INTRA-ARTICULAR INJECTIONS

IN OSTEO-ARTHRITIS

A CRITICAL EVALUATION BY CLINICAL, PHYSICO-CHEMICAL AND EXPERIMENTAL METHODS

A THESIS SUBMITTED BY:

GEORGE DALL

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I N D E X

INTRODUCTION.

The therapy of osteo-arthritis is a problem which we have inherited from our forebears. It is a considerable problem; one which affects the community very vitally. The disease produces marked disability which burdens our civic economy. Various methods of therapy have been advocated from time to time such as hydro-therapy, physiotherapy and analgesics of different kinds. This thesis will deal only with the intra-articular injection therapy of osteo-arthritis.

If one consults the literature on intra-articular injections in osteo-arthritic joints, one finds that very little has been written on the subject. The therapy is either advocated very strongly, or it is made light of as unimportant. No proper assessment of the results seems to have been made. It was, therefore, decided to see whether a critical evaluation of the results of this form of treatment was possible; and if it were found of value, to investigate the possible mechanism of its beneficial effect.

While these investigations have been under way the importance of the subject has grown tremendously. The introduction of endocrine therapy in the treatment of arthritis in general has raised many hopes, perhaps rather prematurely. It was decided to include in these investigations the effects of these newer hormones when injected intra-articularly. Supplies have not been available until fairly recently, with the result that the follow up of these cases has of necessity been short.

The relevant literature on intra-articular injections will first of all be reviewed.

Note: The following terms have been used synonymously:-

Osteo-arthritis, degenerative arthritis and arthritis deformans.

CHAPTER I

A REVIEW OF THE LITERATURE

The first record of intra-articular injections for osteo-arthritis, that it has been possible to trace, is a statement made by Woolf (1938) that J.B. Murphy in 1911 was injecting a solution of formalin and glycerine. Murphy was of the opinion that his results were good, but Woolf comments that these injections have not stood the test of time. Conti (1924) injected colloidal silver intra-articularly but as the original article was unobtainable, the effect is not known. Giocobbe (1928) advised the inflation of a joint with air.

In 1927, Bettman advocated the use of Jodipin - a product of oil of sesame with iodine. He considered the indications for these intra-articular injections to be (1) Surgical tuberculosis (2) spastic contractures (3) the arthrides including degenerative arthritis. He used sesame oil in preference to olive oil because of its poor absorbability and its capacity to retard adhesion formation. To eliminate the pain produced by the injection a local anaesthetic was added. The local anaesthetic also promoted pain-free joint function and improved the vascularity and thereby the joint circulation. The other reasons for using Jodipin were its action as a mechanical buffer which covered

the joint surfaces, especially the uneven surfaces; and its antiseptic action. The dosage suggested by Bettman was two to four cc of 20- 40% Jodipin in 5% "Peikain" base - the latter being the local anaesthetic. He often found one injection sufficient and the relief obtained was most satisfactory. He advised that the joints be kept at rest for one to two days after the injection.

Bettman states that this form of therapy is particularly useful in desperate cases where other methods, including the customary injection methods of phenol, camphor and Pregl's solution have failed. He states that because of lack of space no case histories are given. In conclusion he states that experiments were also conducted using the French lipiodol which was a substitute for the German Jodipin but he could find no advantages in using the lipiodol, which acts in an opposite manner and tends to stimulate adhesion and scar formation.

Riemke in 1930 published a paper on the intra-articular injection of petroleum (vaseline) in arthritic joints. The original article could however not be traced and so it is not known what results he obtained.

Thomson (1933) published his observations on the

the use of intra-articular injections of Pregl's solution into chronic arthritic joints. This solution first appeared as a secret preparation described by Pregl in 1919. He described it as a non-irritating, non-staining, watery solution of free and combined iodine with certain iodides. Pregl advocated its use in infections of all kinds. Thomson produced experimental arthritis in rabbits by introducing infection into the joint directly, or by introducing ½ to 1 cc carbolic solution plus half-strength tincture of iodine. In most instaces a period of two to four weeks elapsed between the operative intervention and the beginning of treatment. An exploratory arthrotomy was performed before treatment was started. One joint was then treated with Pregl's solution and the other acted as a control. 1½ cc of Pregl's solution was injected every three to four days for three to four weeks. The animal's joints were then examined. His photographs are not very convincing and there is no mention of histological examination of the joints. His conclusions, as far as experimental work is concerned, are best given in the following excerpt from the article: "Nevertheless there seems to be something in the use of Pregl's solution that quite definitely affects the synovia, even in the presence of severe infection,

to the extent that it apparently produces an inactivity or diminution of synovial secretion, with an atrophy or shrinking of the synovia very definitely inhibiting an infectious process and perhaps promoting cartilage regeneration". The accent is on the infection but when it is remembered that degenerative arthritis was thought to have an infectious etiology this is easy to understand. As far as the clinical side is concerned he published the results in 14 cases all of which had effusions. In all there was either complete recovery or improvement.

Waugh's first communication on the use of lactic acid intra-articularly appeared in 1938. In 1936 his paper on "Acid Values in Purulent Discharges" led him to conclude that the acidity present in the pus of a wound treated by the Winnett Orr method acts as a probable stimulus to the formation of primary mesoblastic tissue, and the growth of granulations with accelerated wound healing. Subsequently he found that in traumatic effusions the reaction was acid in the initial stages changing to alkalinity by the seventh day. The acidity, he ascribed to the presence of lactic acid. He concluded that the development of acidity was a physiological response to trauma designed to excite local leucocytosis and repair, and

consequently decided to introduce lactic acid into joints disabled as the result of trauma. Using the lactic acid alone considerable pain resulted, so he decided to add novocain to the solution. Following the injection he manipulated the joint and then immobilised it for a fortnight. A synopsis of the traumatic cases treated is given in Table I.

TABLE I

Joint Affected	Clinical Condition	Cases	Result
Knee	Lax Joint	4	Functional recovery complete
Knee	Traumatic (mono-articular) arthritis	2	Functional recovery complete with disappearance of crepitation sounds
Shoulder	Lax joint with recurrent subluxation	2	Full functional activity. No recurrence of subluxation since injection.
Elbow	Arthritis and peri-articular thickening: fibrous ankylosis.	3	Full functional activity; 85% normal range of movement

The injections were made around as well as into the capsule. The amount of solution used was two cc for the elbow and ankle joints and four cc for knee and shoulder joint cases. The results as indicated in the table were as revealed at examination twelve months or more after injection.

The cases treated were those of severe disablement which had resisted various forms of treatment. Waugh suggests that the trauma attendant on manipulation of joints by orthopaedic surgeons and osteopaths in similar cases may provoke a local acidification of the joint content, and in so doing, stimulate the reaction of repair.

His apparent success in the treatment of traumatic arthritis led him to try this method in cases of rheumatoid arthritis, where the disease was no longer active but had left deformity and dysfunction. He proceeded to determine the pH of the synovial fluid in cases of rheumatoid arthritis The absence of effusions in these cases made it difficult to obtain specimens by aspiration, so he first of all injected distilled water (pH 7) into the joint and then aspirated the diluted fluid. He stated that in ten cases the dilute synovial fluid gave the surprisingly alkaline reading of pH 8 and over. Five cases of chronic rheumatoid arthritis were treated. He reported one case in detail in which both hip joints and the right knee was treated with very marked improvement. All five cases derived much benefit. He states that after injecting into and around the joints all adhesions were broken down and the full range of movement was obtained.

It is this forcible manipulation which may be criticised as it is more likely that the benefit derived in these cases was due to the breaking down of adhesions, which was only possible after the injection of a solution containing a local anaesthetic.

In 1945 Waugh's communication on the treatment of mono-articular osteo-arthritis of the hip appeared. His rationale here again was the finding of an alkaline reaction in the synovial fluid in osteo-arthritis. Other than stating it was even as high as 8.8 he gives no experimental results to amplify this statement. He goes on to state that in a case which had received a long and successful course of lactic acid injections into the knee joint, examination of the cartilage removed from the head of the tibia showed a covering of fibrocartilage 1/32 inch thick over the whole weight bearing surface. The procedure Waugh adopted in these cases of osteo-arthritis of the hip joint was again to follow the injection (which was made into and around the joint) by a gentle manipulation, and after this continued exercises without weight-bearing. He treated 108 cases in this way over the preceding five years, but because of bombings, removals etc. he was unable to follow them up completely. He, however, did follow up 26 consecutive cases treated during

1942, and found that between 50 and 60% of these cases had obtained sufficient relief from pain to be able to carry on their normal occupations, including shipyard work and coal hewing in the case of the men. Waugh mentioned that the chief contra-indication to this method of treatment is marked loss of joint space. Five of his 26 cases fell into this category and three more failed to attend regularly for treatment. His figures for the remaining eighteen were as follows:

Number of Cases	Results		
	Very Good	Good	Poor
In-Patients 4	3	0	1
Out-Patients 14	4	7	3

Various other authors have given brief reports on this method of treatment, notably Crowe (1944) who used acid potassium phosphate, and Ramamurthi (1947). Others include Hetherington (1946) Heald and Martin (1947) Mawson (1946) and Howell (1947)

The following table gives a comparison of the results of those authors who gave figures. It should be observed that Crowe (1944) did not use any local anaesthetic and his series consisted of a very large number of "active infective or focal arthritis". Only the figures for the group with osteo-arthritis will be given.

TABLE II

Author	No. of Cases	Result	Conclusion
Crowe	93 (one injection usually sufficient)	18 - Asymptomatic 38 - Objective and Subjective improvement 37 - Subjective alleviation	Useful
Ramamurthi	120 (only 20% required more than one injection)	In 50% of cases pain and stiffness disappeared for 8 to 16 months	Useful
Heald and Martin	25 Knees only .. Hips and knees Knees and wrist Hips alone not included here	16 Pain 8 Stiffness 1 Walking difficulty	Improved: 15, 17, 15 No Change: 8, 7, 7 Worse: 1, 1, 1 Useful
Mawson	18 (average number of injections 4) Hips not included here.	Better: 17 No Change: 1 Worse: 0	Very impressed

Ramamurthi adds that in a few cases with a little effusion, the pH of the fluid was tested before the injection, 48 hours after the injection and three weeks later. It changed from pH 8.0 before the injection to 7.2 in 48 hours. In three weeks it was again 7.8 or 8.0.

Scott (1938) wrote as follows: "To introduce chemical substances into arthritic joints with the object of modifying

the rheumatoid process is in itself not a particularly new departure. Indeed, it might seem the obvious thing to try; but, to judge from the meagre literature available, investigations in this direction have been unsystematic and sporadic". He goes on to say "My interest in this matter was first aroused by examining several arthritic patients who had certainly derived benefit at the hands of a foreign physician, whose refusal to communicate his methods had resulted in the loss of his diploma. It was his custom to inject a small dose of some oily preparation more or less daily for a month, which, he stated, had a nutritive effect on the joint cartilage, an explanation which his medical colleagues doubtlessly found it difficult to accept. It seemed worth while, however, to try to rediscover, if indeed it existed, any principle which he may have found effective".

Scott tested 24 different oils by injecting them into normal joints. Poppy seed oil used by Forestier as a solvent of iodine in lipiodol proved the most irritating of them all, and the least irritating of all the vegetable and animal oil was liquid paraffin. He was of the opinion, however, that oils used by themselves do not produce any permanent benefit in rheumatic joints. Though nothing was

gained from the mechanical effect of an injected oil, the presence of an oil seemed to be necessary for two other reasons; first to prolong the action of any substance dissolved in it and, secondly, to localise that action. Thus when a 10% solution of sodium salicylate in water was injected into an inflamed joint the effect of lessened pain was immediate, but often did not last an hour, traces of salicylates being soon found in the urine. If on the other hand 10% of sodium salicylate was dissolved in oil there was very little immediate effect, but a slow reaction which lasted several days, urinary salicylate not being detected.

Scott found that rheumatoid joints derived no benefit from this therapy. If there was any change it was more likely a deterioration. He found the following mixture, which he called gomenol, the most useful:-

Camphor	5%
Oil of niaouli ..	20%
Ether	2%
Olive oil to ..	100%

He treated eighty knee joints and his results were as follows:

Patients under 70 years of age	-	36	good result
		12	fair result
		2	negative result
Patients over 70 years of age	-	6	good result
		22	fair result
		2	negative result

Woolf (1938) advocated the injection of the patient's own liquefied fat into the osteo-arthritic joints. He selected this material because he considered it would be non-irritant to the joint tissues. He recommended the method of treatment in osteo-arthritis - especially in the "dry" type of joint, considering it valueless in rheumatoid arthritis. The fat was obtained from the abdominal wall and was heated in the theatre until sufficient oil had been extracted. The oil was allowed to cool to 120° F and then injected into the affected joint or joints, approximately 15 cc being the amount used for the average knee joint. There were 24 patients in the series and 30 joints were injected. His results were as follows:-

Successes	16
Failures	7
Doubtful	3
Immediate result good but unable to follow-up ..	4

It should be noted that some of the failures were cases with rheumatoid arthritis.

Fletcher (1943) reported on the use of intra-articular injections of lipiodol. Such a procedure was first advocated by Sicard and Forestier (1932). They said however, that the injections were far from painless and synovial effusions often

followed. Fletcher found that the injections were followed by a marked degree of pain, often necessitating morphia for the first 24 to 48 hours. His results were as follows:-

65% were symptom free, 15% improved and 20% not improved. His successful cases were followed up for lengthy periods ranging from 2 to 7 years. Fletcher also injected a series of 20 cases with Scott's special solution of gomenol. In those 20 cases his results at the time the patients left hospital were:

10 symptom free, 6 improved only and 4 not improved. After one year at least three of the patients who were symptom free had relapsed. The gomenol injections were, however, painless. Fletcher (1951) states that the results with gomenol seem less satisfactory than those with lipiodol, because the results are more temporary. He, however, differs from Scott in recommending gomenol in rheumatoid arthritis.

Kron (1948) advocated the use of intra-articular alkali (sodium bicarbonate) therapy, because he considered alkalinity in a joint to favour the solution of "mucin" in the synovial fluid. This he argued would keep the fluid viscid and in this manner improve lubrication. He

is of the opinion that in "arthritis sicca" the following vicious circle exists:

> Reduced viscosity - friction - pain and inflammation - acidification - viscosity still further reduced and so on.

The alkali therapy he contends breaks the cycle and he mentions satisfactory results obtained in five patients with osteo-arthritis. This is in direct contrast to the injection of an acid into arthritic joints as outlined by Waugh. Kron's theory is supported by the fact that the addition of an acid to the synovial fluid will result in the precipitation of "musin", but this may occur with certain alkalies too. His series of cases is very small and it is difficult to draw conclusions from this single report.

de Leon (1948) reported on the intra-articular injection of Vitamin C added to a novocain solution with an acid pH. He first reasoned that the Vitamin C might be beneficial for the nutrition of the articular cells. Subsequently he felt that it was probably the acidity of the solution that was responsible for the therapeutic effects obtained. Apparently, however, he frequently repeated the injections and it is more than likely that the novocain was playing the chief part in alleviating the symptoms. He does not give any follow up

figures but Jolis (1952) who worked with de Leon is of the impression that the long term results were poor.

Douthwaite (1946) makes the following criticism of the injection of acid into arthritic joints: "The rationale of acidification of arthritic joints is based on the finding of an alkaline pH of the synovial fluid in cases with chronic osteo-arthritis. Even if this be so, the weakness of the reasoning seems to be in (a) the empiricism of a treatment directed to a mere change in pH (b) the improbability that lactic acid affects this more than transiterily (c) the addition of a local anaesthetic to the fluid (d) the willingness to inject around the joint as well as into it and (e) the inclusion of exercises which are well known to help the osteo-arthritic especially if performed with care, in combination with local anaesthesia".

Fletcher (1948 and 1951) feels that the manipulation is probably the most important part of the procedure, especially as far as the hip joint is concerned. He considers that almost identical results can be obtained by injecting the capsule with procaine. He considers that a single injection provides relief for varying periods ranging from hours to days. He suggests that once satisfactory relief is obtained the

injection be repeated every four to five weeks.

Baker and Chayen (1948) treated a series of 52 patients (70 joints) with osteo-arthritis with three types of intra-articular injections. These cases were not confined to cases with involvement of the knee joint only. The three types of injections used were:

Solution I - Lactic Acid in 2% procaine with a pH of 5.4.

Solution II - 0.5% procaine adjusted to a pH of 7.6 with sodium phosphate.

Solution III - Normal saline.

A 10 cc injection was given into the hip and knee joints and the number of injections given to each patient ranged from 2 to 22, the average being ten. Injections were given at fortnightly intervals in most instances. The patients were put to bed for forty-eight hours after each injection and given non-weight-bearing exercises. Then exercises were continued and stressed all the time the patient was under observation. Their results were as indicated in Table III .

TABLE III

Result of Treatment	Solution used		
	I	II	III
No improvement	14	6	-
Slight improvement, continuing injections	5	5	-
Slight improvement, ceased injections	3	1	-
Moderate improvement, continuing injections	5	6	1
Moderate improvement, ceased injections	4	2	-
Great improvement, continuing injections	1	-	1
Great improvement, ceased injections	12	4	-

The authors suggest that the apparently higher percentage of final improvement on lactic acid is due to the fact that they had used the lactic acid treatment longer than the others, with the result that more of the cases treated with lactic acid had been followed to their end results. They arrived at these conclusions:

1) That the method of treatment was most beneficial
2) That they had found no evidence that intra-articular injection with acid fluid had any special advantage over solutions with a physiological pH.

3) They attributed the success of the injection to the lubricating action of the fluid introduced, and also possibly to the fact that the patients might have broken down adhesions while the effect of the procaine was present.

They give no specific follow up figures but mention that the work had been in progress for eighteen months when the article went to press. The number of cases treated with Solution III i.e. the normal saline is too small to allow conclusions to be drawn. Unfortunately no indication is given as to how much longer the cases that received lactic acid had been observed, than those receiving procaine alone. It is indeed difficult to make any deductions from the table.

Sacks (1949) advocated the use of heparin intra-articularly, because of its anti-hyaluronidase activity. Maclean (1942) and Meyer (1947) both report the inhibiting effect of heparin on testicular hyaluronidase. Madinaveitia and Quibell (1941) reported a marked influence of salts especially sodium chloride on the activity of testicular hyaluronidase as determined by viscosimetric methods. Sacks does not mention whether he used sodium heparin or not. The heparin ordinarily available is the sodium salt and would therefore exhibit no

anti-hyaluronidase activity. In a personal communication to Horwitz (1952$) he is of the opinion that both lactic acid and heparin leave much to be desired in the permanent relief of pain in osteo-arthritis.

Of recent years hormonal injections have in many respects revolutioned the alleviation of the lot of the arthritic. Most of the literature on this type of therapy is devoted to their use in rheumatoid arthritis. Hench et alia (1950) report a case of leukaemia, who in addition had osteo-arthritis bf the left knee, treated with cortisone systemically with marked amelioration of the pain and stiffness in the knee. When seen one month later the improvement had been maintained. Thorn et alia (1950) in a paper on the clinical usefulness of A.C.T.H. and cortisone report as follows:-

"One patient with a generalised osteo-arthritis and an associated bilateral malum coxae senilis was treated with A.C.T.H. (10 m.g. every 6 hours) for seven days. Placebos given during the preceding two days had no effect. There was a marked alleviation of pain and increased mobility of joints within twenty four hours of the start of A.C.T.H. Improvement became more marked during the seven day course of therapy".

Boots et alia (1951) treated eleven patients with osteo-arthritis of the hip with oral cortisone with marked subjective improvement in ten patients. The hormone had to be discontinued in some because of untoward symptoms but five out of eight patients followed up were continuing cortisone therapy after nine months.

Brown et alia (1951) disagree with these opinions, however. In a series of eight cases with degenerative hip joint disease treated by oral and systemic cortisone only two cases showed improvement. Because of the dangers of such treatment in the older age group these authors do not consider such treatment justifiable.

Dowdell et alia (1952) are in agreement with the last mentioned authors. They treated ten patients with malum coxae senilis, first with a placebo and later with oral cortisone. Partial relief of pain was noted in eight of the ten patients while receiving cortisone and in six of the ten patients while receiving the placebo. No significant objective improvement occurred and no untoward symptoms were noted.

Hollander et alia (1951) reported on the use of hydro-cortisone and cortisone by intra-articular injection.

They treated a large number of rheumatoid arthritic joints and found hydrocortisone far superior to cortisone when used intra-articularly. The cortisone often produced no response and on occasions proved to be irritating. They then decided to treat osteo-arthritic joints in this way. Hydrocortisone was injected into the joints of 39 patients with osteo-arthritis. Their series of 37 knees will be considered in some detail.

In 36 of the 37 instances a complete or nearly complete disappearance of symptoms and complete return of normal work tolerance was noted within 24 hours after the injection of 25 mg. of hydrocortisone into the painful joint. The duration of relief in these cases averaged three weeks. In one case relief continued for five months. Re-injection was made when the symptoms recurred.

For comparison of effects 25 mg. cortisone was substituted for hydrocortisone, without the patient's knowledge in 22 cases. In no instance was the marked alleviation previously noted after hydrocortisone injection reduplicated by the use of cortisone.

The relapse which occurs after a remission produced by the hydrocortisone has, according to Hollander and his co-workers, never appeared worse than the pre-treatment arthritic state.

These authors do, however, emphasise the fact that before this method of treatment can be called a practical aid in the management of this disease, it must stand the test of time.

