

Department of Orthopaedic Surgery (Head Professor Carl Hirsch, M.D.),
University of Gothenburg, Sweden

SYNOVIAL pH IN RHEUMATOID KNEE JOINTS

II. *The Effect of Local Corticosteroid Treatment*

IAN GOLDIE & ALF NACHEMSON

Received 6.v.69

Chronic inflammation gives rise to a local acidosis (Menkin & Warner 1937), the hydrogen ion concentration increases and the pH ranges around 6.5. The same condition exists in rheumatoid synovium though statements of the pH value differ. Ropes & Bauer (1953) found an average pH of 7.22 as compared to 7.39 in normals and Cummings & Nordby (1966) reported variations from 7.08 to 7.28 with a mean of 7.22 in comparison to 7.43 as a normal value. The above-mentioned values were all measured in synovial fluid withdrawn from the joints.

We have previously described intra-articular pH measurements in knee joints where we found in normal individuals a value of 7.3 and in rheumatoid arthritis 6.6 (Goldie & Nachemson 1969). The study was extended to measurements of synovectomized rheumatoid joints in order to establish whether removal of inflamed synovial tissue might alter the intra-articular pH. The results showed a mean of 6.8. Although the patients were symptom-free in the measured joints, the persistent acidity was believed to be due to a remaining inflammatory state in the regenerating synovial tissues, though of a lesser degree. It was thought that some inflammatory components might be lodged in the new synovium as a local target organ for the general, chronic disease.

As yet there is no complete explanation of the acidity of inflamed tissues. It has been suggested that protein split products such as amino acids (Ropes & Bauer 1953), or increased glycolysis (Menkin 1956, Binzus & Tillman 1968), or release of hydrolytic lysosomal enzymes with subsequent connective tissue destruction (Dingle 1962, de Duve 1963), or depolymerization of hyaluronic acid (Asboe-Hansen 1966), or anoxia (Gardell 1966) may contribute to maintain tissue damage and thus local acidity. A combination of various factors may cause the increased hydrogen ion concentration in inflammation.

In view of this it may be presumed that anti-inflammatory drugs such as salicylates, indomethacin, phenylbutazone, and corticosteroid influence the acidity in inflamed tissues.

This part of the study was designed to follow the pH behaviour for 15–30 minutes after corticosteroids were injected into rheumatoid joints and also 20–24 hours after the injection.

MATERIAL AND METHODS

Twenty-two patients were selected, all of whom fulfilled the requirements for the diagnosis of rheumatoid arthritis according to the American Rheumatology Association (Ropes 1959). The knee joint was chosen and in all there was a swelling and articular exudate. The puncture with the measuring instrument was made from the lateral aspect after 1–2 ml of local anaesthesia with 1 per cent Carbocaine® with adrenaline had been administered intra- and subcutaneously. Care was taken not to inject the joint capsule as this might interfere with the synovial fluid conditions.

The steroids injected were in all patients methylprednisolonacetate, 40 mg (Depomedrone®).

The pH measurements were made by a needle electrode as described in Part I of this study (Goldie & Nachemson 1969).

The joint cavity was reached by a larger needle (diameter 2.1 mm) with a pointed mandrin, which was then extracted and the electrode inserted. Care was always taken to place the electrode in the free joint cavity. Reading was made after 2 minutes' stabilization time. In some cases the electrode was moved also to other parts of the joint without noticeable change in pH, except that when joint cartilage was encountered, an instantaneous drop in pH was noted.

After the readings had become constant, the steroid was injected from the medial aspect of the knee as far as possible away from the pH electrode. Registrations were made immediately on injection and 5, 10, 15, 20, 25, and 30 min after. A tendency to stabilization was noted after 20–30 min. A final registration 20–24 hours following the steroid injection was made in nine patients.

The pH of the hydrocortisone preparations was also measured using the same equipment.

