FROM THE MEDICAL CLINIC OF THE KAROLINSKA SJUKHUSET AND THE KONUNG GUSTAF V:s FORSKNINGSINSTITUT. HEAD: PROF. N. SVARTZ

THE PROTEIN PATTERN OF JOINT EXUDATES

By

B. OLHAGEN

Owing to the difficulty in obtaining sufficient analytic material, our knowledge of the protein conditions of the joint fluid in man is limited to the affections which are incidental to the body's largest joint, that of the knee. With respect to normal synovial fluid, our knowledge is mainly based on the conditions observed in certain animals (horse, cow). Rather little is still known as to the formation of the synovial fluid, but it would seem reasonable to regard it as a dialysate of blood plasma with the addition of the lubricant hyaluronic acid (Ropes et al). The protein components of the normal joint fluid seem to be qualitatively similar to those of the blood, at least from an electrophoretic point of view (Hesselvik). Quantitatively synovial fluid is considerably poorer in protein than is the plasma, the content being 1-2 per cent. Accordingly the proteins which are the most sparsely represented in the blood—α globulin and fibrinogen—are not apparent in an ordinary analysis of the proteins in the joint fluid. Moreover due to their form or size, some of the proteins have difficulty in finding their way out through the capillaries via the articular connective tissue into the joint cavity. For this reason there will be found relatively more of the albumin fraction, which contains the smaller molecules, in the normal synovial fluid than in the plasma. With regard to the pathologic changes of the joint fluid, i.e. the joint exudates, the conditions are otherwise.

If we consider firstly the total protein content in the joint exudate, we find that the values are grouped around two poles, one at 6 per cent and the other 4 per cent approximately. The former group, of which the main part of values lies between 5 per cent and 7 per cent comprises principally the infectious exudates including acute and chronic polyarthritis, and moreover, tuberculosis and other forms of bacterial

arthritis. The latter group, with values between 3 and 5 per cent is represented by the non-infective joint exudates, that is to say above all, the traumatic hydrops, synovitis due to hyperfunction and the exudates found in osteoarthritis. The limits are fluid, however and extreme values are to be found in both directions. In my collocation of 45 cases the lowest was 1.5 per cent and the highest 9.0 per cent.

The qualitative analysis of the proteins in joint exudates has been considerably facilitated by the Tiselius' electrophoretic method. Comparison between the actual exudate and the patient's plasma has been found especially valuable. I will demonstrate a few type examples of electrophoretic diagrams from joint fluid, together with the corresponding plasma patterns. For instance in traumatic hydrops of some week's duration we find that the relative distribution of the protein components in the exudate is about the same as in plasma, with a little higher albumin and γ globulin values. (Fig. 1 A and B). As the trauma, in this case, was sustained by a healthy individual, a normal distribution of the components is found in the plasma. All the plasma gradients are present in the pattern of the synovial fluid with the exception of fibrinogen, although in a quite fresh exudate, a component appears the mobility of which corresponds to fibrinogen.

If the case be one of acute polyarthritis in an exudative phase, the picture is of different type. (Fig. 1 C and D). Even here the exudate reflects the relative distribution of the components in plasma as being fairly constant but with a decrease of β globulin and fibrinogen, which have the largest and longest molecules respectively. As already mentioned the total protein content is about 6 per cent, that is 1-2 gr. per cent lower than plasma. We may interpret the exudate as a sign of a local change of the capillary permeability in the joint capsule. Eppinger long ago demonstrated in tests with salamanda, that sera from patients with rheumatic fever contains a factor which is lacking in normal sera and affects capillary permeability, thus causing the plasma proteins to migrate into the tissue.

Finally, if we look at an exudate of long duration from a patient with rheumatoid arthritis, the electrophoretic pattern has two striking characters, the low or absent fibrinogen peak and the remarkably high γ globulin content. The γ globulin concentration in the joint exudate sometimes attains the same absolute value as that of plasma, and occasionally one meets with values that are absolutely higher than those found in plasma (Perlmann). The change accounted for by the capillary permeability obviously does not suffice here as an explanation of the so greatly deviating relative distribution. It is a very complicated process which has not yet been elucidated, but thanks to Edlund's

investigations among others we are beginning to glimpse some coherence. I will mention a few factors. To begin with, the duration of the exudate is involved. The longer it has continued the higher becomes the rate of γ globulin content. Just as albumin with its low molecular weight penetrates more easily the so-called synovial membrane, it is plausible that the smaller molecule is again reabsorbed more quickly, when the acute exudative phase has ceased and the process of repair has begun. In rheumatoid arthritis the mesenchymal tissue changes—which we recognize by the swelling of the capsule—are more extensive than in the case of acute arthritis, and this may affect the reabsorption velocity. Other factors are the intra-articular pressure which, among other things, is greatly influenced by the movement of the limb. Moreover, in rheumatoid arthritis the altered vasomotor conditions including the deteriorated blood supply undoubtedly play a rôle in the resorption.