The more dramatic response to hydrocortisone is ascribed to the fact that, although more soluble in water than cortisone acetate, it is less soluble in blood plasma. Presumably therefore it would be less soluble in synovial fluid, and consequently disperse more slowly from the joint.

Other reports on the use of intra-articular hydrocortisone have been given by Stevenson et alia (1952) and Kersley and Desmarais (1952) but they have only described its effects in cases with rheumatoid arthritis.

Sacks (1953) in a preliminary report on intra-articular hydrocortisone injections mentions six cases of osteo-arthritis of the knees, who have been relieved for two months after the last injection. He also mentions remissions ranging from one to four weeks.

Kuhns (1953) states that intra-articular injections of hydrocortisone have resulted in temporary relief of pain and stiffness in about two-thirds of patients. This treatment has, however, not changed the pathological picture nor

lessened the deformity. He considers injections of lactic acid or local anaesthetic to be of very little value, and prefers analgesics, physiotherapy and corrective measures to intra-articular therapy.

Before discussing the investigations in this series, the results of lactic acid injections given in the Orthopaedic Department of the Groote Schuur Hospital during 1950 and 1951 will be given. A questionnaire was sent to 21 patients who received these injections for osteo-arthritis of the knee joints and 16 either replied or presented themselves for examination.

The following questions were put in the questionnaire:

1. For how long did your knees trouble you before receiving the injections?
2. Did they prevent you from carrying out your routine duties?
3. Have the injections helped you at all?
4. If they have helped, how much have you improved?
5. Are you at present free from trouble as regards your knees, e.g. can you climb stairs without difficulty?

The injections were given by the various interns who were working in the department during the period.

The results are reflected in Table IV.

TABLE NO. IV : INTRA-ARTICULAR LACTIC ACID INJECTIONS (KNEES ONLY) GIVEN IN THE ORTHOPAEDIC DEPARTMENT, GROOTE SCHUUR HOSPITAL DURING 1950 AND 1951

Case	Age and Sex	Knee producing symptoms	Duration of symptoms before Treatment	No. of injections received	Improvement: No change or Worse	Follow up
S.S.	60 F	R	6 months	6	Marked Improvement	15 months
M.W. R.	69 F	L	6 months	6	Marked Improvement	2 years
E.M.	60 F	L	6 months	6	Marked Improvement	16 months
G.v. Z.	65 F	Both	5 years	3	Marked - stairs still difficult	9 months
J.A. v.M	55 M	R	5 months	5	Marked Improvement - Asymptomatic	18 months
C.A. B.	50 F	Both	1 year	6 each	Marked Improvement	15 months
F.R.	63 F	L	Many Months	5	Marked Improvement- Asymptomatic	2 years
G.v.d M	63 F	Both	10 years	6 each	Moderate Improvement	1 year
S.J. v.R	44 M	R	Several years	6	Moderate Improvement	21 months
A.C.	53 F	L	2 years	6	Moderate Improvement	2½ years
E.W.	68 F	Both	Several years	6	Improved for 9 months since then gradual relapse	22 months
C.G. **	50 F	L	2 years	12	Symptom free for 3 months since then moderate improvement	2 years 4 months
A.V.	59 F	Both	6 years	6 each	No change	2 years
J.V. R.*	62 F	Both	Many years	6 each	No change	2½ years
I.H.	57 F	Both	10 years	6 each	Worse	21 months
A.C.	55 M	Both	1 year	6 each	Worse	20 months

* Associated Paget's Disease ** Thyrotoxic

Marked Improvement - completely asymptomatic or very mild symptoms
Moderate - Much better but with some pain and difficulty with stairs.

Because all the cases did not present themselves for examination no distinction could be made between subjective and

objective improvement.

It will be noted that of the sixteen that replied seven report marked improvement, three moderate and two a temporary remission with subsequent gradual relapse. Two did not change and two considered they were worse after the injections.

CHAPTER II

CLINICAL INVESTIGATIONS

A. MATERIAL

1. The Selection of Cases
2. Salient Points in History and Examination.

B. METHODS

1. The Nature of the Injections used
2. The Technique of the Intra-Articular Injections
3. The Supervision of Cases

C. THE RESULTS OF THE INTRA-ARTICULAR INJECTIONS

1. The Group which received Procaine Injections
2. The Group which received Lactic Acid Injections
3. The Group which received Ammonium Sulphate Injections.
4. The Group which received Cortisone Injections
5. The Group which received Hydrocortisone Injections.

D. COMPARISON OF THE RESULTS

After going through the literature on intra-articular injections it becomes apparent that the majority of the authors favour their own particular type of injection. Each in turn is of the opinion that the injection material he recommends produces the best results In addition the opinion is expressed that the results are most satisfactory and various modes of action are suggested. This produces a degree of suspicion, as the treatment is often most empirical and can at the most be of only symptomatic value. The very fact that the results are so universally good add to this scepticism. The assessment of the results is never very clearly stated and appears to be based on subjective findings.

It was decided to investigate the response to certain intra-articular injections in as critical light as possible. In addition an attempt would be made to elucidate the rationale, if any, of this method of treatment.

A. MATERIAL

1. The Selection of Cases.

Because of the scarcity of hospital beds all patients were outpatients. It was decided to confine the cases to those with osteo-arthritis of the knee joint or joints, as one could be absolutely certain of the injection being intra-articular, whereas in the case of the hip joint this is not always possible. As far as possible the cases selected were those with the disease confined to one knee or both knees. (Often the vertebral column or some other joint showed radiological evidence of osteo-arthritis, although no symptoms referable to these regions were present.)

It is known that rheumatoid arthritis may commence late in life, and may affect one or two joints for a considerable time at first. Horwitz (1952 b) is of the opinion that this type of rheumatoid arthritis very often commences in a large joint. In order to exclude possible cases of rheumatoid arthritis only cases with a normal sedimentation rate were included, with one or two possible exceptions, which will be specifically mentioned when the cases are discussed. Kellgren and Moore (1952) describe a type of osteo-arthritis with a raised sedimentation rate and polyarticular involvement in association with Heberden's

nodes. It is, however, too difficult to be certain that such cases are not in fact cases of rheumatoid arthritis.

Because of this method of selection the series had to be pruned considerably. Forty-two cases (sixty knees) treated with intra-articular injections have been included.

The duration of symptoms varied considerably, but an attempt was made to include cases with long standing disability as well as cases with a relatively short history.

In a few cases trauma was the original factor that predisposed to the osteo-arthritis, whilst in another group malalignment of the joint surfaces was presumably responsible for the resultant arthritis. The largest group, however, consisted of the "idiopathic" type of osteo-arthritis.

Most cases had objective evidence of the disability. The objective change was chiefly an impaired range of active movements.

All the cases included had radiological evidence of the disease in varying degrees of severity. As far as possible no very early cases were included. Some of the cases had very advanced radiological changes, especially in the group that received hydro-cortisone. Here it must be pointed out that the degree of radiological change was no index to the extent of the disability. Very often the joint with the

most advanced X-ray changes was the painless one. These observations have been made by other authors including Kron (1948) and Baker and Chayen (1947).

In all cases the peripheral pulses were palpable, as it was desirable to exclude any possible case of peripheral vascular disease in this series.

2. Salient Points in the History and Examination of Each Patient.

(i) The History

a. Pain Under this heading the intensity, duration and the nature of the pain, were determined. It was particularly noted if the patient could attribute any cause for the onset of the pain. In addition the patients were asked whether pain was present during exercise or at rest or on both occasions. Other questions such as the effect of the pain on the patient's daily routine, and the effect of climbing or descending stairs were asked.

b. Stiffness. Often the major complaint was not pain but the difficulty in performing active movements.

(ii) The Examination.

The following signs were noted particularly:-

a. The presence or absence of an effusion

b. The range of active movements.

c. The mobility of the patella, and if mobile, whether movement produced pain.

d. Whether tenderness on palpation was present.

e. The circumference of the thigh four finger-breadths above the patella.

f. The presence or absence of creaking.

g. The functional performance of each patient. This included the gait, the ease or difficulty of climbing on to the couch, or getting up from an ordinary chair.

B. METHODS.

1. The Nature of the Injections Used.

Five types of injections were used in this series:-

a. 0.5% procaine in 10 cc saline. This is the concentration of procaine present in the preparation of lactic acid supplied by Saphar for intra-articular use. 10 cc were injected so that the volume of fluid injected should be the same as in the lactic acid injections.

b. 10 cc 0.2% lactic acid in 0.5% procaine as supplied by Saphar.

c. 2 to 5 cc of saturated ammonium sulphate, with a pH of 7.0. This substance was selected because like lactic acid it precipitated protein, but did not possess a definite

acid reaction. It was noticed that on boiling the ammonium sulphate solution in order to sterilise it for injection use, the pH was lowered, consequently the solution was sterilised by Seitz filtration. It was not possible to increase the amount of these injections because they proved to be rather painful if increased. The saturated solution was used, because it was felt that after dilution by any synovial fluid present in the joint, about half saturation would ultimately result.

d. 50 to 100 mg. of cortisone acetate i.e. 1 to 2 cc

e. 25 to 50 mg. hydrocortisone i.e. 1 - 2 cc

2. <u>The Technique of the Intra-articular Injections</u>

When the series was first started the lateral infra-patellar route into the knee joint was employed but after the appearance of the paper by Hollander et alia (1951) the medial infrapatellar route was adopted. This route was found to be preferable in many cases as in advanced patello-femoral arthritis the patella is very often immobile and placed rather laterally. This means that access from the medial side is easier than from the lateral side.

After cleaning the skin thoroughly and under strict aseptic precautions the patella was grasped by the fingers

of the left hand and pushed as far medially as possible. This manoeuvre opened up the groove between the patella and the femoral condyles and so made the introduction of the needle very much simpler. The skin and subcutaneous tissues were infiltrated with a little procaine but no procaine was inserted into the joint cavity, except in the cases receiving ammonium sulphate injections, as these injections proved to be painful unless preceded by the introduction of 1 to 2 cc of 2% procaine. Four cases were not given any preliminary procaine. These will be mentioned separately. After the insertion of the needle a clean syringe containing the substance to be injected was attached, and if at all possible a few drops of synovial fluid were aspirated and mixed with the contents of the syringe. If this was not possible a few minims of the fluid to be injected were introduced, and if no resistance was encountered it was clear that the needle was intra-articular and the injection could proceed. After the injection a collodion dressing was applied and the joint put through a single range of active movements to encourage an even distribution of the injected material in the joint. No manipulative procedures were performed and the patient was instructed to continue with his usual routine after the injection.

3. Supervision of Cases

When the patients attended subsequently, they were questioned as to how the joint or joints had behaved during the week following injection. As far as possible no leading questions were asked.

The patients were in no instance aware of the type of injections they were receiving, as the psychological factor, especially in the cases treated with cortisone and hydrocortisone might easily play an important role.

No other therapy apart from analgesics was used. Very many of the cases had had physiotherapy in the past, and had either relapsed or received no benefit from this form of treatment. However, once it was decided to commence the intra-articular injections all other treatment was discontinued to avoid confusion in the assessment of the results. In a few cases once the result of the injection therapy had been assessed, quadriceps exercises were instituted as it was often clear that all pain had been relieved, but that the residual weakness was delaying full return of function.

The analgesics prescribed were tablets of aspirin, phenacetin and caffeine (grs. v). The patients were told to take two tablets if and when the pain was severe, and to

keep a record of the number of tablets taken each week This was noted each time the patient attended, serving as a guide as to whether the intensity of the pain was in any way being decreased by the injections.

After the completion of the course of injections the patients were again seen after approximately four weeks and if there was improvement they were told to report back whenever the symptoms recurred. If no, or only slight, improvement was manifested the patients were seen regularly so that the subsequent course of their treatment could be decided upon. The patients in this series were all seen again just before this account was written.

C. THE RESULTS OF THE INTRA-ARTICULAR INJECTIONS

How the results were assessed.

The disease has its own natural remissions which often made it very difficult to decide how much of the improvement was attributable to the injections. For this reason it was most desirable to follow the cases and see them frequently and get to know them thoroughly. The patients were often physchologically benefitted by the mere fact that they were receiving active treatment. Many of them had previously been told repeatedly that nothing could be done for them. Consequently this was another

factor which increased the difficulty of assessing the results.

The subjective improvement was chiefly judged by the range of active movements before and after injections. In this connection it was important to differentiate between impaired movements due to stiffness on the one hand, and pain on the other hand. Other signs such as the disappearance of effusions or tenderness were valuable adjuncts in assessing the objective improvement.

Finally the question of functional performance was put in a separate category. Every now and then, one of the patients would state that they could climb or descend the stairs with greater freedom. This increased agility could easily be observed and often it was associated with no marked evidence of objective improvement.

The Nomenclature used in describing the Results

The following nomenclature has been used to indicate the degree of improvement in the tables expressing the results of the various injections:

1. Marked improvement, indicating a complete remission symptomatically, or an increase of at least 30° or more in the range of active movements.

2. Moderate improvement, indicating some residual pain, or an increase of 15-30° in the range of active movements.

3. Slight improvement, indicating some change in the intensity of the pain, or an increase of up to 15° in the range of active movements.

4. No change.

5. Worse.

1. <u>The Group of patients which received procaine injections intra - articularly.</u>

As far as possible a course of six weekly injections of 10 cc each were given. If there was no response after this some other injection was substituted. In some cases the change was made after three or four injections. Some cases with both knees affected were given different injections in the opposite knee so as to compare results. The degree of disability was, however, often not parallel and this made the interpretation difficult.

The results in this group are tabulated in Table No. V

Seven cases received procaine injections. Of these seven, three exhibited no change, two were moderately improved and the remaining two had remissions lasting four months and one year respectively.

Of the three patients who did not improve at all two cases I.e. Case No. 1 and 7 did no better on other injections. Case No. 1 received ammonium sulphate after the procaine injections and had a slight remission for two months. Case no 7 received ammonium sulphate and later lactic acid into the right knee and procaine into the left. The knee which received procaine showed slight objective improvement. This case, however, proved to be a very difficult case to assess, because of

TABLE NO. V : INTRA-ARTICULAR PROCAINE INJECTIONS

Case No.	Age and sex	Knee producing symptoms	Duration of symptoms before treatment	No. of injections received	Improvement			Follow Up
					Subjective	Functional Performance	Objective	
1	60 F	Left	1 year	6	No change	No change	Worse (?)	1 year
2	45 F	Right	6 months	3	No change	No change	No change	6 months
3	64 F	Both R:proc L:L.A.	12 years	6	Moderate	Moderate	Moderate movements increased by 15°	6 months
4	50 F	Both R:proc. L:L.A.	2 years	2	Remission lasting 1 year then given lactic acid with marked improvement			22 mths
5	82 M	Both R:proc. L:A.S.	2 months	6	Moderate, but relapsed after 4 months.	Then given lactic acid with marked improvement		14 mths
6	32 M	Both L:proc. R:L.A.	3 years	4	Moderate	Moderate	Marked	22 mths
7	40 F	Both L:proc. R:A.S.	18 mths.	6	No change	Slight	Moderate	11 mths

proc. - procaine L.A. - lactic acid A.S. - ammonium sulphate
L: L.A.- means left knee received lactic acid injections and so on

Case 1 This patient subsequently received ammonium sulphate injections with no improvement.

Case 2 Subsequently received 5 injections of lactic acid with marked improvement.

Case 3 The left knee is included in the table of the lactic acid injections and was more severely affected.

Case 5 The left knee is included in the table of the ammonium sulphate injections

Case 7 See also Tables Nos. VI and VII

The above notes have been included so as to indicate which of the patients received other injections as well.

complicating domestic disturbances. Case No. 2, the third case not to benefit from the procaine injections subsequently responded very well to intra-articular lactic acid. She was quite unaware of any change in the form of treatment.

The two cases (Nos. 4 and 5) with temporary remissions each subsequently received lactic acid with marked improvement. These two cases also received different injections into the opposite knees. At the time of the procaine injections. In Case No. 4 it was lactic acid whereas in Case No. 5 it was ammonium sulphate. Both these knees improved markedly and have maintained the improvement for 22 and 14 months respectively.

2. The Group which received Lactic Acid Injections

Twenty two patients received intra-articular lactic acid injections. Twenty five joints were injected. The results are tabulated in Table No. VI. As far as possible six weekly injections of ten cc each were given. If there was no response or only a slight one, after six injections, other injections were substituted or the case was followed and the progress noted.

TABLE NO. VI : INTRA-ARTICULAR LACTIC ACID INJECTIONS

Case No.	Age and Sex	Knee producing symptoms	Duration of symptoms	No. of injections	Improvement			Follow Up
					Subjective	Functional Performance	Objective	
2	45 F	Right	6 mths	5	Marked	Marked	Marked Movements increased by 50°	4 mths
3	64 F	Both L-L.A. R-proc.	12 yrs.	6	Moderate	Moderate	Moderate Movements increased by 20°	6 mths
4	50 F	Both	2 yrs.	L:2 R:5	Marked	Marked	Marked. Movements R:increased by 15° L:increased by 50°	L:22 mth R:7 mths
5	82 M	Both R:L.A.	2 mths	4	Marked	Marked	Marked	9 mths
6	32 M	Both R:L.A. L:Proc	3 yrs	4	Marked	Marked	Marked	22 mths
7	40 F	R	18 mths	4	No change	No change	Moderate	9 mths
8	35 F	R	Several months	6	Marked	Marked	Marked	2 yrs.
9	68 M	Both	6 mths	6	Marked	Marked	Marked	7 mths
10	69 F	Both	Several years	6 each	Marked	Marked	Marked. Movements: R increased by 90° L increased by 60°	19 mths

TABLE NO. VI CONTINUED - INTRA-ARTICULAR LACTIC ACID INJECTIONS

Case No.	Age and Sex	Knee producing symptoms	Duration of symptoms	No. of injections	Improvement			Follow Up
					Subjective	Functional Performance	Objective	
11	57 M	Both	4 years	2	Marked	Marked	Not been able to re-examine	3 mths
12	64 F	L	4 mths	4	Moderate	Moderate	Marked	8 mths
13	60 F	R	1year	5	Marked	Marked	Marked-movements increased by 65°	1 yr.
14	54 F	Both	1 year	6 each	Slight	Moderate	Moderate - R:increased by 10° L:increased by 45°	3 mths
15	60 F	Both R:L.A L:A.S.	2 mths	6	Moderate	Moderate	Moderate	10 mths
16	47 F	L	2 years	6	Marked	Marked	Marked	6 mths
17	58 F	L	few mths	6	Slight	Moderate	No change	9 mths
20	65 M	R	1 mth	6	Marked	Marked	Marked	18 mths
37	53 F	L	several years	8	Moderate	Moderate	Moderate	few weeks
38	60 M	L	4 mths	6	Marked	Marked	Marked	few weeks
39	45 F	R	3 years	4	Moderate	Marked	Marked	6 wks
40	55 F	R	14 mths	8	Moderate	Marked	Moderate	few wks
42	70 F	L	3 mths	3	Marked	Marked	Marked	Relapsed after 11 mths then given hydrocortisone

proc. - procaine L.A. - Lactic Acid A.S. - ammonium sulphate

Notes on Cases

Case No. 2 After three injections of procaine 0.5% in 10 cc saline with no change

Case No. 3 The right knee is included in the Table of procaine injections and was less severely affected.

Case No. 4 Twenty-two months ago the right knee received two injections of procaine 0.5% in 10 cc saline and a remission lasting one year followed

Case No. 5 After procaine injections had produced a moderate remission lasting four months.

Case No. 10 This case first of all received six injections each of 10,000 units heparin into the right knee with no change.

Case No. 15 The left knee is included in the table of the ammonium sulphate injections

Case No. 17 This patient first of all received six injections of ammonium sulphate with moderate improvement.

It will be noted that fourteen cases have improved markedly, five moderately, two slightly and one was unchanged. A few of these require special comment.

Case No. 10 responded dramatically to lactic acid therapy after the right knee had failed to respond to six weekly injections of heparin sodium. Cases No. 2, 4 and 5 have already been mentioned when discussing the procaine series. Case No. 42 relapsed after eleven months and was then given hydrocortisone injections with marked response.

Five cases have shown moderate improvement. In this category Case No. 3 has been discussed in the procaine series. In the case of No. 15, this patient received lactic acid into the right knee and ammonium sulphate injections into the left knee. The left knee in this case showed the best response.

Two cases showed only slight response. One of these No. 14, improved moderately, objectively, but she still complained of pain especially at night. The other case, No. 17, must be qualified. This case also appears in the group which received ammonium sulphate injections. She received the latter injections first and showed moderate response. Subsequently she was given lactic acid to see whether a complete remission could be achieved. She, however, only exhibited a slight further improvement.

Only one case in this group did not change, i.e. No. 7. She is the case discussed previously in the procaine series and was most difficult to assess. Once again she did show some evidence of objective improvement.

No cases became worse after treatment.

3. The Group which received Ammonium Sulphate Injections

There were thirteen cases in this group. Here again the aim was to give six weekly injections of from two to five cc each. Usually the first injection was small so as to note the effect produced. If this did not prove particularly painful the next injection was increased. Unfortunately, as already stated, two cc of procaine had to be introduced into the joint because of the painful effect of the ammonium sulphate without procaine.

The results in this group are reflected in Table No. VII.