Four of the patients (Nos. 19, 20, 21, 22) received systemic steroid treatment at the time of measurements. Two (Nos. 15, 16) had previously been synovectomized. Three patients (Nos. 17, 18, 19) had received an intra-articular injection of steroids 4–6 weeks prior to this investigation.

RESULTS

The injected steroid solution itself had a pH around 5.0.

As seen from Table 1 most of the rheumatoid knee joints showed an elevated hydrogen ion concentration prior to injection. The mean pH in the non-treated joints (Cases 1–14) was 6.7 ± 0.3 which agrees

Table 1. Intra-articular pH in earlier untreated patients following local injection of hydrocortison

Patients nos.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15*	16*	Mean
Before inj.	6.9	6.6	6.4	6.6	7.0	7.0	6.6	6.9	6.0	6.9	6.4	7.1	6.5	6.6	6.9	6.9	6.7
Immed. follow. steroid inj.	6.3	6.2	6.0	6.3	6.5	6.6	6.3	6.3	5.7	6.6	6.5	6.7	6.1	6.3	6.4	6.7	6.3
5 min after	7.0	6.6	6.6	6.7	7.0	7.3	6.3	7.0	6.1	6.9	7.0	6.9	6.5	6.6	6.9	7.1	6.8
10 min after	7.1	6.7	6.7	6.8	7.1	7.5	6.7	7.4	6.3	6.8	7.2	7.2	6.8	7.3	7.0	7.1	7.0
15 min after	7.1	6.7	6.8	6.9	7.2	7.5	6.9	7.3	6.8	6.9	7.2	7.3	7.0	6.9	7.0	7.1	7.0
20 min after	7.2			6.9			7.0	7.0	7.1	6.9	7.3	7.4	7.1	7.3		7.2	7.1
25 min after									7.1	6.9	7.2	7.5	7.2	7.3			7.2
30 min after									7.1	6.9	7.2	7.5	7.2	7.3			7.2
20-24 hours after									7.1	7.3	7.3	7.6	7.4	7.4			7.3

* These patients previously synovectomized in the measured knee joint.

Table 2. Intra-articular pH in earlier steroid-treated patients following local injection of hydrocortisone

Patient no.	17*	18*	19*	20§	21§	22§	Mean
Before inject.	7.7	6.7	7.5	7.2	7.1	7.1	7.2
Immed. follow.							
steroid inj.	7.3	6.6	7.1	7.0	6.5	6.6	6.9
5 min after	6.8	6.9	7.6	7.5	7.4	6.7	7.2
10 min after	6.8	6.9	7.6	7.9	7.7	6.9	7.3
15 min after	7.8	7.1	7.5	7.9	7.7	6.9	7.5
20 min after	7.8	7.4	7.5	7.9	7.7	7.0	7.5
25 min after	8.0	7.3	7.5				7.6
30 min after	8.0						—
20–24 hours after	8.0	7.0	7.4				7.5

* These patients received intra-articular injection of steroid in the measured joint 1–2 months prior to investigation.

§ These patients received systemic steroid treatment.

with the previously published measurements (Goldie & Nachemson 1969) where the pH in the diseased knee was 6.6 ± 0.2 .

Cases 17–22, presented in Table 2, had clearly elevated pH (7.2 ± 0.3) as compared with the others, which is assumed to be due to systemic or intra-articular steroid treatment previously administered.

Immediately following the injection there was a sharp drop in pH (average 0.4 ± 0.2 pH units) probably due to the steroid solution itself. This decrease in pH remained for some minutes but then there was a slow increase in all subjects, which became noticeable in all instances after 10 minutes (see Tables 1 and 2). Thereafter a slight increase was observed up to 30 minutes. In nine patients recordings after 20–24 hours showed the pH still maintaining an increased value equal to the measurements 30 minutes following injection with one exception (Case 10) where there was no change in pH after 30 minutes but 0.4 pH units after 22 hours.

In all but three patients, the pH after 15 minutes had surpassed the original value. In Cases 10 and 19 the pH was the same as before injection and in Case 22, 0.1 unit less. The increase was on an average 0.3 pH units (Figure 1). The average intra-articular pH in all the subjects measured at the particular intervals is seen in Figure 2.