Seeing that the γ globulin is to a great extent composed of antibodies, one has been inclined to make immunologic events responsible for the high rate of γ globulin content in the joint fluid. In 1938, Levinthal published observations which told that streptococcal agglutininins are found more frequently in the joint exudates than in the serum of patients with rheumatoid arthritis; his interpretation of this finding was that there was a local accumulation of antibodies in the affected joint capsule. One may also suspect an autochthonous production of antibodies in the rheumatic granuloma. Still, I am of the opinion that it is not necessary to have recourse to the antibody theory in order to explain the high γ globulin values in the joint fluid. An argument directly in opposition to this explanation is that in an old exudate from a case of osteoarthritis, where antibodies can scarcely be suspected, I have found a relative γ globulin concentration as high as is found in rheumatoid arthritis.

There now arises a question of both practical and theoretical importance. Is it possible, with electrophoretic aid, to distinguish between the acute exudate in the initial stage of rheumatoid arthritis and the joint fluid in rheumatic fever? Apparently it is not; at all events, I have not been able to exclude the possibility of acute polyarthritis in two cases of knee exudate with high fever which later proved to have been in the initial stage of rheumatoid arthritis. It seems, however, as if serologic analysis may be of a differential diagnostic value in such cases. I refer particularly to the agglutination of sensitized sheep red cells in rheumatoid arthritis (Rose and collab, Svartz and Schlossmann).

Similarly, with regard to other infective joint exudates such as are

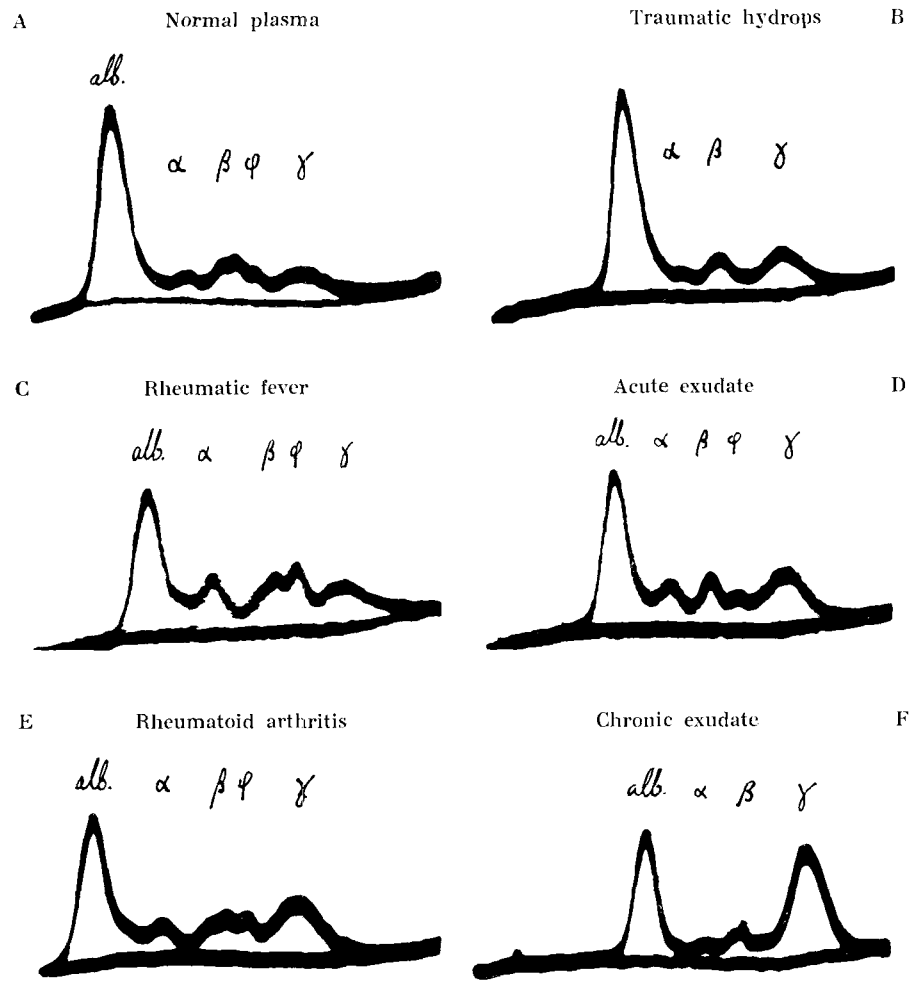

Fig. 1.
Electrophoretic diagrams. A. Normal plasma. B. Synovial fluid from a case of traumatic hydrops. C. Plasma from a case of rheumatic fever. D. Corresponding acute exudate from the knee joint. E. Plasma from a case of rheumatoid arthritis. F. Corresponding chronic exudate.

seen in tuberculous and septic arthritis conditions, there are no specific protein changes which make possible a distinction between them and the rheumatic exudates. From a practical viewpoint, the differential diagnosis between tuberculous and non-specific exudates is undoubtedly most important. My material is still too small to allow of a definitive statement, but it seems as if no reliable guidance can be given by the electrophoretic method. A high total protein content and a relative

increase of globulin argue more in favour of tuberculosis, while a total protein below 4 per cent together with low γ globulin values suggest non-specific hydrops. Such a finding, as the last mentioned, is generally found in conjunction with a normal protein distribution in the plasma and a correspondingly normal sedimentation rate, which is not often encountered in tuberculous synovitis.