TABLE NO.VII - INTRA-ARTICULAR INJECTIONS OF SATURATED AMMONIUM SULPHATE

Case No.	Age and sex	Knee producing symptoms	Duration of symptoms	No.of injections	Improvement			Follow Up
					Subjective	Functional	Objective Performance	
1	60 F	Left	1 year	6	No change	Slight	No Change	9 mths
5	82 M	Both L:A.S. R:Proc then L.A.	2 mths	6	Marked	Marked	Marked	14 mths
7	40 F	Both R:A.S. L:proc	18 mths	6	No change	Slight	Slight	11 mths
15	60 F	Both L:A.S. R:L.A.	2 mths	6	Marked	Marked	Marked	10 mths
17	58 F	L	few mths	6	Moderate	Moderate	Marked	11 mths
18	47 M	R	2 yrs	6	Moderate	Marked	Moderate	15 mths
19	55 M	L	1 year	6	Marked	Marked	Slight	13 mths
20	65 M	L	2 mths	4	Marked	Marked	Marked:Movements increased by 150.	21 mths
21	47 F	R	Few yrs	6	Marked	Marked	Marked	1 year
22	40 M	L	Many yrs	6	Marked	Marked	Marked:Movements increased by 50°	16 mths
23	60 F	L	1 mths	2	Marked	Marked	Marked:Movements increased by 70°	10 mths
24	75 M	L	6 mths	2	Slight	Slight	Marked	1 year
25	54 F	R	1 year	3	No change	No change	No change	15 mths

L.A. - Lactic Acid Proc - procaine A.S. Ammonium Sulphate.

It will be noted that of the thirteen cases in this group, seven improved markedly, two moderately, one slightly and three showed no change.

Cases No. 5 and No. 15 have already been discussed. It may be repeated, however, that in the case of No. 15, the left knee, which received the ammonium sulphate injections, responded even better than the right which received lactic acid injections. The left was in addition the more severely affected knee.

Case No. 19 has been included, as having shown marked improvement, despite the fact that the objective improvement was only slight. This man was severely incapacitated and is now symptom-free. His functional performance is, by comparison, markedly improved and he is perfectly satisfied with the result. He has in fact recommended the injections to his friends.

Case No. 20 presented with complete inability to move the left knee. The duration of symptoms was two months, and he could not move the knee because of pain. On X-ray, however, several loose bodies were noted so it was decided to do an arthrotomy. At operation a few particles of "joint mice" were removed but no appreciable loose body was found. There were several pronounced osteophytes but none of these were unattached. When the patient did not improve posteoperatively, he was given the injections of ammonium sulphate with dramatic results. When last seen he had no difficulty in achieving free extension of

the knee and could flex it to 150°. He is back at work and climbs ladders without difficulty.

Two cases in this group have improved moderately. One of these, Case No. 17, is the case already discussed in the group receiving lactic acid injections. The other No18 has gained much agility but still occasionally has pain and objectively his movements have only increased by 20°.

One case, No. 24, showed only slight improvement. He has been placed in this category because of a fair amount of residual pain although objectively his movements are much improved.

As far as the three cases with no change are concerned, the first two, Case No. 1 and No. 7, have been discussed in the procaine series. The third, No. 25, had only three injections and had a temporary remission lasting three months. She has a marked valgus deformity of the affected knee and was unfortunately not prepared to have any further treatment.

No cases became worse after these injections.

4. The Group of Patients which Received Cortisone Injections.

There were six patients in this group and nine knees were treated. The quantity was first of all 100 mg. and the injections were given bi-weekly. This dose of cortisone acetate, however, proved to produce an irritant effect and so the amount was reduced to 50 mg. and later the injections were given at weekly intervals. Because it was impossible to be certain how much of the hormone would be absorbed, it was not deemed advisable to give another type of injection to the opposite knee, in cases of bilateral involvement. If an improvement occured in the opposite knee it would be difficult to know to what it should be attributed.

In this group it was considered inadvisable to give a definite course of any particular number of injections. This, after all, was an entirely different type of injection and the investigation was in the nature of an experiment, there being no previous reports to indicate what might be expected from the use of cortisone intra-articularly in osteo-arthritis.

The results in this group are given in Table No. VIII.

TABLE NO. VIII : INTRA-ARTICULAR INJECTIONS OF CORTISONE

Case No. Age and Sex	Knee producing symptoms	Duration of symptoms	No. of injections received	Improvement			Follow Up
				Subjective	Functional Performance	Objective	
26 48 F	Both	4 mths	6x100 mg. then 5x50 mg. weekly	Marked	Marked	Marked. Each knee active movements have increased by 30°	11 mths
27 46 F	Both	L: 5 yrs R: 1 yr.	70x50 mg weekly	Marked	Marked	Moderate. Each knee active movements have increased by 20°	3 mths
28 76 F	R	12 yrs	3x50 mg. weekly	Moderate	Marked	Marked, active movements have increased by 35°	7½ mths
29 56 F	Both	1 mth	4x100 mg bi-weekly 6x50 mg. bi-weekly 2x50 mg. weekly. 4 wks later 50 mg.	marked	Marked	Marked, active movements have increased by R. Knee 55° L. Knee 20°	7 mths
30 77 F	L	8 yrs.	7x50 mg. weekly then hydrocortisone	slight	No change	No change	changed to hydrocortisone injections
31 74 M	L	3 yrs	3x50 mg. weekly then hydrocortisone	Moderate	No change except for 3-4 days after injection	No change	changed to hydrocortisone injections

The follow up in this group has not been very long. Supplies of the hormone were at first very difficult to procure.

In this group three cases have shown marked improvement. These will be discussed first.

The first case, No. 26, began to improve after the fourth injection and after this continued to improve steadily and maintain the improvement. She received eleven injections

in all had has now been followed for eleven months after the last injection. She was severely incapacitated as she is a charwoman, but she has been back at work for ten months and experiences only very slight pain on kneeling.

The second case, No. 27, has been included in this category as she had no symptoms whatever, although she has only showed an increase of 20° in her active movements. Her main disability was pain. Before the injections she could not climb or descend stairs, because of pain, but she now finds no difficulty whatever. She, likewise, started improving after the fourth injection.

The third case, No. 29, began responding after the third injection. After her twelfth injection the treatment was discontinued because of marked improvement. Four weeks later she had a mild relapse and so a further injection was given with dramatic results, which have been maintained.

One case No. 28 has improved moderately. She had a complete remission for six months but during the past six weeks has experienced occasional pain. Objectively her improvement has been marked.

Two cases have been tabled as having exhibited no change. Both showed some symptomatic improvement, but it was certainly not striking objectively. The one case, No. 31,

did, however, have a marked remission after the first injection lasting six days. Both these cases were subsequently given hydro-cortisone injections.

5. The Group which Received Hydrocortisone "Compound F" Injections.

There were nine cases in this group and twelve knees received injections. Hydrocortisone has not been available for very long. Consequently the follow up period has been much shorter than in the other groups. It was decided to adopt the method of Hollander et al (1951) i.e. to give injections as they were required. Two cases were, however, given weekly injections instead.

The results are reflected in Table No. IX.

TABLE NO. IX - INTRA-ARTICULAR HYDROCORTISONE INJECTIONS

Case No Age and Sex	Knee producing symptoms	Duration of symptoms	Number of injections	Improvement Subjective	Functional Performance	Objective	Follow up
30 77 F	L	8 yrs	13x25 mg hydrocortisone	Marked while remission lasts	Marked	Moderate Active range increased by 20°	Still under treatment receives injections every 3-4 weeks
31 74 M	L	3 yrs	6 injections hydrocortisone ranging from 25-50 mg. each	Marked during remission, with relapse no change			Longest remission 6 days usually 2-3 days Treatment discontinued
32 45 M	R	3 yrs	7 ranging from 25-37.5 mg. each	Marked	Marked	Marked	At first had remissions of 14 days now symptom free for 6 mths
33 55 F	Both especially L.	4 yrs	5 ranging from 25-37.5 mg. each	No change	No change	No change	Discontinued treatment
34 66 F	Both	6 yrs	7	Marked during remission then moderate			6 months
35 54 F	Left	3 yrs	7	Slight remissions for 3-4 days on the whole no change			Discontinued treatment
36 65 F	Both	3 years	9	Marked during remission afterwards no change			Longest remission 1 wk
41 52 M	R	1 yr	9x50 mg weekly	Marked	Marked	Marked	Symptom free for two mths
42 70 F	L	3 mths	After L.A injections 6x25 mg. weekly	Marked	Marked	Marked	Symptom free for two mths

In this group seven cases have responded satisfactorily by having marked temporary remissions. Two cases did not benefit from these injections.

Case No. 30, had not responded satisfactorily to cortisone acetate injections, but after receiving the hydrocortisone she immediately experienced remissions lasting seven days at first and more recently up to 28 days. During the treatment it became obvious that weakness of the quadriceps group of muscles was delaying the recovery, so it was decided to depart from the proposed plan of action and to institute quadriceps exercises. These exercies resulted in marked improvement in her functional performance. She now receives an injection of hydrocortisone every three or four weeks.

Case No. 31 also failed to respond satisfactorily to cortisone acetate and was subsequently given the hydrocortisone injections. He experienced marked remissions but the longest was six days. After the remissions there was no change and treatment was eventually discontinued.

Case No. 32, a case of post traumatic arthritis with effusion, had a sedimentation rate of 26 mm Westergren, but because of the clear cut history of trauma and because of the X-ray changes it was decided to include him in the series. He first of all had remissions lasting 14 to 21 days and has now been symptom free for six months.

Case No. 34 had marked remissions lasting up to 21 days. The last injection was given on 26th September, 1952. Since then she has experienced stiffness but no pain.

Case No. 36 is a case of very severe ostec-arthritis with marked disability. She experienced excellent remissions of approximately seven days but after a remission relapsed to her previous state. She requested that the injections be discontinued as she found it difficult to present for weekly injections.

Cases No. 41 and 42 received weekly injections and have responded very well. Their follow-up is, however, of short duration.

Case No. 33 did not respond to hydrocortisone injections. She has very severe ostec-arthritis, the worst knee being associated with a condition resembling localised Paget's disease of the lower end of the femur.

Case No. 35, a case of post traumatic arthritis following a compound fracture of the left tibia involving the articular surface, showed poor response.

D. COMPARISON OF THE RESULTS.

A comparison of the results of the various types of intra-articular injections is given in Table X.

TABLE NO. X COMPARISON OF THE RESULTS.

Result of Treatment	Procaine	Lactic Acid (i)	Lactic Acid (ii)	Ammonium Sulphate	Cortisone	Hydrocortisone
Marked Improvement	2	12	14	7	3	7
Moderate Improvement	2	3	5	2	1	-
Slight Improvement	-	2	2	1	-	-
No Change	2	1	1	2	2	2
Worse	-	-	-	-	-	-

It will be noted that the lactic acid results have been subdivided into two columns. The second column includes four cases that have only been followed up for a matter of weeks. They have consequently been kept separate so as not to influence the other results.

Statistical analysis of these results is difficult because of the absence of suitable controls. The ideal

controls would be a large group of patients, with symptomatic osteo-arthritis of the knees, who received no therapy whatever. It is almost impossible to withhold all forms of treatment for a sufficiently long period of time. The other possible control would be a group of patients who received only physiotherapy. In the cases treated in this series a very large proportion were referred from the physiotherapy department after failing to respond to or having relapsed after physiotherapy.

The results have, however, been tested by the likelihood ratio method (Mood, 1950) against the arbitrarily chosen hypotheses that in untreated patients the percentage falling in the four categories would be:

	Marked Improvement	Moderate Improvement	Slight Improvement	No Change
Hypothesis (a)	25%	25%	25%	25%
Hypothesis (b)	10%	10%	40%	40%

Hypothesis (a) probably exaggerates the proportion of untreated patients showing either marked or moderate improvement. As no patients became worse as the result of intra-articular therapy this category has not been included.

The results of the treatment with lactic acid (both columns) and hydrocortisone differ significantly at the 1% level from hypothesis (a) but the results of the other treat-

ment do not. In the case of hypothesis (b) the results for all treatments except procaine differ significantly at the 1% level.

It would seem reasonable, therefore, to conclude that lactic acid and hydrocortisone have produced some beneficial effect on these patients. In the case of the procaine the results are statistically far less significant. It would appear that the procaine present in the lactic acid preparation could consequently not account for the beneficial effect. In the case of hydrocortisone it should be remembered that all cases with remissions - no matter how long these were - have been included in the category showing marked improvement.

CHAPTER 111

PHYSICO-CHEMICAL INVESTIGATIONS ON SYNOVIAL FLUID

A. INVESTIGATIONS

1. Viscosity Values
2. Whether Heparin is present in Synovial Fluid
3. The Action of "Hyalase" on Synovial Fluid
4. The Action of Lactic Acid on Synovial Fluid
5. The Action of Ammonium Sulphate on Synovial Fluid
6. Synovial Fluid Proteins
7. pH Values

B. DISCUSSION

In the preceding chapter the results of intra-articular therapy in a series of cases of osteo-arthritis were recorded. In many cases subjective improvement was noted and in a number of cases objective changes were demonstrated. It was decided that it would be worth investigating the possible effects of intra-articular injections on the synovial fluid, so as to determine whether the explanation of the success of this type of treatment could be found here.

The viscosity of normal human synovial fluid may vary according to difference in temperature, concentration and ionic environment (Gardner, 1950). The average viscosity of human knee joint fluid is given by Bauer et alia (1940) as 124 times that of water at 25° C. The viscosity values obtained during these investigations varied from 11.4 to 200.

The mucin content of synovial fluid distinguishes it from other dialysates and is responsible for its viscosity. The exact nature of the synovial fluid mucin is still a matter of controversy. (Gardner, 1950). In 1939 Meyer et alia reported that a sulphate free muco-polysaccharide (i.e. a compound of protein and a polysaccharide) isolated from synovial fluid appeared identical with the hyaluronic acid

which had been isolated from vitreous humor and umbilical cord. It was felt that this compound, which could be precipitated by acetic acid, was either free or united to protein by salt linkage only. Meyer et alia found that the protein in synovial mucin could be precipitated by half saturation with ammonium sulphate and the carbohydrate obtained from the viscous supernatant solution by alcohol precipitation. They found hyaluronic acid to consist of equimolar parts of d-glucosamine, glucoronic acid and acetic acid. The protein component of the carbohydrate-protein complex was thought to be a globulin which apparently forms an insoluble salt with the acid-polysaccharide on acidification.

Schurch (1950), Hesselvik (1940) and Blix (1940) used electrophoretic method to separate components of synovial fluid. The faster component was found to be hyaluronic acid and these authors all concluded that, in the native state, hyaluronic acid is in no way combined with protein but exists solely in the form of salts of inorganic bases present They regarded the mucin formed by precipitation with acetic acid as an artificial product.

1. Viscosity Estimations.

First the viscosity of various specimens of synovial fluid was measured using the Hess viscosimeter. The majority of the specimens were obtained at arthrotomies for injuries to the menisci of the knee joint. A few were obtained from aspiration of osteo-arthritic knees with effusions. The effect of dilution on the viscosity of the synovial fluid was determined. The results are given in Table XI. The viscosities are expressed relative to the viscosity of water.

TABLE NO. XI : VISCOSITY VALUES - EFFECT OF DILUTION

Contents of Test Tube	Viscosity of Different Specimens				
	1	2	3	4	5
0.3 cc Synovial Fluid	40 x H_2O	20 x H_2O	27xH_2O	114xH_2O	200xH_2O
0.3 cc Synovial Fluid plus 0.2 cc water	11.4 x H_2O	11.4xH_2O	10xH_2O	5xH_2O	8xH_2O

It will be noted that dilution appreciably reduced the viscosity and that the decrease is out of all proportion to the degree of dilution.

2. Heparin in Synovial Fluid

The next investigation was to ascertain whether heparin is present in synovial fluid. Sacks (1949) stated that because heparin is present in all connective tissues of the body it is

therefore a constituent of synovial fluid. It is known that heparin is chemically closely related to hyaluronic acid, but it seemed most unlikely that it should be a constituent of synovial fluid. The following simple test was consequently performed:

> 0.2 cc synovial fluid was added to 1 cc of freshly obtained whole blood and the coagulation time determined using the method of Lee and White. The coagulation time of a control using normal saline instead of synovial fluid was also determined.

The results are given in Table No. XII.

TABLE NO XII

Tube No.	Contents	Coagulation Time
1	0.2 cc Saline plus 1 cc fresh blood	5 min 35 secs.
2	0.4 cc Saline plus 1 cc fresh blood	4 min 53 secs.
3	0.2 cc Synovial fluid plus 1cc fresh blood	5 min 5 secs
4	0.4 cc Synovial fluid plus 1 cc fresh blood	5 min 25 secs

It will be noted that the synovial fluid exerted no heparin-like effect as the coagulation time was not prolonged. Using 0.4 cc synovial fluid made no appreciable difference. These tests were repeated with similar results.

3. The action of hyaluronidase on synovial fluid

In 1929 Duran-Reynols observed that aqueous extracts of normal testicle, when added to vaccinia virus and injected intra-dermally, produced unusually widespread lesions. He called this unknown substance the "spreading factor". Chain and Duthie (1940), showed that this "spreading factor" was an enzyme which they named hyaluronidase. They found that testicular extract reduced the viscosity of synovial fluid of cattle to that of water with the liberation of reducing substances. In 1940 Robertson et alia reported an enzyme "mucinase" isolated from broth cultures of clostridium perfrigens which "hydrolysed" synovial fluid mucin.

The substrate of hyaluronidase is hyaluronic acid There are actually a number of hyaluronidases and at least two may be involved in the depolymerization of hyaluronic acid (Ropes et al 1947).

Hyaluronidases may reduce synovial fluid viscosity in vivo (Regan and de Lamater, 1942). These authors aspirated synovial fluid and then injected testicular extract into arthritic joints with effusions and after periods varying from 16 to 170 minutes, withdrew a specimen of fluid again. Viscosity measurements before and after injections revealed the depolymerising effect of the testicular extract in vivo.

After a week in most cases the viscosity of the joint fluid had returned approximately to its original level. There was no change in the tendency of the fluid to re-accumulate in the joint and no mention is made of the effect on the clinical condition of the joints. The hyaluronidase used in these experiments was the product of Benger Laboratories "Hyalase". Each ampoule of "Hyalase" contains 1000 Benger units of hyaluronidase. At the present time no international hyaluronidase standard is available. To each ampoule was added 1 cc. of distilled water and then 0.1 cc of this dilution was used. The action of hyaluronidase is to depolymerize the hyaluronic acid in synovial fluid and reduce its viscosity very appreciably. This observation was verified by these experiments and the results are reflected in Table No. XIII.

TABLE NO. XIII : EFFECT OF HYALURONIDASE ON VISCOSITY OF SYNOVIAL FLUID

Contents of Test Tube	Viscosity Relative to Viscosity of Water														
0.3 cc.Synovial Fluid 0.2 cc H_2O	10	8	13·3	26	20	10	26	10	20	11·4	9	11·4	11·4	10	8
0.3 cc Synovial Fluid 0.1 cc hyalase 0.1 cc H_2O	1·3	1·3	1·8	1·2	1·2	1·8	1·4	1·3	1·3	1·8	1·2	2·4	1·8	2·3	1·2
0.3 cc Synovial Fluid 0.1 cc hyalase 0.1 cc heparin	1·3	1·3	1·6	1·2	1·2	1·2	1·8	1·2	1·3	1·9	1·2	1·3			
0.1 cc Synovial Fluid 0.1 cc hyalase 0.1 cc 0.2% lactic acid	1·3	1·6	1·4	1·2	1·3	1·3	1·4	1·2	1·2	1·8	1·2	1·8			
0.3 cc Synovial Fluid 0.1 cc hyalase 0.1 cc 1% lactic acid	1·8	1·6	1·6	1·2		1·3	1·4	1·2	1·1					1·8	1·8
0.3 cc Synovial Fluid 0.1 cc Hyalase 0.1 cc saturated ammonium sulphate						2·0	1·8	1·6	1·6	1·8	1·3				

Other substances e.g. heparin, lactic acid and ammonium sulphate were added to synovial fluid before the addition of the "Hyalase" so as to determine whether they exerted any anti-hyaluronidase effect. The heparin used was "Heparin Sodium" of Abbott Laboratories, 0.1 cc containing 1 mg. of heparin. This preparation did not on occasion prevent or minimise the action of "Hyalase". This bears out the previous contention that the sodium ions will inhibit the anti-hyaluronidase activity of the heparin. In addition the time taken for depolymerization to occur was in no way prolonged when comparing it with the tube not containing heparin. Depolymerization

invariably took place within one minute after the addition of the "Hyalase".

Lactic acid likewise exerted no anti-hyaluronidase activity even when the concentration was increased from 0.2% to 1% solution. Ammonium sulphate in saturated solution in a few instances did appear to diminish the depolymerizing effect of the "Hyalase" very slightly.

4. Lactic Acid and Synovial Fluid

The next investigation was one to determine the effects produced by the addition of lactic acid in different concentrations to synovial fluid. The first effect to be noted was that on adding 0.1 cc of 1% lactic acid to a tube containing 0.3 cc of synovial fluid and 0.1 cc of water a sticky precipitate formed. This precipitate was also evident when the water was replaced by "Hyalase". Using 0.2% lactic acid the precipitate was transient and it required a larger amount of the dilute lactic acid to produce a permanent precipitate.

The addition of "Hyalase" did not dissolve the precipitate formed by the lactic acid but if the "Hyalase" was added first and left to stand for a while and then 1% lactic acid added a precipitate formed, which on shaking decreased in amount. The residual precipitate was not sticky. The effect of the addition of lactic acid to the

synovial fluid on its viscosity was also determined.

