may be said that the outlook is not good as far as complete recovery is concerned if the joint fluid is infected and the leukocyte count high; on the other hand, the better results were seen in patients with low cell counts and non-infected fluids. The results are tabulated in Table IV.

TABLE IV

The outcome of thirty-three cases of gonococcal arthritis with cell counts in synovial fluid above and below 40,000 per cubic millimeter

	Infected fluids	Non-infected fluids	Died	Well	Chronic joint disease
Patients with cell counts in synovial fluid over 40,000 per cubic millimeter.	7	4	2 0	0 0	5 4
Patients with cell counts in synovial fluid under 40,000 per cubic millimeter.	2	20	0 0	2 6	0 14

DISCUSSION

From the data presented, we may now return to the two questions we set out to answer. First, what information of diagnostic value can be obtained from the examination of the synovial fluid in a suspected case of gonococcal arthritis, and, second, does the character of the joint fluid provide any information regarding the prognosis in a given case?

It will be universally agreed that the most important aid in establishing a diagnosis of gonococcal arthritis is the demonstration of gonococci in the synovial fluid. However, in most of the cases we studied it was not possible to cultivate organisms from the synovial fluid or stain them in

the exudate at the time it was examined. In these, the diagnosis, as far as the joints are concerned, must be based upon indirect evidence. The chemical examinations of the fluid revealed no information of specific diagnostic value. The nonprotein nitrogen of the joint fluid was the same as that of the blood. The amount of sugar in the synovial fluid depended upon three factors; namely, the level of the sugar in the blood, the number of leukocytes and the presence of micro-organisms. Inasmuch as high leukocyte counts and low synovial fluid sugar content were found in non-infected fluids, the presence of a low sugar content did not indicate the presence of organisms in every case. The total protein and the total and differential cell count were of significance insofar as they indicated the presence of an exudate, but the wide variations in the number and types of cells, in both the infected and non-infected fluids, forced one to the conclusion that these findings in a given case were of little value in discriminating the infected from the non-infected fluids. The gonococcal complement fixation test with the synovial fluid, as well as with the blood serum was of distinct value and, since it was found to be positive in a large percentage of cases and highly specific, it proved of considerable diagnostic aid.

From the diagnostic point of view the most important examinations were the bacteriological, the cytological, and the serological tests. The chemical examination yielded very little significant information.

From the point of view of prognosis, the characteristics of the fluid were of some importance. While it was found that the prognosis was poor in the group as a whole, as far as complete recovery was concerned, the cases with the poorest outlook were those with high synovial fluid cell counts and infected fluids. As a rule, the patients who recovered completely were those with non-infected fluids and low leukocyte counts, or those with infected fluids and low leukocyte counts.

SUMMARY AND CONCLUSIONS

The synovial fluids from forty cases of gonococcal arthritis were studied to determine: (1) the various biological and chemical characteristics of the fluid and (2) whether or not information of value in diagnosis and prognosis could be discovered. The following results were obtained.

1. When the joints became involved as a result of a gonococcal infection, the synovial fluid was either infected or non-infected. In either case, the fluid had the characteristics of an exudate as judged by both the total protein and cell content.

2. The total synovial fluid cell count was increased in both types of fluid but, as a rule, it was somewhat higher in the infected fluids. There were, however, wide variations.

3. The differential cell count was of greater importance than the total cell count in the two groups of cases. In practically all, the polymorpho-

nuclear cells predominated. In the non-infected fluids, the clasmatocytes, monocytes and lymphocytes were present in much larger numbers than in the infected fluids.

4. The nonprotein nitrogen content of the synovial fluid was the same as that of the blood regardless of the presence of organisms or of a high cell count.

5. The sugar content of the synovial fluid varied with the level of the blood sugar, the number of leukocytes and the presence of bacteria. Of these factors the first two were of greater importance than the third.

6. The results of gonococcal complement fixation tests on the synovial fluid and blood were in agreement.

7. The bacteriological, cytological and serological tests were of the greatest value in providing information of diagnostic value.

8. The chemical examination of the fluid revealed no information of diagnostic importance.

9. While the prognosis, as far as complete recovery was concerned, was poor, the presence of micro-organisms and a high leukocyte count were more often followed by chronic joint disease than when there was a low leukocyte count and a sterile fluid.

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BIBLIOGRAPHY

1. Keefer, C. S., Parker, F., Jr., and Myers, W. K., The histological changes in the knee joint in various infections. *Arch. Path.* (In press.)
2. Scott, T. F. McN., and Finland, M., The cytology of pleural effusions in pneumonia studied with a supravital technique. *Am. J. M. Sc.* (In press.)
3. Myers, W. K., and Keefer, C. S., The gonococcal complement fixation test in the blood and synovial fluid of patients with arthritis. *New England J. Med.*, 1934, **211**, 101.
4. Cajorie, F. A., Crouter, C. V., and Pemberton, R., The physiology of synovial fluid. *Arch. Int. Med.*, 1929, **37**, 92.
5. Allison, N., Fremont-Smith, F., Dailey, M. E., and Kennard, M. A., Comparative studies between synovial fluid and plasma. *J. Bone and Joint Surg.*, 1926, **8**, 758.