A statistical analysis between Cases 1–14 and Cases 17–22 showed that at most times there was a significant difference in pH, with

Mean pH change
after injection

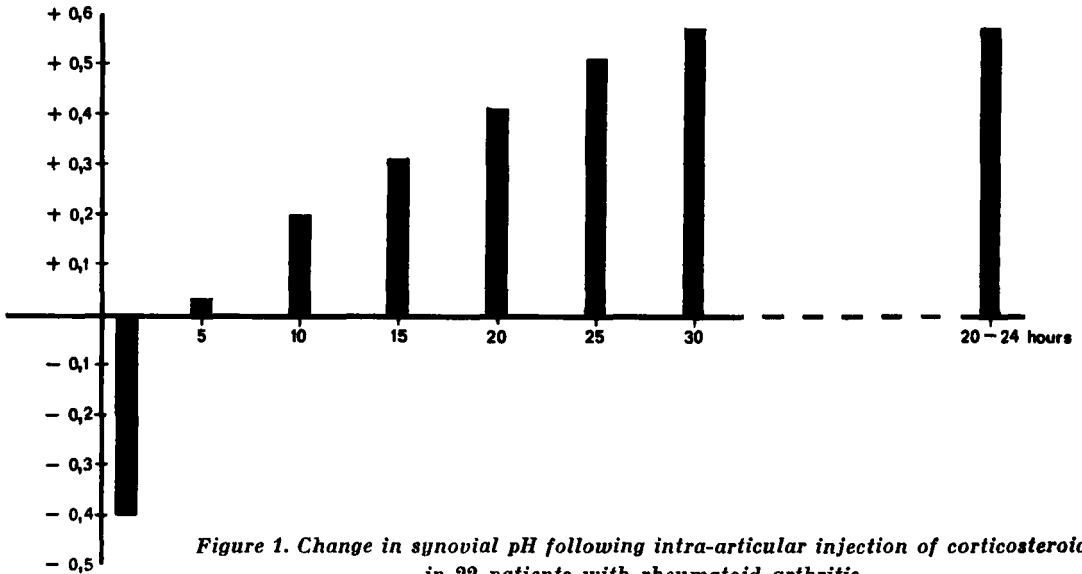


Figure 1. Change in synovial pH following intra-articular injection of corticosteroid in 22 patients with rheumatoid arthritis.

higher values in Cases 17-22 who had received earlier steroid treatment (Table 3).

On the other hand, the statistical analysis did not demonstrate any major difference between the two groups with regard to the increase in pH following the injection (Table 4). In these comparisons the two

Table 3. Mean values and *t*-statistics of the intra-articular pH following hydrocortisone injection in earlier untreated (Cases 1-14) and earlier steroid-treated (Cases 17-22) patients

	Cases 1-14 Mean \pm SD	Cases 17-22 Mean \pm SD	<i>t</i> -value
Before inject.	6.7 \pm 0.3	7.2 \pm 0.3	3.48*
Immed. follow. steroid inj.	6.3 \pm 0.3	6.9 \pm 0.3	3.89*
5 min after	6.8 \pm 0.3	7.2 \pm 0.4	2.38*
10 min after	7.0 \pm 0.3	7.3 \pm 0.5	1.76
15 min after	7.0 \pm 0.2	7.5 \pm 0.4	3.17*
20 min after	7.1 \pm 0.2	7.5 \pm 0.3	not perf.
25 min after	7.2 \pm 0.2	7.6 \pm 0.4	not perf.
30 min after	7.2 \pm 0.2	—	not perf.
20-24 hours after	7.3 \pm 0.2	7.5 \pm 0.5	not perf.