The addition of 0.2 cc 0.2% lactic acid reduced the viscosity of the fluid more than could be accounted for by pure dilution. When 1% lactic acid was used the viscosity was still further reduced.

Meyer et alia (1939) prepared the so called synovial "mucin" from the stringy precipitate obtained after acidifying synovial fluid. This would account for the reduced viscosity of the synovial fluid after the precipitation following the addition of lactic acid. The greater the concentration of lactic acid the less viscid was the supernatant fluid. The fact that the precipitate which formed when "Hyalase" was first added to the synovial fluid was not sticky would suggest that only part of this precipitate was "Mucin" or hyaluronic acid. The "Hyalase" had no effect on the precipitate if already formed.

3. Ammonium Sulphate and Synovial Fluid

Ammonium sulphate, on the other hand, when added to synovial fluid produced a less gelatinous precipitate. "Hyalase" had no effect on the precipitate. The viscosity of the supernatant fluid was higher than that of the supernatant fluid in the lactic acid precipitate. It would seem that the addition of lactic acid or ammonium sulphate to synovial fluid precipitates it protein component, but in the case of the former the hyaluronic acid is precipitated as well.

6. Synovial Fluid Proteins

Two specimens of synovial fluid were submitted to chemical and electrophoretic analysis, so as to determine their protein content. The first specimen was obtained from Case No. 16 and the second from Case No. 32. The latter case was one with an elevated sedimentation rate of 26 mm. (Westergren). The results of the chemical analysis are given in Table No. XIV.

TABLE NO. XIV : PROTEIN ESTIMATIONS BY CHEMICAL METHODS

Proteins Estimated	Case No.16	Case No.32
Total proteins in synovial fluid	3.66 Gm.%	5.4 Gm.%
Albumin	2.5 Gm.%	3.2 Gm.%
Globulin fraction	1.16 Gm.%	2.2 Gm.%
After treating with ½ volume 1% lactic acid		
Total proteins in supernatant fluid	3.6 Gm.%	
Total proteins in precipitate	0.06 Gm.%	
Albumin fraction in supernatant fluid	2.6 Gm.%	
Globulin fraction in supernatant fluid	1.0 Gm.%	
After treating with half volume 1% lactic acid		
Total proteins in supernatant fluid		4.1 Gm.%
Albumin fraction in supernatant fluid		2.9 Gm.%
Globulin protein in supernatant fluid		1.2 Gm.%
Total proteins in precipitate		1.3 Gm.%
Albumin fraction in precipitate		0.3 Gm.%
Globulin fraction in precipitate		1.0 Gm.%

Electrophoretic estimations were also done on these two specimens of synovial fluid, using a method of micro-electrophoresis on filter paper.

The fluids were centrifuged and set up as depicted in Table XV.

TABLE NO. XV

Tube No.	Contents
1	0.3 cc synovial fluid
2	0.3 cc synovial fluid 0.2 cc H_2O
3	0.3 cc synovial fluid 0.1 cc H_2O 0.1 cc "Hyalase"
4	0.3 cc synovial fluid 0.1 cc H_2O 0.1 cc lactic acid
5	0.3 cc synovial fluid 0.2 cc 1% lactic acid
6	0.3 cc synovial fluid 0.1 cc "Hyalase" and later 0.1 cc 1% lactic acid
7	0.3 cc synovial fluid 0.2 cc 0.2% lactic acid
8	0.3 cc synovial fluid 0.2 cc ammonium sulphate.

These were again centrifuged and the supernatant fluids used for the electrophoretic estimations.

The results are reproduced in figs. 1 and 2.

The staining of the paper with synovial fluid only resembled that seen when doing plasma protein estimations. The hyaluronidase (tube 3) did not alter the picture obtained. The supernatant fluid from tubes 4 and 5 i.e. those which had been precipitated by lactic acid showed a decrease in the albumin and globulin bands, this being more marked in tube 5. The more dilute lactic acid (tube 7) did not reflect any marked change. Tube 8, however, containing the supernatant fluid after the precipitation by ammonium sulphate reflected a decrease in the globulin fraction. The addition of 0.2 cc ammonium sulphate to 0.3 cc synovial fluid reduces the saturation to approximately half and this would account for the precipitation

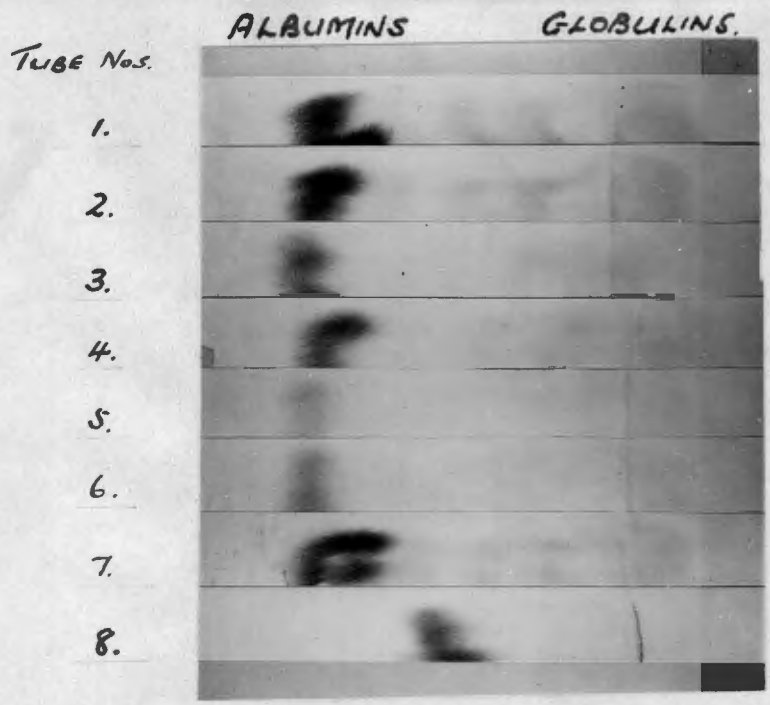


Figure 1: Electrophoretic protein estimations on Synovial Fluid of Case No. 16.

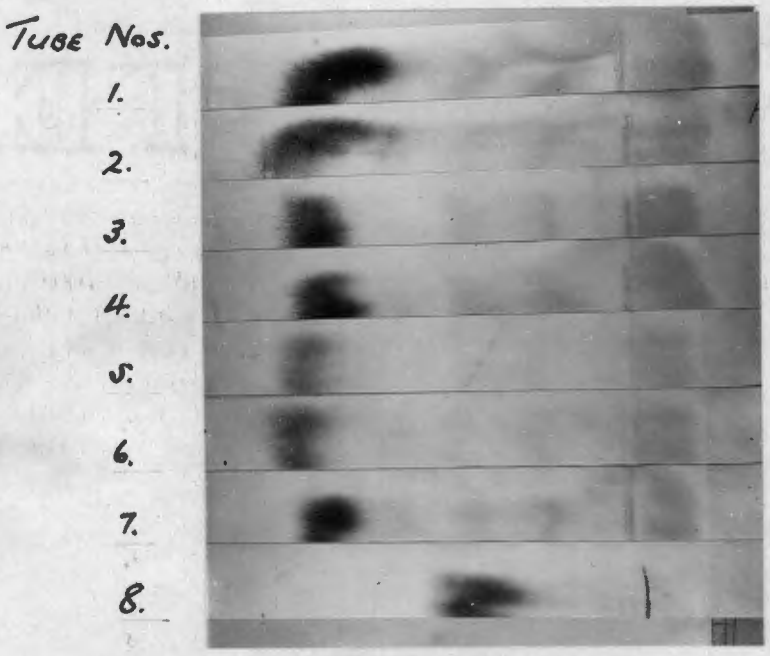


Figure 2.: Electrophoretic protein estimations on Synovial Fluid of Case No. 32.

of the globulins only.

Normal synovial fluid has a protein content of probably less than 2.5 Gm. %. The average albumin : globulin ratio is about 4 : 1 (Bauer et alia, 1940). In addition to albumin and globulin the synovial fluid contains "musin" or hyaluronic acid, the average concentration being 0.85 Gm.%. As stated earlier the hyaluronic acid fraction has been shown by electrophoretic methods to be the faster component because of its pronounced negative charge. In the electrophoretic estimations in these investigations, the hyaluronic acid did unfortunately not take the stain used.

The high protein content of the synovial fluid obtained from Case 32 suggests an inflammatory basis which would account for the raised erythrocyte sedimentation rate.

The viscosimetric studies indicated the precipitation of hyaluronic acid and the chemical analysis verified the precipitation of a portion of the albumen and globulin fraction as well. This would explain the less gelatinous nature of the precipitate if lactic acid was added after the "Hyalase" had already been allowed to depolymerize the hyaluronic acid. Ammonium sulphate, on the other hand, precipitates the globulin fraction but does not materially alter the hyaluronate content.

7. pH Values

Finally pH estimations were done on various specimens of synovial fluid. The estimations were done using "oxyphen" papers. The results are recorded in Table No. XVI.

TABLE NO. XVI : pH VALUES

Contents of Test Tube	Synovial Fluid Nos. 1	2	3	4	5	6	7	8	10	11	12	16
0.3 cc syn.fl.		7.0									7.5	8.0
0.3 cc syn fl. 0.2 cc H_2O	7.5	7.0	7.5	7.5	7.5	7.0	7.0	7.0	7.5	7.5	7.5	
0.3 cc syn.fl. 0.1 cc H_2O 0.1 cc Hyalase	7.5	7.0	7.5	7.5	7.5	7.0	7.0	7.0	7.5	7.5	7.5	
0.3 cc syn.fl. 0.1 cc H_2O 0.1 cc heparin	7.5	7.0	7.5	7.5	7.5	7.0	7.0	7.0	7.5	7.5	7.5	
0.3 cc syn.fl. 0.1 cc H_2O 0.1 cc ammon. sulph						7.0	7.0	6.5*	7.5	7.5		
0.3 cc syn.fl. 0.1 cc "Hyalase" 0.1 cc 0.2% lactic acid	7.5	7.0	6.5	6.5	6.5	7.0	7.0	6.5	7.0	6.5	7.0	
0.3 cc syn.fl. 0.1 cc "Hyalase" 0.1 cc 1% lactic acid	6.5	6.0	4.0	4.0		4.0	4.0	4.0			6.0	

* using boiled ammonium sulphate

The lowest figure obtained was 7.0 and the highest 8.0. The pH of 8.0 was obtained from a knee opened for menisectomy and the presence of osteochondritis dissecans was noted. The highest reading in an osteo-arthritis joint was 7.5

In five cases the pH of the synovial fluids was determined before and after lactic acid therapy. These results are given in Table XVII.

TABLE NO. XVII : pH VALUES BEFORE AND AFTER LACTIC ACID THERAPY.

Case No.	No. of Lactic Acid Injections	pH Before	pH After
4	2 x 10 cc	7.5	7.5
16	3 x 10 cc	7.0	7.0
38	4 x 10 cc	7.0	7.0
43	2 x 10 cc	7.0	7.0
44	4 x 10 cc	7.5	7.5

The pH of normal synovial fluid obtained post mortem is given as 7.4 by Bauer et alia (1940). Stach et alia (1948) report it to be slightly alkaline in vivo.

As stated earlier Waugh reported the finding of an alkaline pH in specimens of synovial fluid obtained from rheumatoid and even osteo-arthritic joints. In 1946, he, however, made the following statement while discussing lactic acid therapy in active atrophic or rheumatoid arthritis: "My admittedly inadequate observation of the joint pH in this phase tends to show that it is certainly not alkaline".

In the present examinations of the pH of the synovial fluid was a reading of 8.0 only once obtained. The other readings were all either 7.0 or 7.5. The highest reading in an osteo-arthritic joint was 7.5. In the fluids examined before and after lactic acid injections there was no change in the pH in this series.

B. DISCUSSION

Helfet, (1950) in a personal communication, mentioned that he had had occasion to do an arthrotomy on a joint which had previously received lactic acid injections. He noted a fleshy film covering the articular surfaces which he had not noted beforehand.

It seemed possible, therefore, that this film was actually a deposition of protein precipitate on the articular surfaces. These investigations show that lactic acid precipitates a portion of the proteins in the synovial fluid depending on its concentration. Lactic acid, however, also precipitates the hyaluronate in the synovial fluid and in so doing reduces its viscosity. It is most unlikely that the 0.2% lactic acid solution which is used therapeutically would precipitate any protein in a joint with effusion. In joints which are practically "dry" it may precipitate a small quantity. This would hardly be sufficient to cover large articular surfaces and it would in all probability be rubbed off very easily.

The fact that the viscosity is reduced is a distinct disadvantage as regards the lubrication mechanism in the joint.

Ideally, one requires a small quantity of a very viscid fluid to maintain effective lubrication. According to Gardner (1950) a decrease in synovial fluid viscosity would decrease its resistance to shearing strains. It is true that the dilute solution of lactic acid namely 0.2% would not markedly reduce the viscosity because of its action on the hyaluronate, but the diluting effect produced by the introduction of ten cc or more into a knee joint for example, would assist in decreasing the viscosity still further.

It was decided to determine what effect protein precipitators with a neutral pH would have. Ammonium sulphate was selected and the saturated solution was used, because after dilution with the fluid the resultant solution would be approximately half saturated. Ammonium sulphate does precipitate a portion of the proteins and like lactic acid the globulin fraction chiefly. It, however, being nearly neutral, does not affect the hyaluronate concentration in the fluid. Ammonium sulphate for this reason should be preferable to lactic acid if the therapeutic action is merely via the precipitation of the proteins.

If on the other hand the therapeutic mechanism is brought about by the lowering of the pH then lactic acid

should be superior. Once again if an effusion is present in the joint the 0.2% lactic acid would have little effect on the alteration of the pH. If the joint were practically "dry" the effect would be more marked but very temporary. The lactic acid would be absorbed very readily. These investigations reveal no change in pH after lactic acid therapy. Admittedly only five fluids were examined but the difficulty in obtaining fluid from an osteo-arthritic joint prevented a larger series being done. The estimations of the pH were done one week after the previous injection in each case.

Ramamurthi (1947) in a paper on the usefulness of intra-articular lactic acid states, that in a few cases with a little effusion, the pH of the fluid was tested before the injection of lactic acid, 48 hours after the injection, and again three weeks later. The pH changed from 8.0 before the injection to 7.2 after 48 hours and at three weeks it was 7.8 or 8.0 again.

These observations all help to show that if there is any pH change it is a very temporary one. Waugh has on no occasion reported experimental proof of his statement, that the pH in osteo-arthritic joints is invariably alkaline, and in this series the pH was neutral in most cases.

As far as heparin is concerned, Sacks (1949) suggested that it be used intra-articularly because of its anti-hyaluronidase action. The present investigations show that no heparin is present in synovial fluid and that the heparin sodium used therapeutically would have no anti-hyaluronidase effect whatever.

It is difficult to accept Waugh's contention that lactic acid exerts its therapeutic influence because it lowers the pH of the joint fluid. Possibly the fact that it precipitates a portion of the protein content may account for the improvement noted. If this were the case then one would expect to find either macro- or microscopic evidence of such effect after intra-articular therapy. Because of the difficulty in determining whether any changes occurred in the human joint, it was decided to investigate the possible effects of intra-articular injections in the experimental animal.

C H A P T E R I V

INVESTIGATIONS ON EXPERIMENTAL ANIMALS

A. A Review of the Literature on Experimental Degenerative Arthritis

B. The Physiology of Joints

C. Experimental Investigations

D. Discussion of these Results.

It was decided to investigate the effect of intra-articular injections in the experimental animal. In addition it was decided to induce arthritic changes, if possible, and then to "treat" the experimental arthritis with the intra-articular injections in clinical use and note their macroscopic and histological effects.

A. A REVIEW OF THE LITERATURE ON EXPERIMENTAL DEGENERATIVE ARTHRITIS

A brief review of the literature on experimental degenerative arthritis follows:

Wollenberg (1909) produced degenerative and hypertrophic changes in the patella in dogs by passing silk ligatures through the tissues around the bone and thus shutting off its blood supply. This crude experiment was designed to amplify his theory that degenerative arthritis was the result of vascular deficiency. Axhausen (1911 and 1912) applied tincture of iodine or ammonium hydroxide to the knee joints of a series of animals. The strong chemicals caused local necrosis of the cartilage and when the joints were examined several months later they were found to resemble those of chronic arthritis. Axhausen believed arthritis deformans to be due to the aseptic necrosis of cartilage.

Axhausen and Pels (1911) repeated Wollemberg's experiments and obtained almost identical results. They, however, ascribed the changes to the presence of the necrosed cartilage and not to the ischaemia.

Fisher (1922) removed a small portion of articular cartilage from the femoral surface of rabbits' knee joints. He reported marginal proliferation of bone around the cartilaginous margins. This he considered to be a compensatory mechanism.

Burckhardt (1924) repeated Axhausen's earlier experiments in a series of guinea pigs by opening the joint and placing a drop of carbolic acid or iodine in the joint. In some of the animals he immobilised the joint. In others he allowed the animals to use the joint normally. In the used joints the pathological changes characteristic of arthritis deformans developed in from three to five months, while in the joints he immobilised, the cartilage remained intact for a long time and this was gradually replaced by connective tissue and imperfect cartilage with possible subsequent ankylosis. Villi developed in the used joints and pannus in the immobilised joints. Burckhardt concluded that degenerative arthritis followed on injury to cartilage, with subsequent stimulation by use of the joint.

Key (1931) created defects in the articular cartilage of rabbits' joints under aseptic conditions. He maintained that many of the changes of hypertrophic arthritis followed. Consequently he concluded that actual death of cartilage as suggested by Axhausen was not the responsible factor in the production of degenerative arthritis. He produced illustrations of these defects being repaired by a primitive type of connective tissue, which he calls early callus. A joint examined 60 days after the defect had been produced, showed the defect being filled by atypical hyaline cartilage. Repair was however very imperfect. Key found the bone marrow fibrosed in three animals with some eburnation of the bone at the floor of the defect. He stresses the marginal proliferation and new bone formation on either side of the femoral condyles in these cases.

Bennett et alia (1932) working on the knee joint of adult dogs repeated Key's experiments by creating defects of the articular surfaces. They found that if the defect was superficial and entirely within cartilage, some form of repair occurred. The superficial defects on the weight bearing surfaces of the femoral condyles showed more reparative powers than the superficial defects on the non-weight-bearing surfaces. The repair in these superficial defects was by imperfectly formed

hyaline cartilage, presumably, by independent proliferation of cartilage cells. In the defects which extended into subchondral bone, repair was by way of fibrous tissue and fibrocartilage to the formation of an imperfect form of hyaline cartilage. The fibrous tissue originated in the connective tissue of the bone marrow and in these instances the bone marrow was filled with red blood corpuscles, and there was much osteoblastic activity on the part of the subchondral bone. They did not find the marginal proliferation described by Key, except in cases where the patella had remained displaced after the operation to produce the defect.

Bennett and Bauer (1935) repeated these experiments using young instead of adult dogs. They found no accelerated healing of the defects in the younger animals. They concluded that defects extending into subchondral bone are most rapidly filled by fibrous tissue from the subchondral bone. This is gradually replaced by fibrocartilage and eventually by a form of hyaline cartilage.

Key (1934) in an article on contusion of cartilage as an etiological factor in chronic arthritis, suggests removing the contused portion, and is prepared to accept that the marginal proliferations he noted previously could not have been

due only to the defects created in the articular surface.

Key (1933) produced arthritic changes in the knee joints of rabbits by injecting N/50 HCl, N/50 NaOH, distilled water, 0.85% NaCl and 10% NaCl into respective joints. He injected 1 to 2 cc on each occasion, gave the injections three times a week, and gave from 8 to 28 injections. His illustrations of photomicrographs of the joints, which received saline and water respectively, are not very convincing, but he maintains that death of the deeper cartilage cells occurred. In the joints which received the HCl superficial erosions are illustrated. It is difficult to see the reason for the differential selection exhibited by these fluids.

Habler (1929) is quoted by Key (1933) as having also produced arthritic changes following the injection of distilled water, and Habler contends that the cartilage damage was caused by a change in the osmotic pressure of the synovial fluid.

Before describing the experimental investigations a short account of the physiology of joints will be given.

B. THE PHYSIOLOGY OF JOINTS

The composition of synovial fluid has already been outlined. A brief resume of the anatomical physiology of the the articular cartilage and the synovial membrane follows.

The Articular Cartilage

With few exceptions the articular surfaces are covered by hyaline cartilage. Macroscopically this is of bluish-white, ground glass appearance. Its structural components are the typical cartilage cells found in lacunae, and intercellular system of fibrils and the undifferentiated hyaline matrix. The preponderance of matrix over cells is striking. A major portion of this matrix appears to be a protein salt of chondroitin sulphuric acid, which, according to Gardner (1950) is present in cartilage as a gel and contains about 70% water. The origin of chondroitin sulphuric acid is uncertain. Its manufacture may of course be a particular function peculiar to the chondrocytes. The cells in the articular cartilage, in the superficial layers are flat and lie parallel to the joint surface. In the deeper layers the cells are round and large and are arranged in rows perpendicular to the articular surface. Beneath the deepest layer one encounters calcification of the matrix.

Articular cartilage is not supplied by nerves or blood vessels. It is presumably nourished by the synovial fluid. Loose cartilagineus bodies have been observed to grow in the joint cavity, apparently deriving nourishment from the synovial fluid.