I should like to conclude by saying that in cases of exudates of undetermined genesis there are good reasons for analysing the protein pattern of the plasma also, as this analysis provides useful hints for the diagnosis of a joint affection. As an extreme example let me mention a case of an atypical polyarthritis with knee joint exudate which was sent to the medical clinic for examination. The plasma analysis revealed a blood protein pattern which led to the diagnosis—myeloma. The knee exudate showed a total protein value of 2.9 per cent and remarkably high β globulin value, a rather uncommon finding.

Another method of examination, as I have already intimated, is to perform a thorough serological analysis of the patient's serum, including gonococcus complement fixation tests, determinations of the antistreptolysin and antistaphylolysin titres, and also investigations of the agglutination of streptococci and sensitized sheep red cells.

SUMMARY

The protein content in joint exudates of different origin shows great dispersion; however, in the author's collocation of 45 cases the distribution curve exhibits two maxima, one at 6 gr/100 ml and the other at 4 gr/100 ml approximately. The former group comprises principally the infective exudates including the rheumatic diseases; in the latter are found mainly the non-infective cases (traumatic and degenerative conditions). Electrophoretically the acute exudate shows close correspondence to the plasma protein pattern, as regards the relative concentration of the components. The fibrinogen content tends to be reduced and eventually disappear with increasing duration of the effusion. The chronic exudate is also characterised of a striking enhancement of the γ globulin, which often equals the absolute values of the corresponding plasma component.

The influence of various factors on the protein pattern of the synovial fluid is discussed and some diagnostic viewpoints are put forward.

RESUME

Il y a de grandes divergences dans la teneur en protéine des exsudats articulaires de différentes gènes. Toutefois, dans le matériel d'observation de l'auteur qui comprend 45 cas, la courbe de sa distribution montre deux maxima, l'un d'environ 6 gr aux 100 ml et l'autre de 4 gr. aux 100 ml. Le premier groupe englobe surtout les exsudats infectieux y compris les cas rhumatisants, le second principalement les cas non-infectieux (traumatiques ou dégénératifs).

L'exsudat aigu montre une concordance électroforétique assez proche du diagramme du plasma correspondant en ce qui concerne la répartition des composants. Au point de vue fibrinogène, il a par contre une tendance à diminuer et éventuellement à disparaitre avec une longue durée de l'épanchement. Dans les exsudats chroniques, on est d'ailleurs frappé de l'augmentation des γ globulines qui est souvent de parité avec la valeur absolute des composants du plasma correspondant.

Il est discuté des différents facteurs qui interviennent et différencient le tableau de la protéine du liquide articulaire, de même que sont présentés certains points de vue se rapportant au diagnostic différentiel.

ZUSAMMENFASSUNG

Der Eiweissgehalt im Gelenkexsudat verschiedener Herkunft weist grosse Verschiedenheit auf, doch zeigt die Verteilungskurve im Materiale des Verfassers zwei Maxima, das eine ungefähr bei 6 gr./100 ml. und das andere bei 4 gr./100 ml. Die erste Gruppe umfasst im wesentlichen die infektiösen Exsudate inklusive der rheumatischen Zustände, die letztere hauptsächlich die nicht infektiösen Fälle (traumatische und degenerative Erkrankungen).

Elektrophoretisch zeigt das akute Exsudat eine nahe Übereinstimmung mit dem korrespondierendem Plasmadiagram hinsichtlich der relativen Verteilung der Komponenten. Das Fibrinogen zeigt eine Neigung zur Abnahme und eventuel zum Verschwinden bei steigender Dauer der Ergüsse. Im chronischen Exsudat frappiert ausserdem eine Zunahme der γ-Globuline, die oft eine Parität mit den absoluten Werten der korrespondierenden Plasmakomponente erreichen.

Die Wirkung verschiedener Faktoren auf die Eiweisszusammensetzung der Gelenkflüssigkeit wird diskutiert und gewisse differentialdiagnostische Gesichtspunkte werden dargelegt.

REFERENCES

Edlund, T.: Acta Physiol. Scand. Vol. 18. Suppl. 62, 1949.
Eppinger, H.: Verhandl. Deutsch. Ges. Kreislaufforschg. 11, 166, 1938.
Hesselvik, L.: Acta Med. Scand. 105, 153, 1940.
Levinthal, W.: Proc. Int. Congr. Rheumat. Hydrol. Bath. 1938, p. 345.
Olhagen, B.: Proc. Int. Congr. Rheumat. Dis. New York 1949 (in press).
Perlmann, G.: Personal communication.
Ropes, M., Rossmeisl, E., and *Bauer, W.:* J. Clin. Investig. 19, 795, 1940.
Rose, H., Ragan, C., Pearce, E., and *Lipman, M. O.:* Proc. Soc. Exp. Biol. Med. 68, 1, 1948.
Svartz, N. and *Schlossmann, K.:* Nord. Med. 42, 1390, 1949.