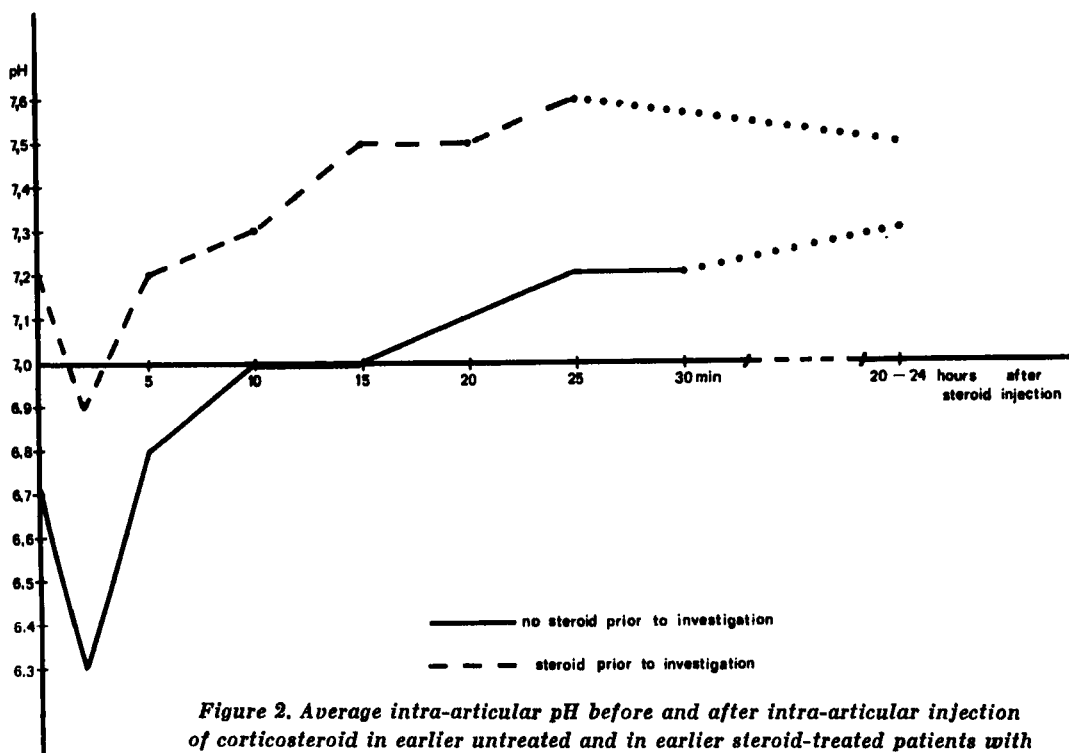


Figure 2. Average intra-articular pH before and after intra-articular injection of corticosteroid in earlier untreated and in earlier steroid-treated patients with rheumatoid arthritis.

synovectomized patients were excluded. The pH measured in these joints was the same as presented in Part I of this study (Goldie & Nachemson 1969).

The increase in pH noted from 15 minutes and thereafter following the injection of steroid is statistically highly significant ($p < 0.01$).

No complications following the measuring procedure were observed.

COMMENT

It is evident from this investigation that intra-articular deposited corticosteroid preparations, though very acid themselves, cause an alteration towards the normal side of the pH scale in rheumatoid arthritis. In Part I of this study the pH of normal knee joints was 7.3 ± 0.2 (Goldie & Nachemson 1969). The initial sharp drop as registered on the introduction of the steroid obviously seems to be a direct action of the injected fluid. The ensuing increase may be explained by the various

Table 4. Change in pH following injection of steroid in rheumatoid knee joints

	Cases 1-14 Mean \pm SD	Cases 17-22 Mean \pm SD	t-value
Immed. follow.			
steroid inj.	- 0.4 \pm 0.2	- 0.4 \pm 0.2	< 1
5 min after	+ 0.1 \pm 0.2	- 0.1 \pm 0.5	< 1
10 min after	+ 0.3 \pm 0.2	+ 0.1 \pm 0.6	1.14
15 min after	+ 0.3 \pm 0.2	+ 0.3 \pm 0.4	< 1
20 min after	+ 0.5 \pm 0.3	+ 0.3 \pm 0.4	< 1
25 min after	+ 0.6 \pm 0.4	+ 0.3 \pm 0.3	not perf.
20-24 hours after	+ 0.7 \pm 0.2	+ 0.2 \pm 0.2	not perf.