According to Harris (1933) growth occurs in the zone bordering on the deeper lying calcifying cartilage, a zone which in young bones is continuous with that of the proliferating cartilage in the epiphysial plate. Although different views have been expressed about the degree of possible regeneration of articular cartilage Bennett et alia (1932) consider it to have very little power of intrinsic repair. This question will be discussed again when the experimental findings in these investigations are given.

The Synovial Membrane

The inner surface of the articular capsule is not formed by a distinct membrane but by a connective tissue modified as the synovial surface is reached. Although the surface is relatively smooth a variable number of folds and villi project from it.

An intimal layer is described which is in parts distinguishable from the outer fibrous layer. The intimal layer may extend for a short distance on to the marginal

cartilage as it does regularly in the embryonic state, while the fibrous layer blends with the periosteum or perichondrium. The fibrous layer is rich in collagen while a few elastic fibres are present too.

The presence of bloodvessels in the articular capsule were first demonstrated by Hunter in 1743. In this year he described the "circulus articuli vasculosus". The vessels extend through the fibrous layer close to the synovial surface.

Synovial cells can be replaced from other connective tissue cells. It is therefore unlikely that the synovial epithelial cells are specialised cells. Key (1925) showed that in the rabbit the knee joint is approximately normal 60 days after hemi-synovectomy. Regeneration occurred by metaplasia of underlying connective tissue, with little or no tendency for surface growth from the edges.

Bauer et alia (1940) are of the opinion that no glandular cells exist in the synovial membrane, and that synovial fluid is an ultra-filtrate of plasma to which albumin, globulin and "mucin" have been added. The presence of albumin and globulin can be ascribed to increased capillary permeability, whereas "mucin" originates as the mucinous component of the connective tissue lining the joint.

C. EXPERIMENTAL INVESTIGATIONS

Of recent years much attention has been focussed on the intracellular matrix or "ground substance" of the articular cartilage. Sacks in 1949 suggested that altered biochemical processes in the matrix of the cartilage might be responsible for degeneration of the articular cartilage. He suggested a most attractive theory: that following mild infection of joints by organisms capable of producing hyaluronidase, this enzyme "hydrolysed" the hyaluronic acid in the synovial fluid and in the cartilage matrix. This then caused a change in the pH towards alkalinity with resultant depolymerization of the chondroitin sulphate in the matrix. The loss of chondroiton sulphate would dispose to calcification of the cartilage especially in the presence of alkaline phosphatase which would become active in the alkaline pH.

It was consequently decided to see what effect hyaluronidase would have if injected into the joints of animals. At the same time it was decided to determine, if possible the effect of lactic acid, normal saline, an alkaline buffer and ammonium sulphate on the joints of experimental animals.

The first animals used were rats.

Six adult male rats were used and the following substances were injected into their respective knee joints at bi-weekly intervals.

Animal No. 1

0.1 cc "Hyalase" into right knee
0.1 cc normal saline into left knee

Animal No. 2

0.1 cc alkaline buffer* (pH 9.0) into right knee
0.1 cc saline into left knee

Animals No. 3 and 4

0.1 cc 0.2% lactic acid into right knee
0.1 cc saline into left knee

Animal No. 5

0.1 cc saturated ammonium sulphate into right knee
0.1 cc saline into left knee

Animal No. 6

No injections.

*The alkaline buffer was made up as follows:

50 cc of 0.2 M Boric Acid in 0.2 M potassium Chloride then 21.3 cc of 0.2N sodium hydroxide was added.

The solution was then made up to 200 cc.

X-ray photographs were taken of the knee joints before the injections were started and at regular intervals thereafter. During the course of the injections the animals were exercised in a revolving drum, but this later appeared unnecessary as they were certainly not loth to use their limbs.

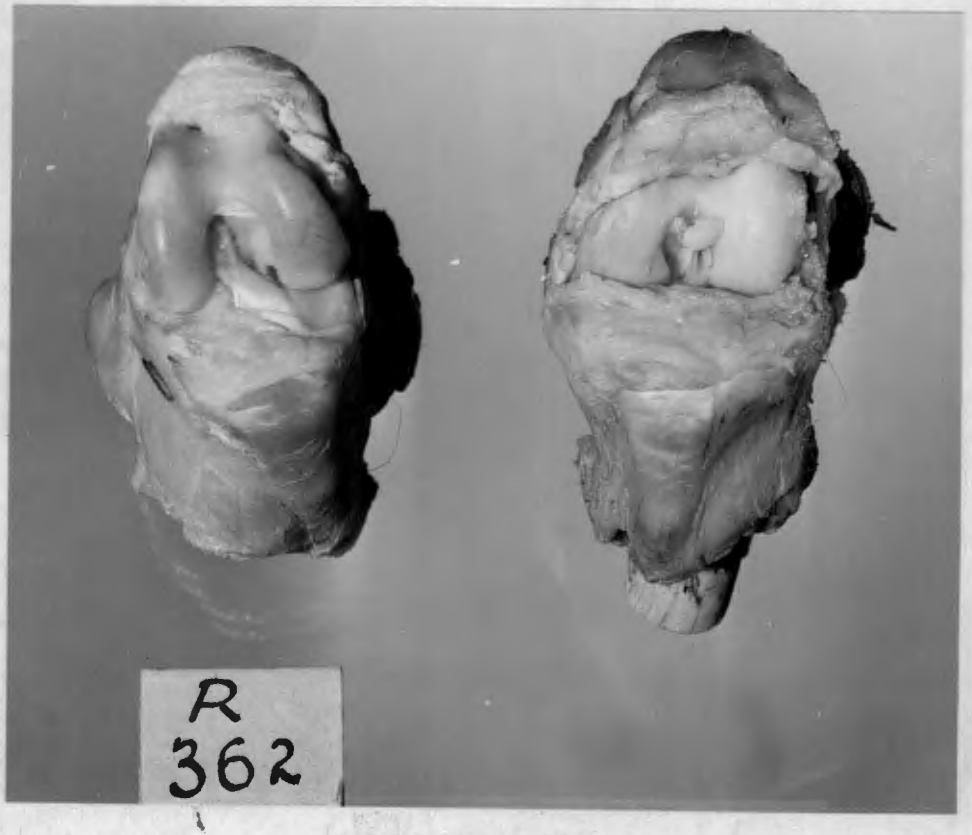
At no stage was there any evidence of radiological changes. A total of 19 injections were given into each knee joint. The first three animals were sacrificed four weeks after the cessation of injections, whereas the last three were killed one week after stopping the injections. No macroscopic nor microscopic changes were noted in any of the joints. The joints were, however, very small and it was decided to repeat similar experiments on larger animals.

<u>The monkey was chosen as a more suitable experimental animal</u>.

The animals were given numbers which will be adhered to in the account of the work, as their numbers appear on the photographs of the joints.

The nature of the injections each animal received will be stated with the relevant photographs.

The injections were given at Bi-weekly intervals.

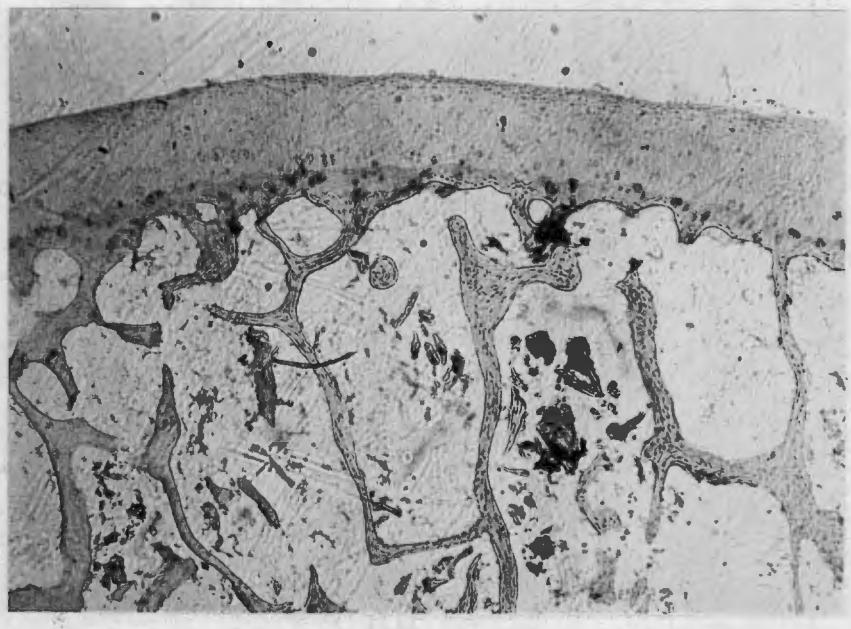


Animal No. 362

One ampoule of "Hyalase" dissolved in 2 cc of water was injected into the right knee of this animal. The left knee received 2 cc of normal saline. Twelve injections were given and the animal sacrificed seven weeks after the last injection.

Macroscopically The right knee appeared quite normal.

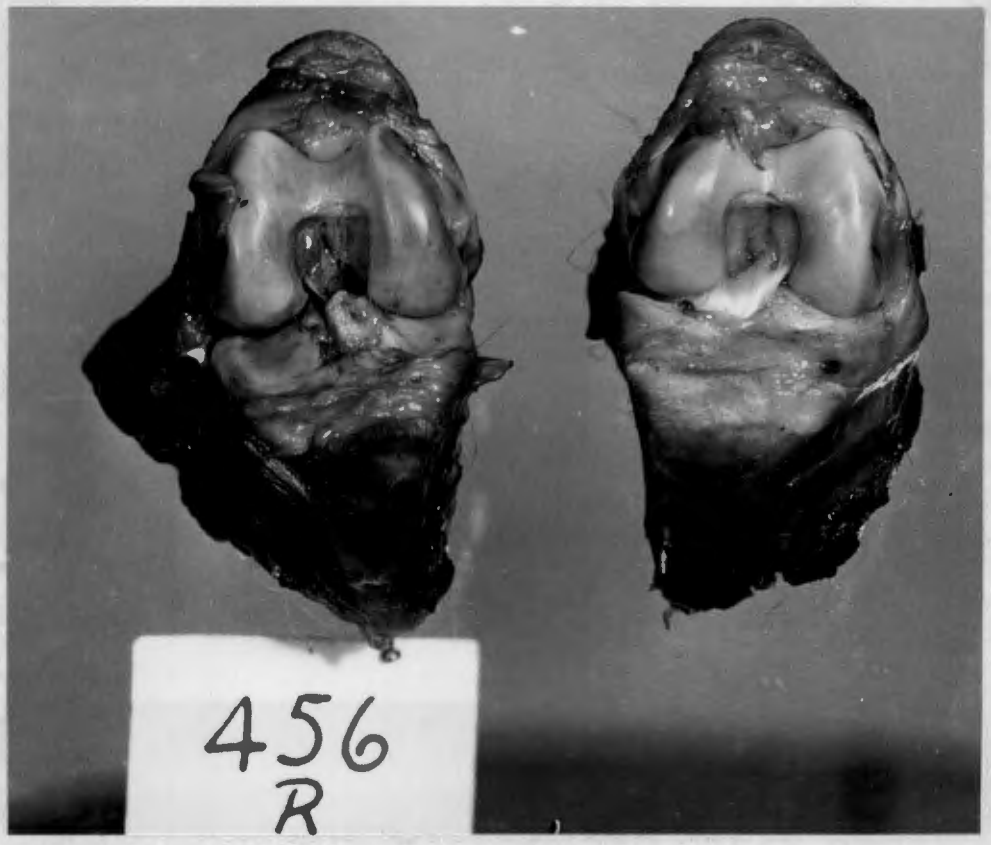
The left knee, however, surprisingly showed minute erosions on the margins of the articular surfaces.



Photomicrograph of histological section of left knee joint of Animal No. 362

This section appears normal although there may be an increase in the number of horizontal cells in the superficial layers.

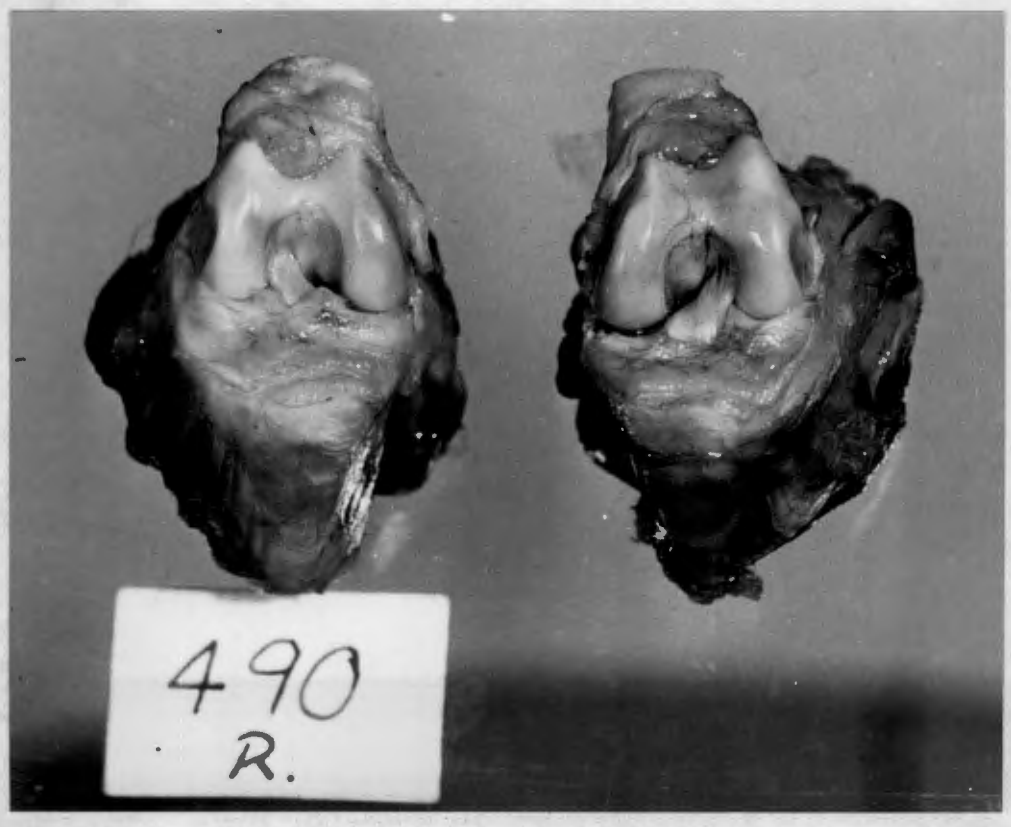
The finding of these small erosions in the knee receiving saline injections made it imperative to do more controls with saline.



Animal No. 456

This animal was given injections of half an ampoule of "Hyalase" in one cc of water as well as 25 mg. cortisone into the right knee and two cc saline into the left knee. Twelve injections were given into each knee.

Both joints were perfectly normal macroscopically and so were not sectioned.

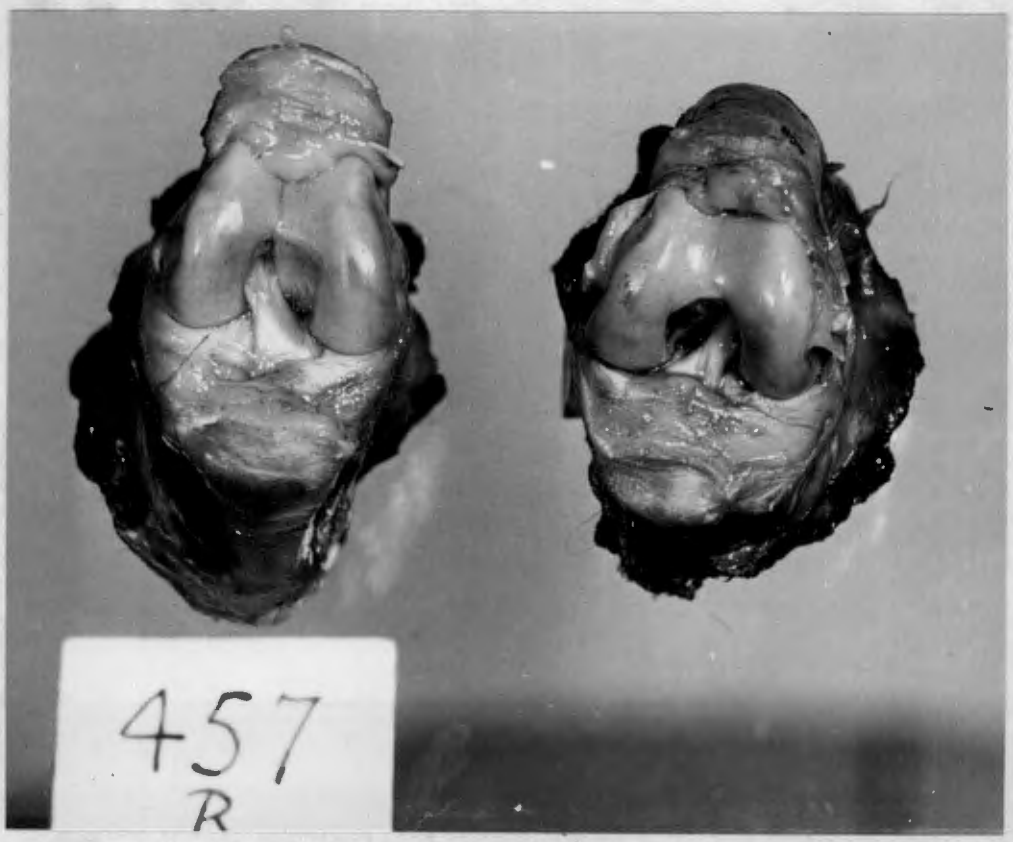


Animal No. 490

The right knee joint of this animal received twelve injections of one ampoule of "Hyalase" dissolved in two ccs water.

The left knee joint received twelve injections of two ccs normal saline.

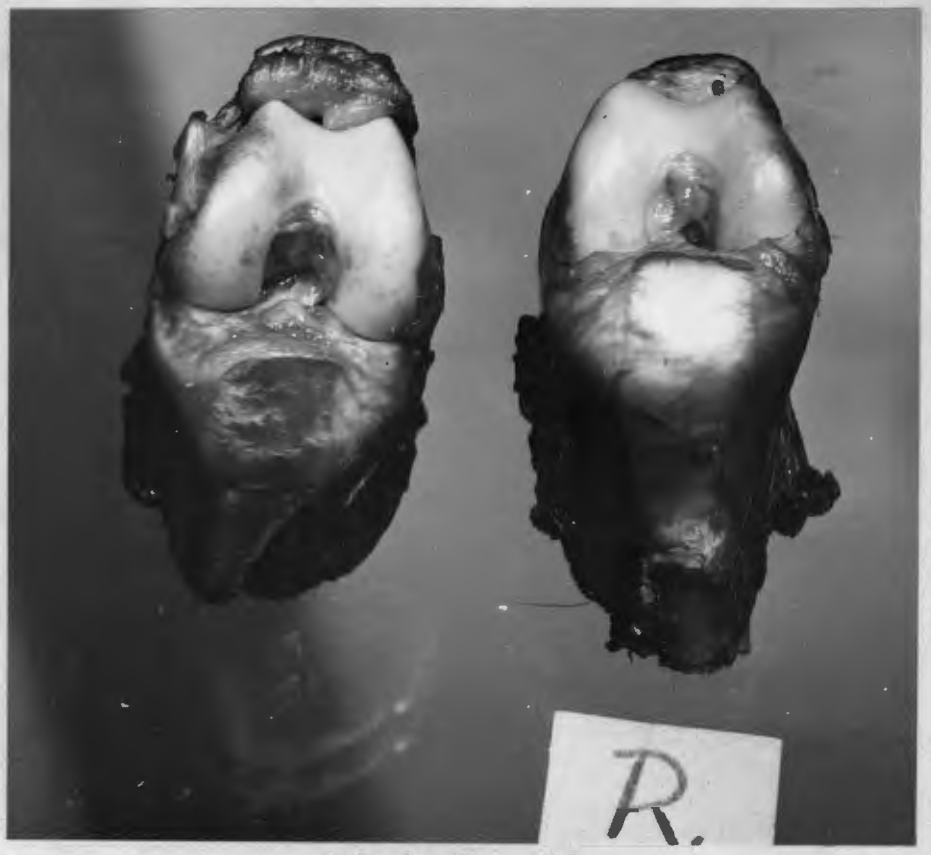
The animal was sacrificed two weeks after the last injection and no macro- nor microscopic change was evident.



Animal No. 457

In the case of the above animal the right knee did not receive any injections but a needle was inserted intra-articularly on twelve occasions. The left knee received twelve bi-weekly injections of 2 cc normal saline.

Both knees were normal after these procedures.

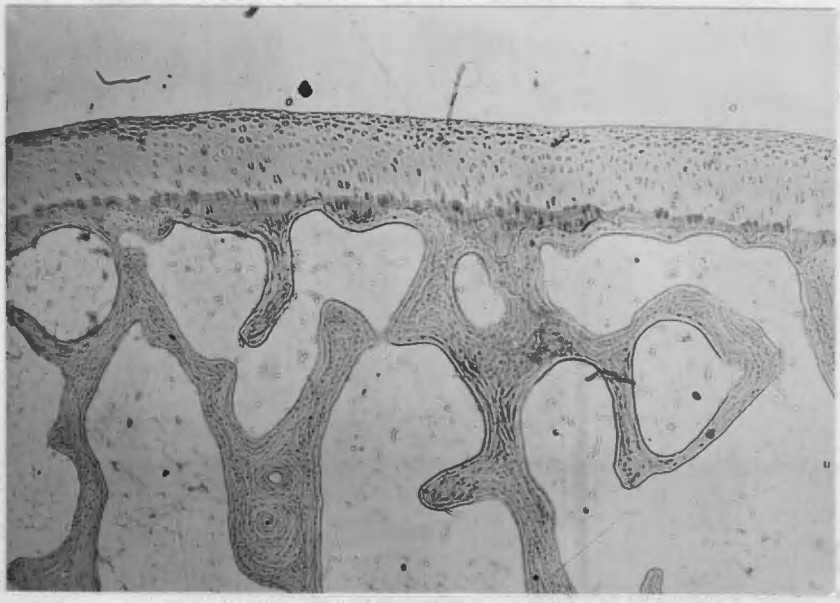


Animal No. 208

The right knee received injections of 2 cc 0.2% lactic acid in 0.5% procaine base.