buffering mechanisms which regulate the hydrogen ion concentration in both blood and extravascular tissues (Salenius 1957, Saunders et al. 1960). The buffering requires a normal fluid equilibrium and cannot exert its full influence in damaged tissues. It appears that the steroid has to be given some time, 10-20 minutes, to interact with the tissue dynamics before buffering takes place. The turnover of intra-articular deposited steroids is rapid, ranging from 5 to 120 minutes (Wilson et al. 1953, Peterson et al. 1959, Winter et al. 1967, Murphy & West 1968). After this time the buffering mechanisms may come into force. This investigation indicates such a possibility. Our findings are also in agreement with those of Binzus & Tillman (1968) who noted a drop in $p\text{CO}_2$ and increase in $p\text{O}_2$ on prednisolon injection in rheumatoid knees.

In rheumatoid synovial inflammation small organelles are encountered within granulated cells preferably neutrophils, but also macrophages. These organelles, lysosomes, normally play no part in intracellular metabolism. By phagocytosis of foreign materials and by anoxia, the lysosomes disrupt and release their proteo- and hydrolytic enzymes (de Duve 1963, Weissmann 1965, Gardell 1966). They contribute to maintaining inflammation and acidity. Part of the steroid action—like that of salicylic acid, phenylbutazone, and indomethacin—is stabilization of the lysosomal membranes (Weissmann & Thomas 1964, Holt et al. 1938).

Hyaluronic acid is of importance to the capillary wall function. Depolymerization increases the permeability of the vessel wall. Corticosteroids polymerize hyaluronic acid (Nettelbladt & Sundblad 1963) and the abnormal permeability of the capillary wall is ceased. This occurs via an antihyaluronidase action by the corticosteroids (Brunius 1968).

The relationship between increased hydrogen ion concentration in tissues and pain has been investigated by Revici et al. (1949) and Lindahl (1961) among others. Revici et al. believe that local changes in damaged tissues may bring about a lowering of the nerve threshold for pain and that end organs ordinarily concerned with other forms of sensation are altered in such a way that the impulses originated by them evoke the sensation of pain. Lindahl has offered evidence of the relationship between increased hydrogen ion concentration and severe pain in the skin whereby the hydrogen ion may be the chemical mediator which triggers the pain stimulæ in the nerve endings.

A variety of pain mechanisms could be at play in rheumatoid arthritis, for example, capsule and ligamentous engagement and bone involvement. The low synovial fluid pH may be part of the mechanisms which elicit joint pain. It is generally accepted that local steroid treatment relieves pain in rheumatoid joints. The reason for this may be the demonstrated tendency to normalize the pH.

SUMMARY

Previous studies have shown that the pH in rheumatoid joints is decreased below the normal of blood and organ tissues and also below that of normal joints.

By using a direct intra-articular method we have been able to confirm our results in an earlier investigation that the hydrogen ion concentration in rheumatoid joints averages a pH of 6.7. The problem in this study has been to investigate whether local application of corticosteroids influences the synovial pH. In 22 patients it was found that within 20 minutes after steroid injection a statistically significant increase of pH followed, to a level well above the initial values in all except one joint. On an average the increase was 0.3 pH units. In nine patients measurements were made 20–24 hours after the injection and the pH still remained increased.

Although from the start a significant difference existed in pH between those knees that were previously not treated (6.7 ± 0.3) and those earlier treated with steroid (7.2 ± 0.3), the response to the injected steroid, with regard to pH increase, was not significantly different.

REFERENCES

- Asboe-Hansen, G. (1966) in *Inflammationen inom kirurgin*, ed. S. Bengmark, Hässle, Göteborg, p. 21.