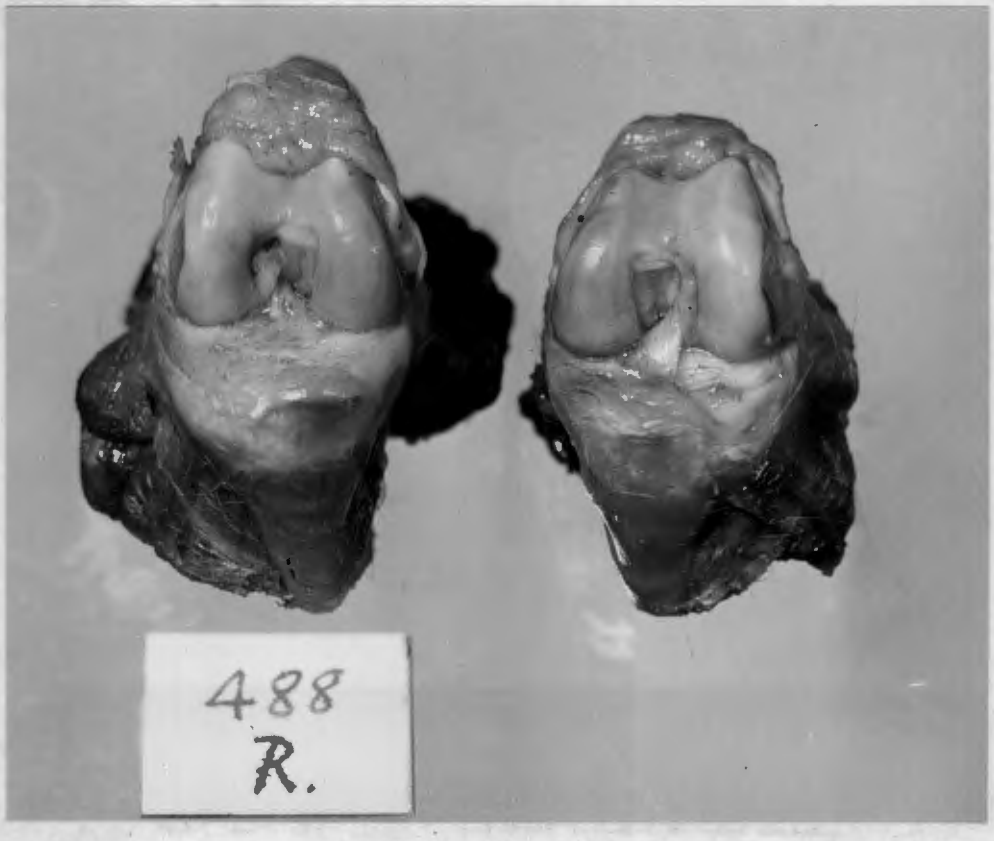
The left knee received injections of 2 cc normal saline. After eleven injections the animal succumbed as the result of an abscess of the abdominal wall, presumably following an injury in the cage.

On macroscopic examination the left knee joint appeared normal in all respects. The bluish white appearance of the articular cartilage had its normal pearly lustre. The cartilage appeared transparent and the underlying blood vessel shadows could be easily recognized. In the case of the right knee joint the articular surfaces had a creamy appearance and the normal lustre was not evident. No shadows cast by the underlying blood vessels could be seen. At the time it was felt that this change, if any, might be a change affected by the lactic acid on the cartilage matrix. In retrospect however one feels that this change is sometimes the earliest change to occur in degeneration of cartilage. Bennett et alia (1942) state this appearance indicates a firmer substance but at the same time a progressive loss of elasticity.



Photomicrograph of histological section of right knee of Animal No. 208

No abnormality was detected in the sections of either knee joint of this animal.

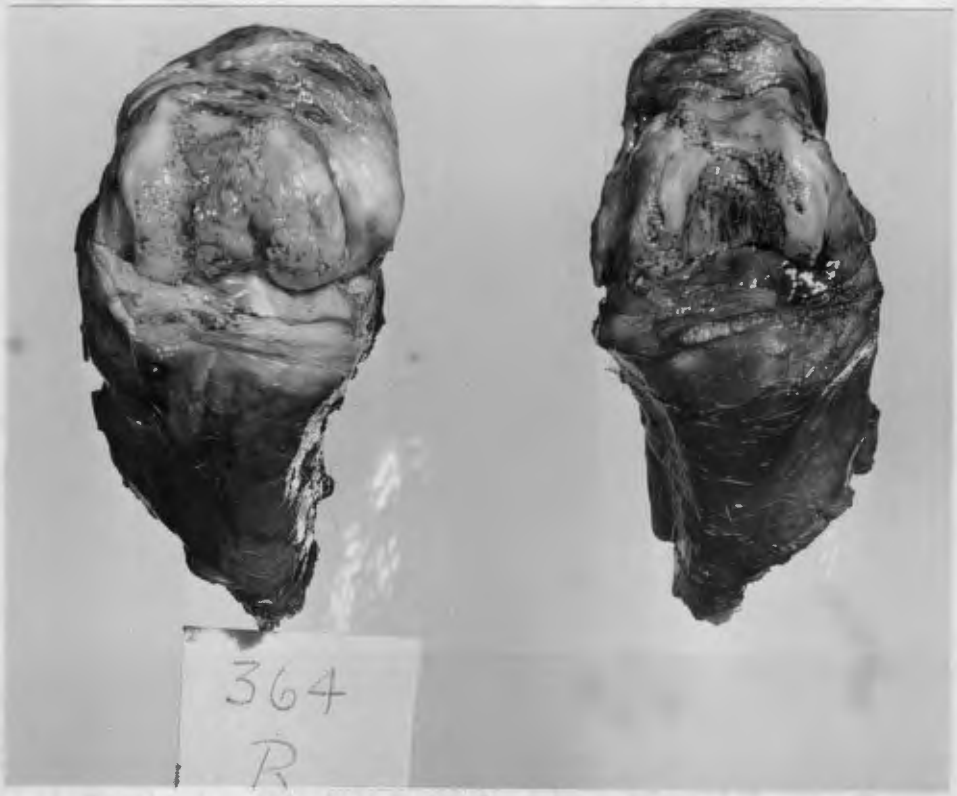


Animal No. 488

This animal also received injections of 2 cc lactic acid into the right knee joint and 2 cc normal saline into the left knee joint. In view of the findings in the previous animal this one was given 18 injections into each knee and was sacrificed 15 days after the last injection was given.

Macroscopically, both knee joints showed the normal bluish-white appearance. Both joints also displayed the pearly lustre, a feature of complete normality.

Microscopically, there was no departure from the normal.



Animal No. 364

The above animal received injection of 2 cc of 0.5% silver lactate into the right knee and 2 cc of 0.25% silver lactate into the left knee.

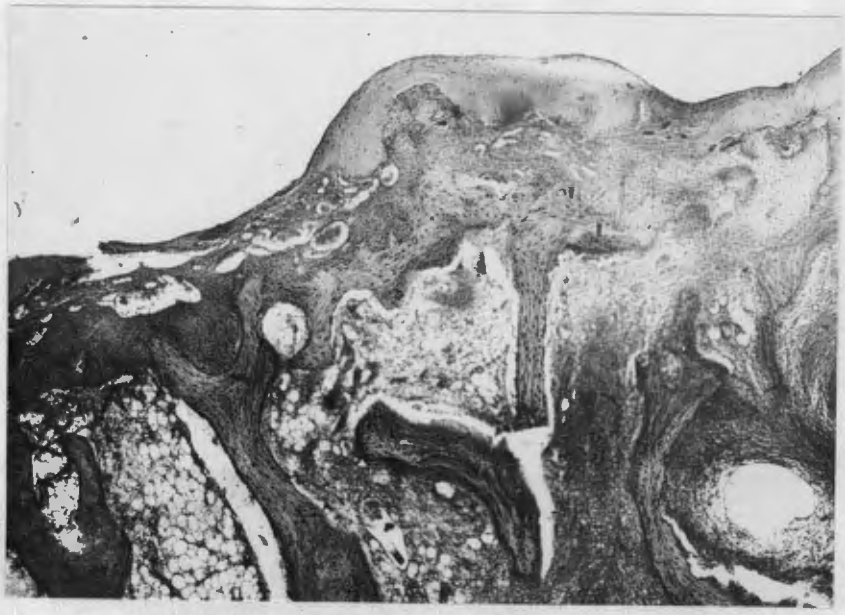
It was decided to introduce this mild irritant which at the same time was an excellent precipitator of protein. If the irritant effect did not harm the joint it was contemplated to use this substance therapeutically, because at that time the effect of protein precipitators on joints was being investigated. The animal was given 12 injections into each knee and was sacrificed 4 weeks after the last injection. The resultant picture was indeed alarming!

Macroscopically the articular surfaces of both joints were markedly eroded with much capsular thickening. There was no evidence of marginal proliferation.

Photomicrograph of histological section of right knee joint of Animal No. 364

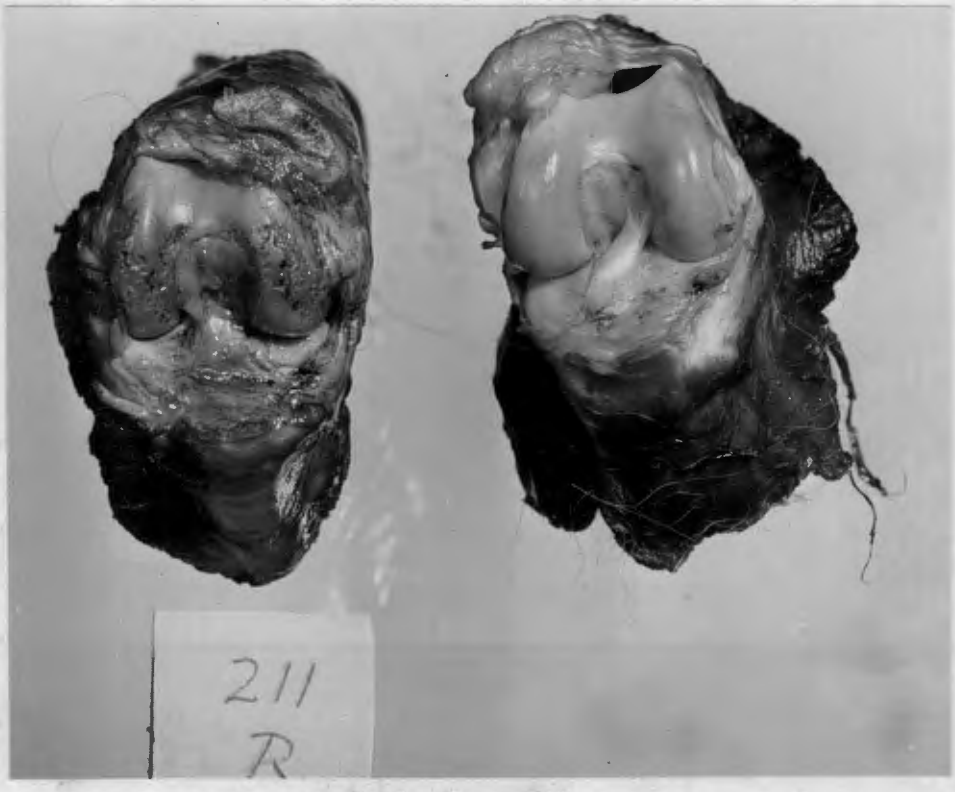
The histology showed considerable areas where the cartilage had undergone necrosis, especially in the superficial layers. In parts the deeper layers were still present. The subchondral bone was very reactive and there was an invasion by primitive fibroblasts, apparently originating from the subchondral bone, of the articular cartilage. Large areas of dead cartilage were present in the subchondral bone and osteoclasts were seen in many areas. In other areas calcification of the dead cartilage was occurring.

The section shown in the photomicrograph is an area where the cartilage has remained reasonably viable.



Photomicrograph of histological section of left knee joint of Animal No. 364

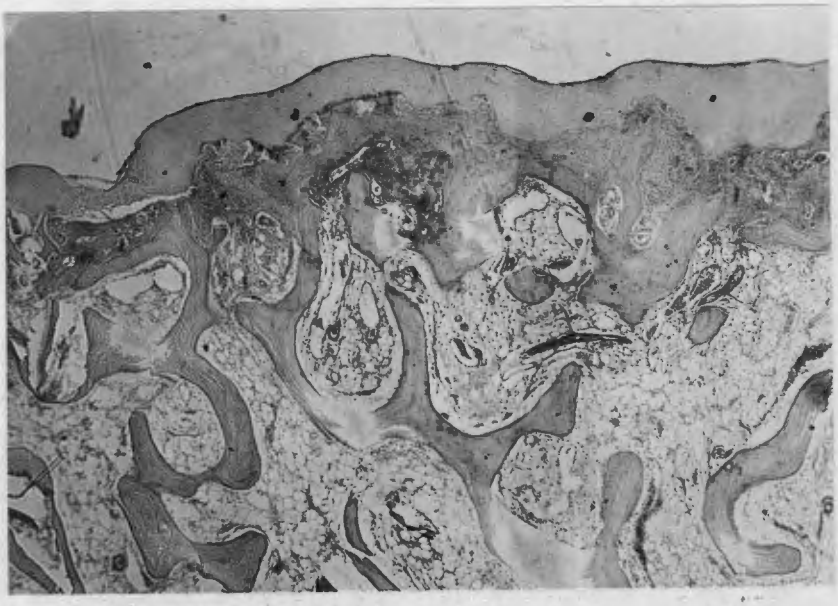
The section of the left knee is similar to that of the right. There is much eburnation on the part of the subchondral bone. The photomicrograph was taken of an area which shows a small strip of viable cartilage with complete absence of cartilage adjacent to it.



Animal No. 211

This animal received injections of ice 0.5% silver lactate as well as 25 mg. cortisone into the right knee and the left knee was not given any injections. It was decided to see whether the cortisone would minimise or counteract the irritant effect of the silver lactate. Twelve injections were given and the animal was killed four weeks after the last injection.

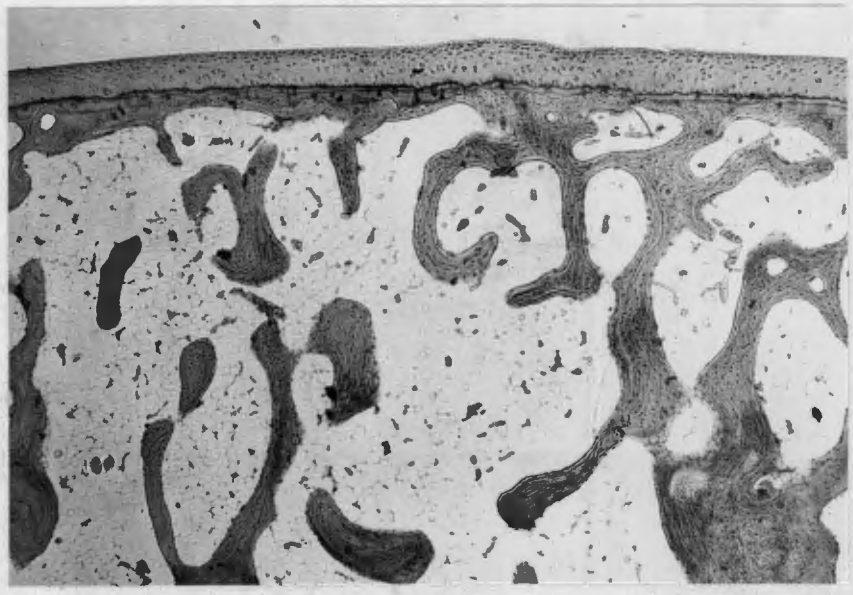
Macroscopically there was less erosion of the articular surfaces than in the previous animal's joints. The left knee was normal.



Photomicrograph of histological section of right knee joint of Animal No. 211

This shows even less death of cartilage than in the left knee of animal 364. Areas of cartilage show the deeper layers active whereas other areas are being invaded by osteoclasts. There are however also areas of immature fibroblastic activity with reactive subchondral bone.

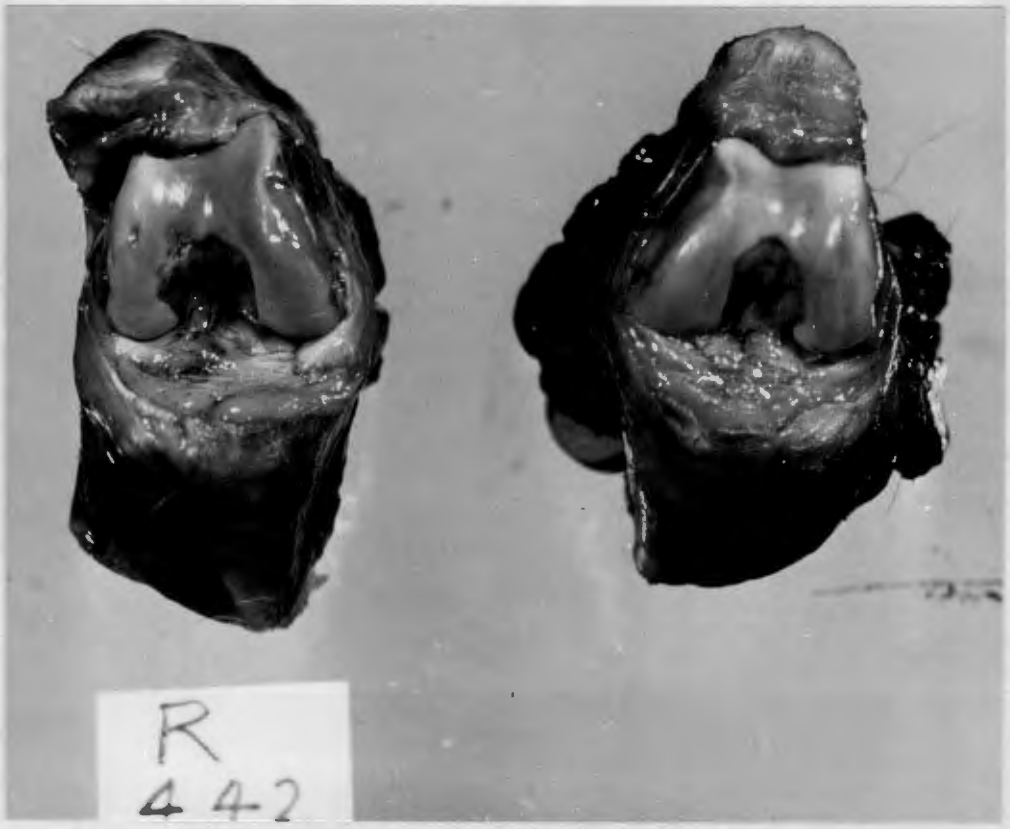
It does appear as if the cortisone slightly minimised the irritant effects of the silver lactate.



Photomicrograph of histological section of left knee joint of Animal No. 211

No abnormality was detected on this section.

In view of the findings in the animals that received silver lactate injections it was decided to continue the investigations on further animals. It was decided to attempt to produce less severe erosions than in the case of Animal No. 364 and then to "treat" these animals with different intra-articular injections.

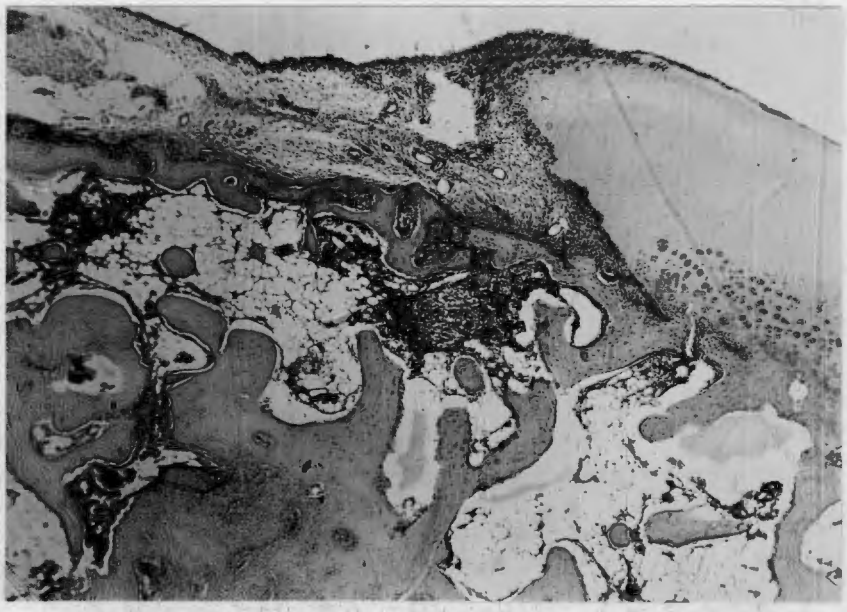


Animal No. 442

This animal first of all received four bi-weekly injections of 2 cc 0.25% silver lactate into each knee. After these injections effusions were present in each knee, so one could assume that some irritation had been produced. The animal was then rested and four weeks later "therapy" of the right knee was started.