- Binzus, G. & Tillman, K. (1968) Glykolyse und Atmung der Bindegewebe rheumatischer Gelenke und ihren pharmakologische Beeinflussung. *Z. Rheumaforsch.* **27**, 334.
- Brunius, W. (1968) Wound healing impairment from sutures. *Acta chir. scand.* Suppl. 395.
- Cummings, N. A. & Nordby, G. L. (1966) Measurements of synovial fluid pH in normal and arthritic knees. *Arthr. and Rheum.* **9**, 47.
- Dingle, J. T. (1962) Aetiological factors in the collagen diseases. Lysosomal enzymes and the degradation of cartilage matrix. *Proc. roy. Soc. Med.* **55**, 109.
- de Duve, C. (1963) in *Lysosomes Ciba Foundation Symposium*, ed. de Renck & Cameron, Churchill, London, p. 1.
- Gardell, S. (1966) in *Inflammationen inom kirurgin*, ed. S. Bengmark, Hässle, Göteborg, p. 24.
- Goldie, I. & Nachemson, A. (1969) Synovial pH in rheumatoid knee-joints. I. The effect of synovectomy. *Acta orthop. scand.* **40**, 634-641.
- Holt, P. J. L., How, M. J., Long, V. J. W. & Hawkins, C. F. (1968) Mucopolysaccharides in synovial fluid. *Ann. rheum. Dis.* **27**, 264.
- Lindahl, O. (1961) Experimental skin pain. *Acta physiol. scand.* **51**, Suppl. 179.
- Menkin, V. & Warner, C. R. (1937) Studies on inflammation. XIII. Carbohydrate metabolism, local acidosis and the cytological picture in inflammation. *Amer. J. Path.* **13**, 25.
- Menkin, V. (1956) Biology of inflammation. *Science* **123**, 527.
- Murphy, D. & West, H. F. (1968) The metabolism of cortisol in rheumatoid synovial tissue. *Arthr. and Rheum.* **11**, 696.
- Nettelbladt, E. & Sundblad, L. (1963) Om intraartikulär steroidbehandling. *Svenska Läk.-Tidn.* **60**, 1315.
- Peterson, R., Black, R. L. & Bunim, J. J. (1959) Disposition of intra-articular injected cortisone and hydrocortisone. *Arthr. and Rheum.* **2**, 433.
- Revici, E., Stoopen, E., Frenk, E. & Ravich, R. A. (1949) The painful focus. II. *Bull. Inst. appl. Biol.* **1**, 21-38.
- Ropes, M. & Bauer, W. (1953) *Synovial fluid changes in joint disease*. Harvard Univ. Press, Cambridge.
- Ropes, M. (1959) Diagnostic criteria for rheumatoid arthritis. *Ann. rheum. Dis.* **18**, 49.
- Salenius, P. (1957) A study of the pH and buffer capacity of blood plasma and red cells. *Scand. J. clin. Lab. Invest.* **9**, 160.
- Saunders, S., Irvine, R., Crawford, M. & Milne, N. (1960) Intracellular pH of potassium deficient voluntary muscle. *Lancet* **468**.
- Weissman, G. & Thomas, L. (1964) The effects of corticosteroids upon connective tissue and lysosomes. *Rec. Progr. Hormone Res.* **20**, 215.
- Weissman, G. (1965) Lysosome. *New Engl. J. Med.* **273**, 1084-90; 1143-49.
- Wilson, H., Glyn, J., Scull, E., McEwen, C. & Ziff, M. (1953) Rate of disappearance and metabolism of hydrocortisone and cortisone in the synovial cavity in rheumatoid arthritis. *Proc. Soc. exp. Biol. (N.Y.)* **83**, 648.
- Winter, J., Sandberg, A. A., Saroff, J. & Slaunwhite, W. (1967) Disposition and metabolism of intra-articularly injected 4-C¹⁴-cortison in rheumatoid arthritis. *Arthr. and Rheum.* **10**, 352.