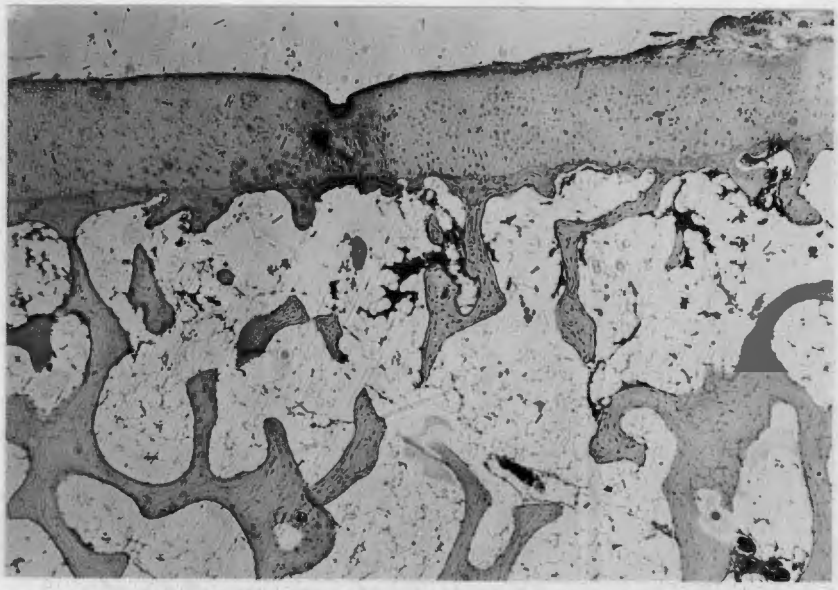
Eight bi-weekly injections of lactic acid were given into the right knee while the left knee was not given any further injections. Two weeks after the last injection of lactic acid the animal was killed.

Macroscopically there was evidence of small eroded areas which had apparently been covered by a "filmy" layer in the right knee. The left knee seemed less eroded than the right except for an area in the intercondyloid notch of the femur.



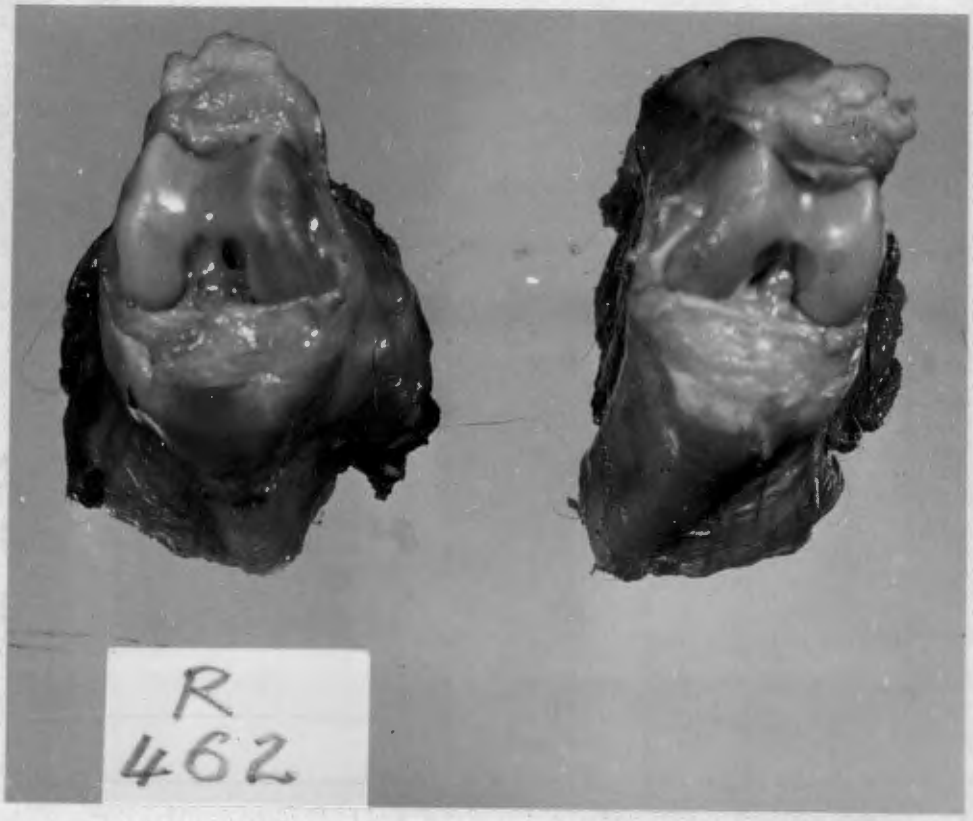
Photomicrograph of histological section of right knee joint of Animal No. 442

This section shows a large defect in the articular cartilage filled with primitive connective tissue. This is apparently the "filmy" layer seen macroscopically. There is marked reaction exhibited by the subchondral bone with osteoclastic invasion of areas of dead cartilage. In other areas the deeper layers of the articular cartilage show active chondrocytes.



Photomicrograph of histological section of left knee joint of Animal No. 442

The section of the left knee shows less departure from normality. A very small superficial defect of the cartilage is evident but there are areas where the superficial cells have been removed and have been replaced by primitive fibroblasts. The deeper layers of the cartilage again appear reactive. It is of course possible that the eroded area was missed by the section.



Animal No. 462.

Both knees were given 4 injections of silver lactate as in the case of Animal no. 442. The right knee was subsequently given eight injections of 25 mg. cortisone bi-weekly.

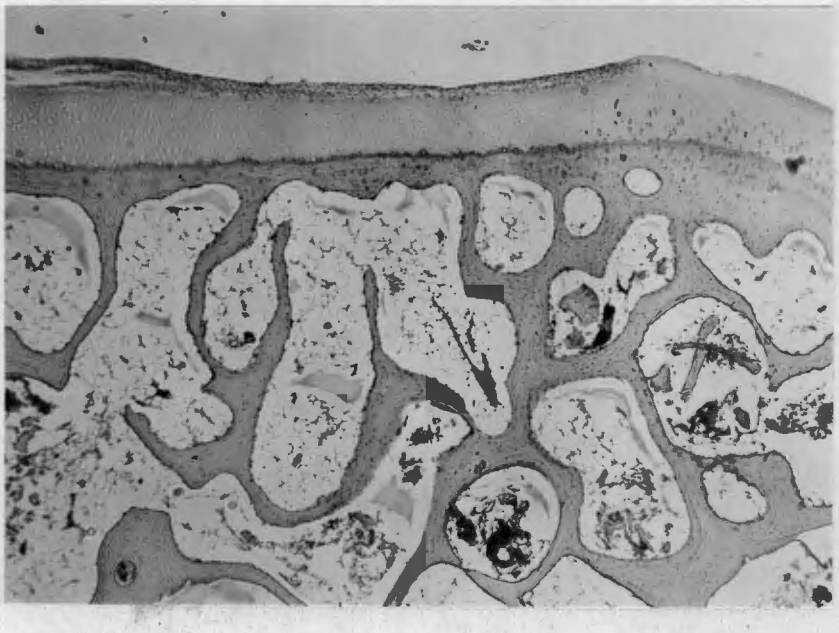
The left knee was not given further injections.

Macroscopically there was erosion of both articular surfaces.

Photomicrograph of histological section of right knee joint of Animal No. 462

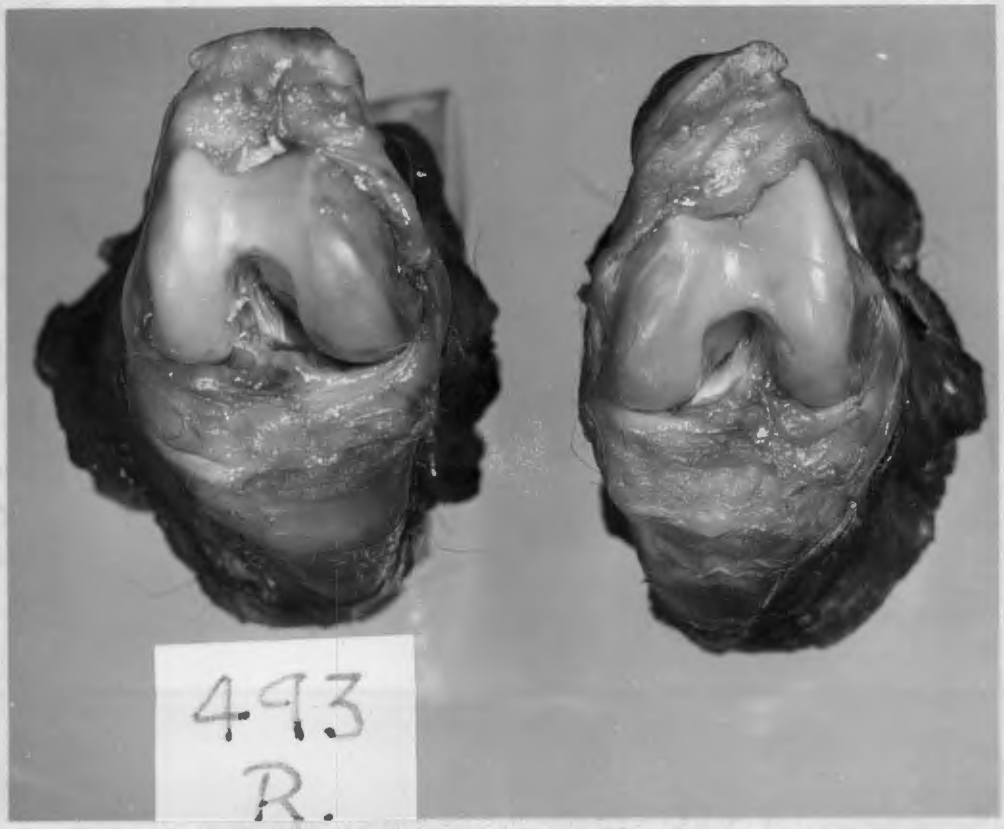
This section showed a large defect of the cartilage very poorly filled with fibroblastic connective tissue. The subchondral bone shows evidence of eburnation.

The defect however is sharply demarcated and would suggest that in the preparation of the section some of the fibrous tissue became detached.



Photomicrograph of histological section of left knee joint of Animal No. 462

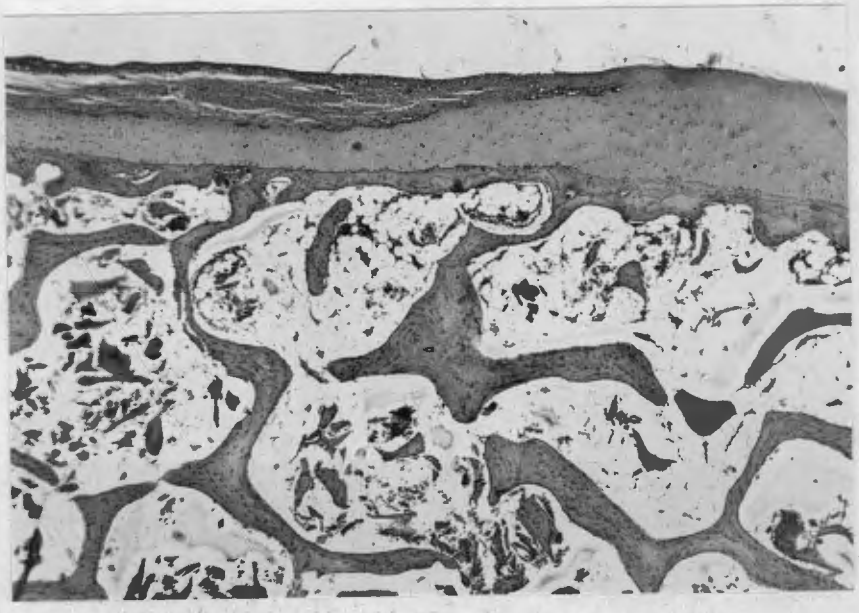
The section of the left knee joint shows superficial defects of the cartilage with some areas covered by fibroblasts. There is no defect extending to the subchondral bone in the section examined.



Animal No. 493

This animal also received silver lactate as in the case of No. 442 and the right knee was subsequently given eight bi-weekly injections of 12.5 mg. hydrocortisone. The left knee received no further injections after the silver lactate.

Macroscopically, both knees showed erosions but the erosion on the right femoral surface seemed shallower than that on the left femoral articular surface.



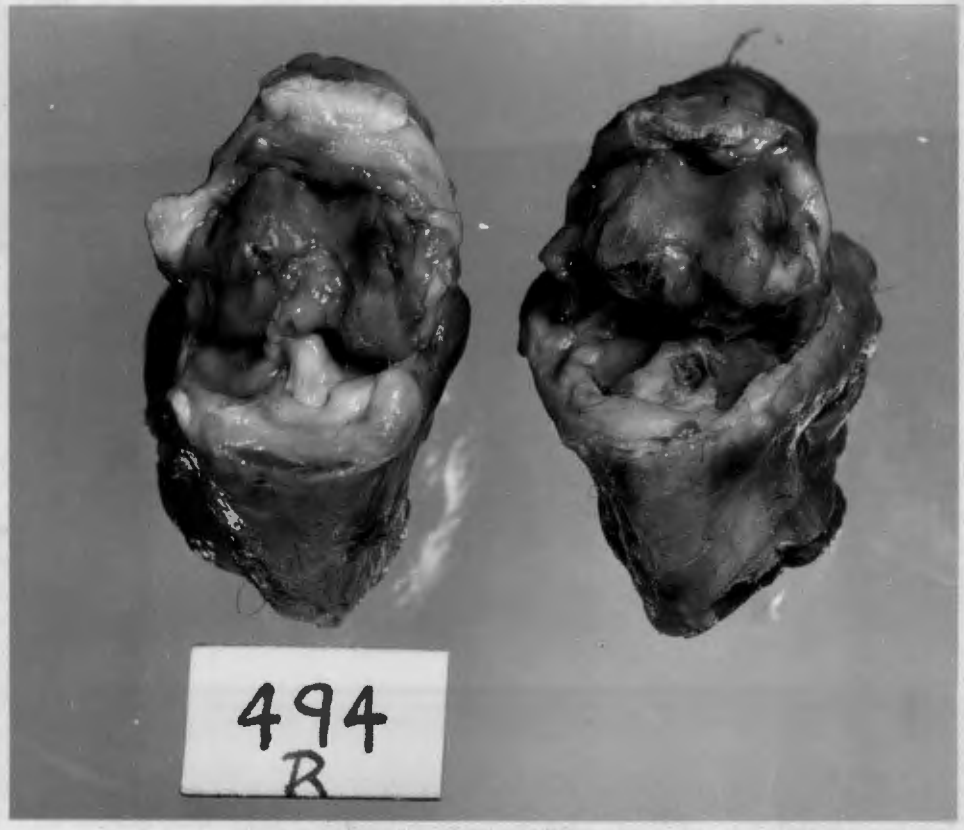
Photomicrograph of histological section of right knee joint of Animal No. 493

This section shows a defect in the cartilage which does not extend to the subchondral bone and it is well filled by primitive connective tissue. The chondrocytes appear to be in a proliferative state.

Photomicrograph of histological section of left knee joint of Animal No. 493

The section of the left knee joint shows the defect deeper than in the right, extending to subchondral bone. Again primitive fibroblasts are attempting to repair the defect. Also the chondrocytes appear to be in a similar state of proliferation.

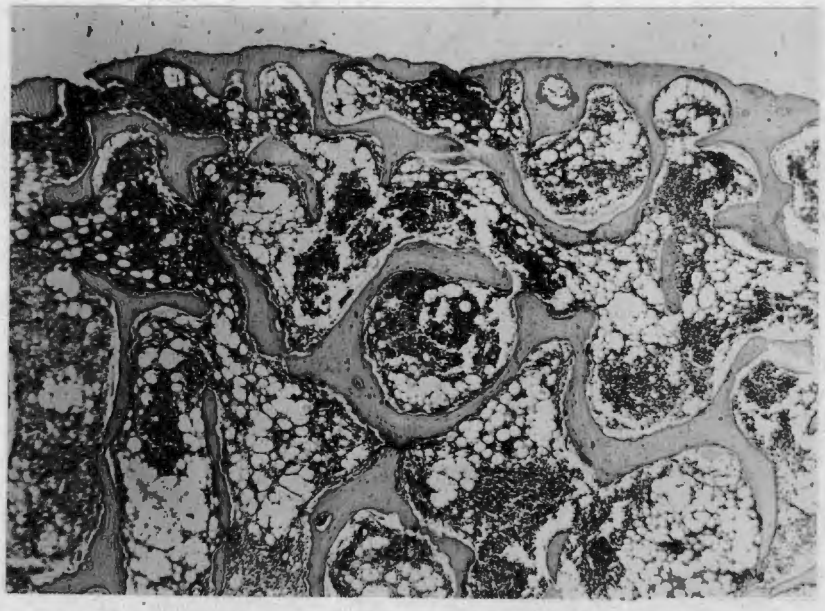
In the case of these sections care was taken to cut them from exactly corresponding portions of the femora.



Animal No. 494

This animal also first of all received silver lactate injections and was then given lactic acid into the right knee and hydrocortisone into the left.

Unfortunately despite the usual aseptic precautions the animal developed a suppurative arthritis in both knees; staphylococcus aureus was cultured. The accompanying figure illustrates the marked disorganisation and destruction of the joints.



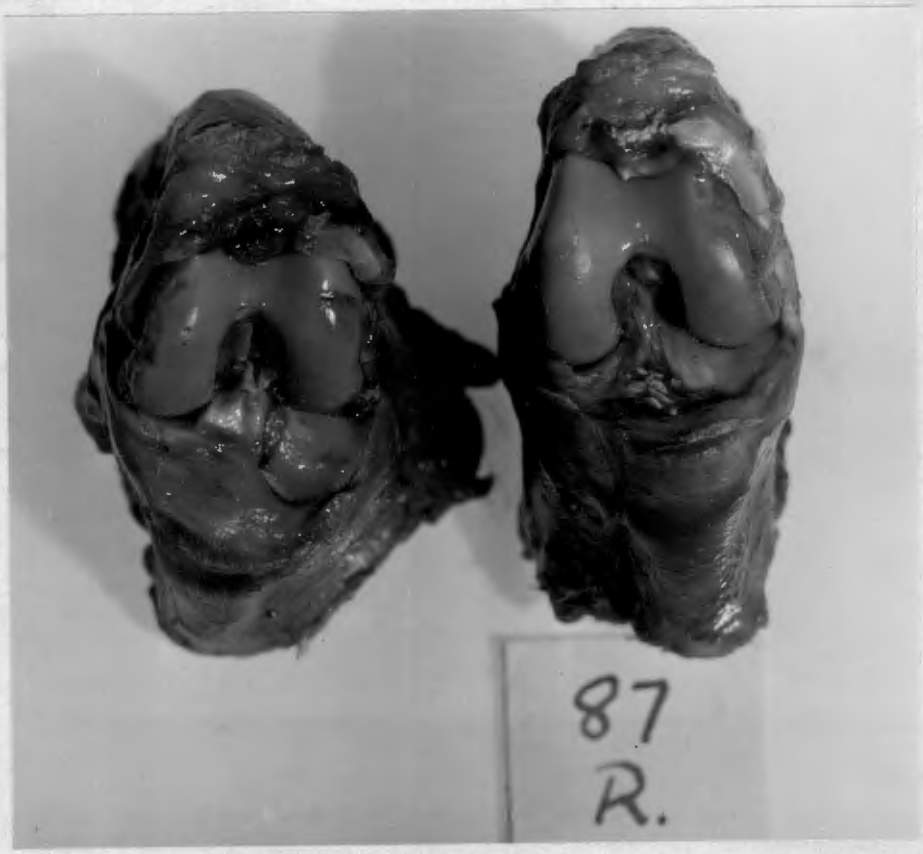
Photomicrograph of histological section of left knee joint of Animal No. 494

This section shows the complete destruction of the entire articular surface with much subchondral reaction.

Summary

The animals which at first received silver lactate and then lactic acid or hydrocortisone revealed interesting changes. In the case of the lactic acid (Animal No. 442) the knee which received lactic acid appeared worse than the opposite knee. In the case of the hydrocortisone (Animal No. 498) the knee which received hydrocortisone revealed less departure from the normal than the "untreated" knee.

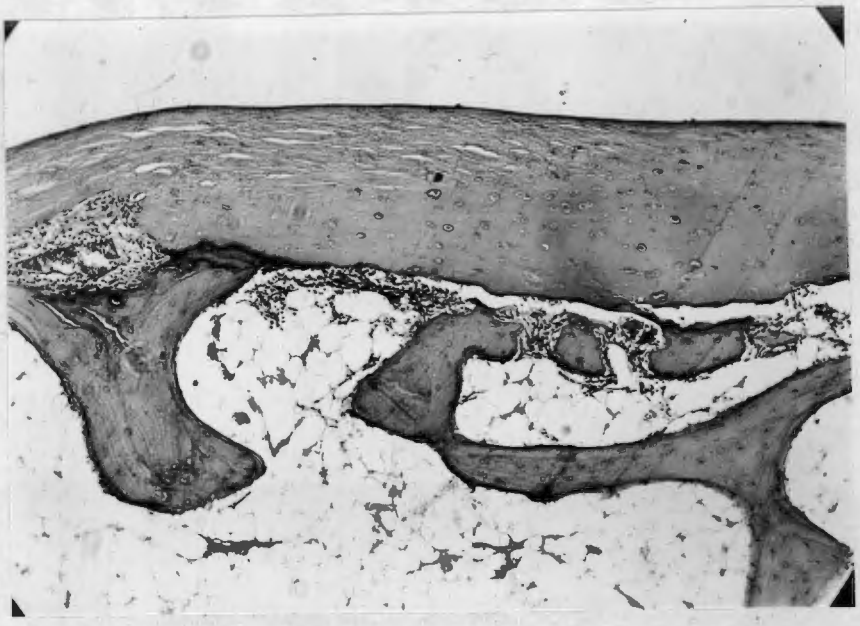
In view of these findings it was decided to repeat these particular experiments. The animals were first given six instead of four bi-weekly injections of 2 cc of 0.5% silver lactate in an attempt to produce a little more change in the articular surfaces. After this, the same procedure was followed by eight bi-weekly injections of either lactic acid or hydrocortisone.



Animal No. 87

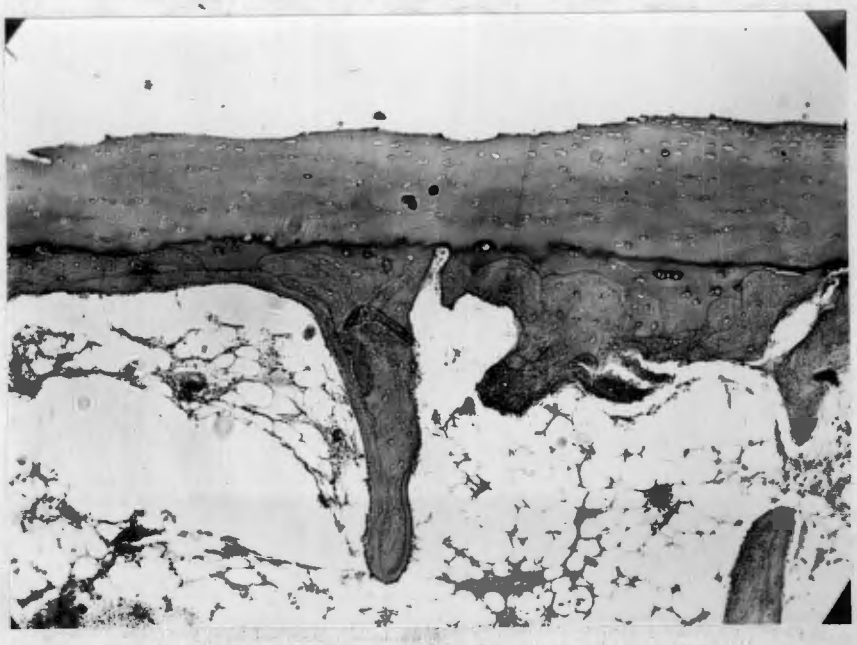
This animal received lactic acid injections after the silver lactate, into the right knee. The left knee received only the silver lactate injections.

Macroscopically, both knees showed small erosions, the left worse than the right. On the right there was an erosion over the medial condyle undergoing repair.



Photomicrograph of histological section of right knee joint of Animal No. 87

This section shows superficial fibrillation of the cartilage but no actual erosion.



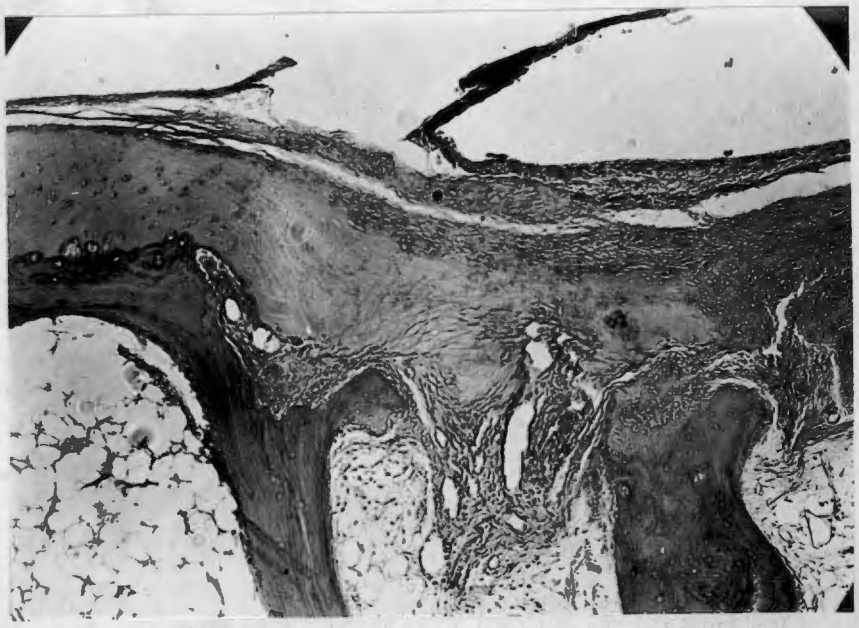
Photomicrograph of histological section of the left knee joint of Animal No. 87

The superficial layers of the cartilage have been worn away and the articular surface has lost its smooth surface on this section.

Animal No. 89

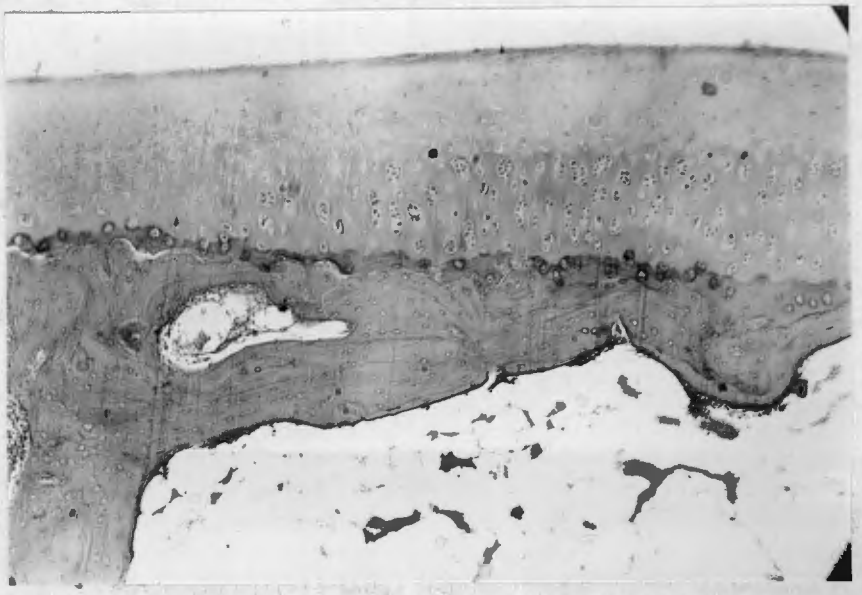
This animal also received lactic acid injections after the silver lactate into the right knee, and no injections except the silver lactate into the left knee.

Macroscopically, both knees were again eroded. On this occasion the right knee appeared worse than the left. On the left the articular margins were however more hypertrophic.



Photomicrograph of histological section of right knee of Animal No. 89

The section of the right knee shows a deep defect extending into the subchondral bone. An imperfect type of repair by way of fibrous tissue has taken place. There is evidence of marked reaction on the part of the subchondral bone and there are islands of cartilage imprisoned in the subchondral bone.



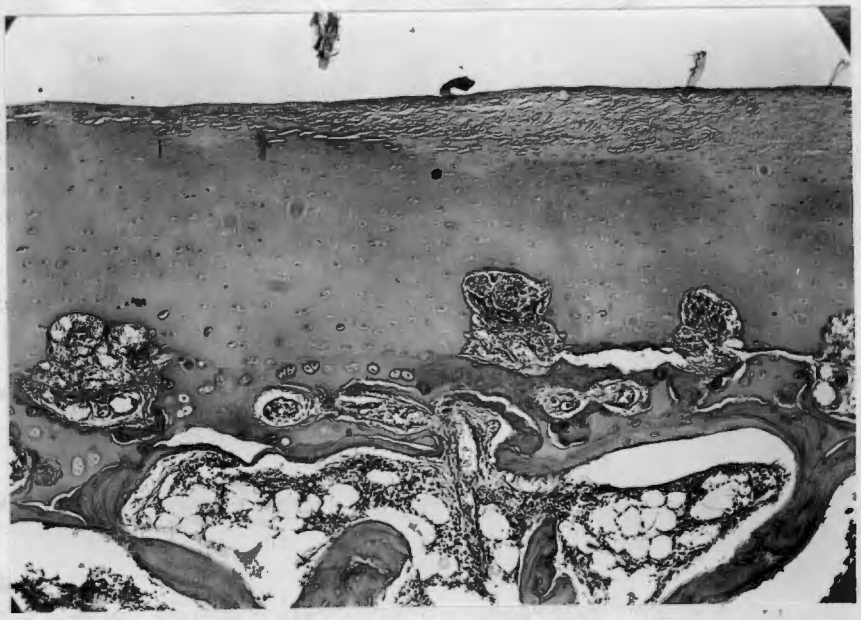
Photomicrograph of histological section of left knee joint of Animal No. 89

This section has not passed through an erosion but it shows numerous giant cells in the deeper layers of the cartilage.

Animal No. 88

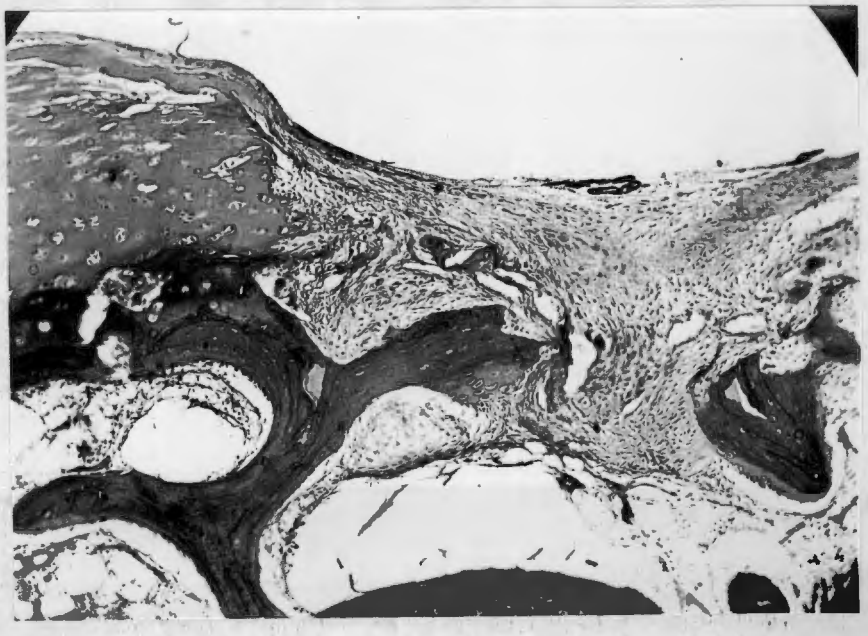
This animal received hydrocerticone injections after the silver lactate into the right knee. Into the left knee only silver lactate injections were given.

Macroscopically, both knees showed erosions. The left was much worse than the right. In the case of the right knee there appeared to be several areas undergoing repair.



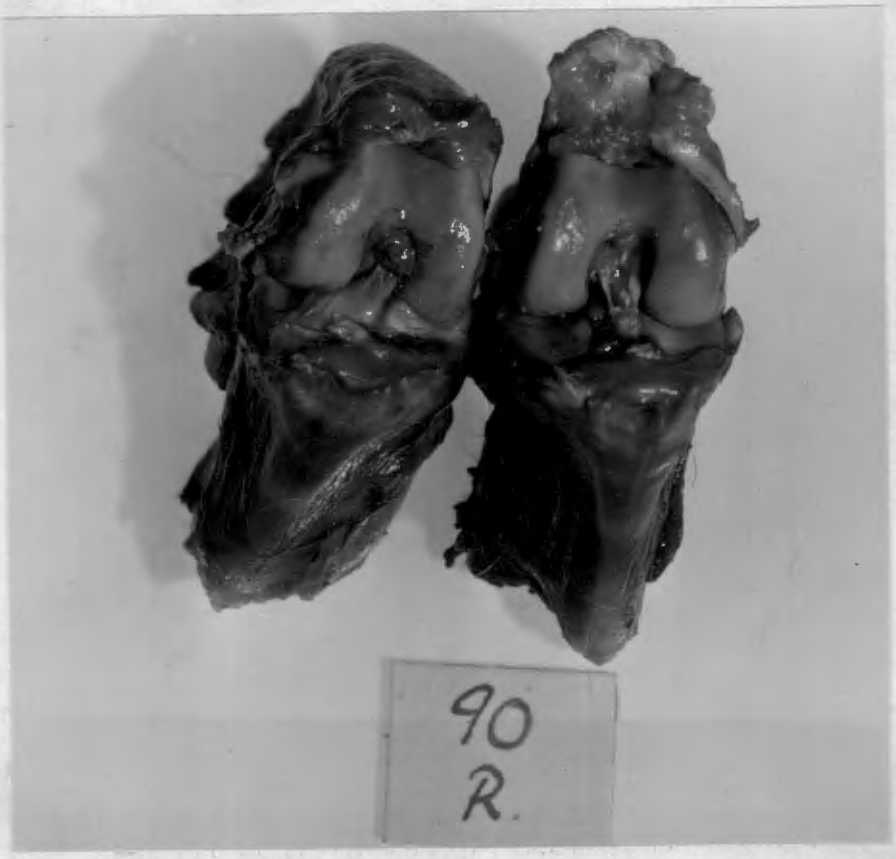
Photomicrograph of histological section of right knee joint of Animal No. 88

This section shows an area where the superficial cartilage cells have disappeared and are replaced by fibrous tissue. The repair is primitive but the surface is well preserved. There is evidence of subchondral reaction being present, and capillary networks have invaded the deeper layers of the articular cartilage.



Photomicrograph of histological section of left knee joint of Animal No. 88

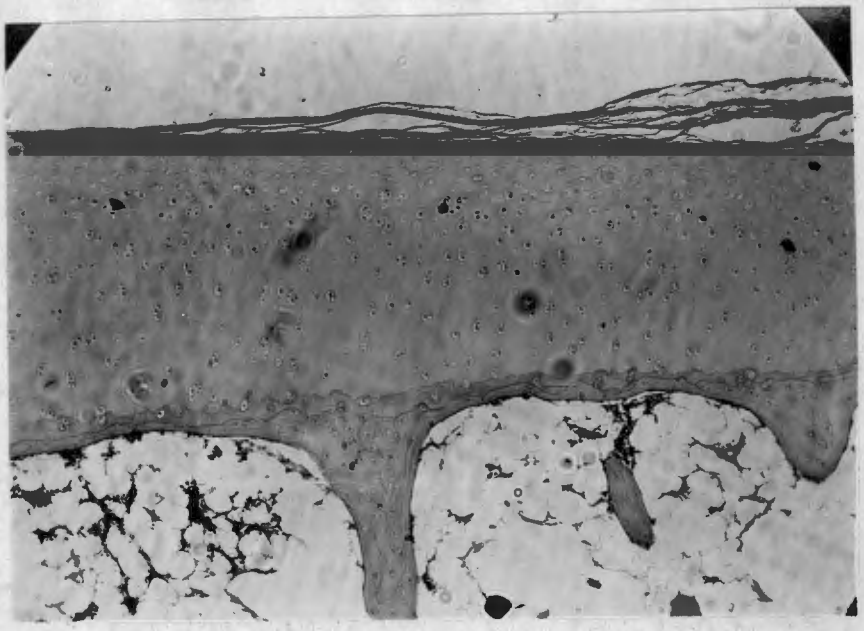
The section of the left knee shows an erosion that extends into the subchondral bone which is partially filled with fibrous tissue. The repair process is more haphazard than in the right knee. Once again there is marked subchondral reaction. Other areas of cartilage show the giant cells seen in the left knee of animal No. 89.



Animal No. 90

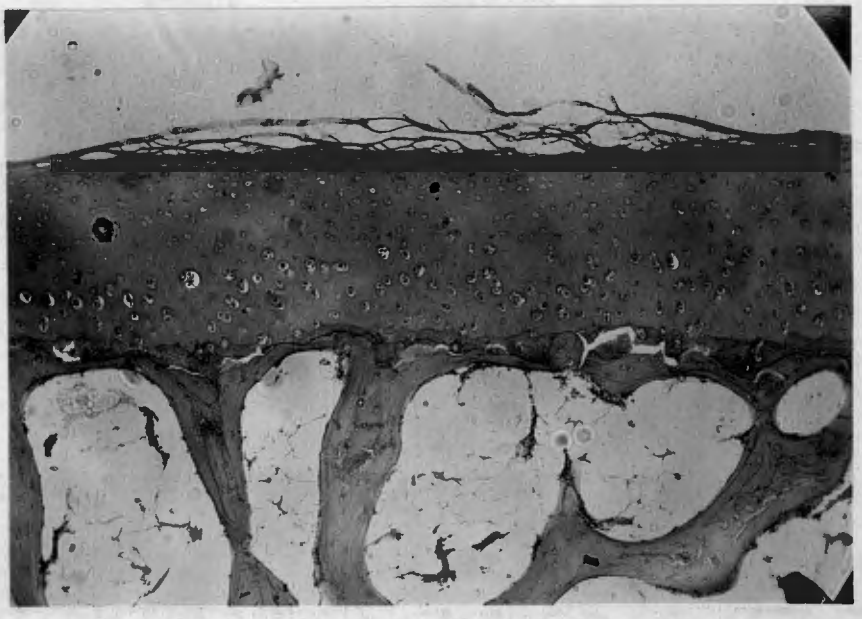
This animal was treated in the same way as animal No. 88 i.e. with hydrocortisone injections into the right knee and only silver lactate into the left knee.

Macroscopically, both knees showed erosions of the femoral articular surfaces. The right was again less eroded than the left. This is noted particularly when the intercondylar notches are compared.



Photomicrograph of histological section of right knee joint of animal No. 90

This section shows superficial fibrillation and fibrous tissue replacing this defective area.



Photomicrograph of histological section of the left knee joint of animal No. 90

The section of the left knee also shows superficial fibrillation. There are however areas present where no repair has taken place. The giant cells noted previously are well shown.

D. DISCUSSION OF THESE RESULTS

1. The Risks of Intra-articular injections

It may be stated at the outset that intra-articular injections of any type carry a small risk as can be seen when dealing with previously normal joints.

(a) The Risk of Infection

During these investigations one monkey developed a septic arthritis. It is extremely difficult to maintain strict asepsis in experimental work of this nature. The possibility of a general septicaemia does exist, especially seeing the suppurative arthritis was bilateral. It does, however, serve to emphasise how very strict aseptic precautions should be, when giving intra-articular injections.

(b) The Risk following the Injection of Bland Materials

As seen in the case of the left knee of Animal No. 362 normal saline produced very minimal damage to the femoral articular surfaces, small erosions being evident on the margins of the articular surfaces. It is most unlikely that these changes were present before the injections and there was no evidence of infection accounting for the departure from normality.

As previously mentioned Key (1933) produced arthritic changes in the knee joints of rabbits by repeatedly injecting 1 to 2 cc distilled water, saline etc. It seems possible that the amount injected (2cc) was rather large for the capacity of the rabbits' knee joint. Repeated overdistension of a joint must surely have deleterious effects. In these investigations the rats received 0.1 cc into their knee joints without harmful effect. Six monkey joints received injections of 2 cc saline and only one showed evidence of slight abnormality. The knee, which received no injections, but only the insertion of the needle intra-articularly, did not show any departure from the normal.

The changes seen in the left knee joint of Animal No. 362 emphasise, however, the fact that intra-articular injections, whether bland or not, need not be entirely non-injurious to the delicate structure of the joints.

2. <u>The Effect of Intra-articular Injections on previously Normal Joints.</u>

(a) <u>The Effect of "Hyalase" on Previously Normal Joints</u>

No injurious effects were evident in the joints which received the "hyalase" injections. Sacks' (1949) theory that the depolymerisation of the hyaluronate would affect the matrix of the cartilage has not been substantiated by these experimental investigations. Even the staining of the matrix

on the section did not differ in any way from the normal.

(b) The effect of Lactic Acid on previously Normal Joints

In the case of Animal No. 208, the absence of Lustre of the right femoral articular surface was noted. No histological changes were evident. As already mentioned this is perhaps the earliest change in the degeneration of cartilage. Animal No. 488, however, received 18 injections of 2 cc lactic acid without any change to the articular surfaces.

(c) The Effect of Silver Lactate on previously Normal Joints

The animals that received silver lactate displayed pathological changes, similar to those described by previous workers. The changes were at first very extensive and produced a rather artificial type of arthritis. It was, therefore, decided to try and produce a milder form of arthritis, by reducing the number of injections of silver lactate. At first four injections were given, but the changes were not marked enough, with the result that the last group of animals each received six injections before starting "therapy".

3. The Effects of Intra-articular injections in the Experimental Arthritis produced by Silver Lactate

(a) The Results of Lactic Acid Therapy in the Experimental Arthritis

Three joints received lactic acid injections after the injection of silver lactate. In two of these (Animals Nos. 442 and 89) the macro- and microscopic apearances displayed

more pathological changes than the control joints. In the third animal, No. 87 there is not much difference between the knee which received lactic acid and the control knee. In the case of Animals Nos. 442 and 89 deep erosions have been repaired by primitive fibroblasts. It is unlikely that the lactic acid has had any influence on the repair of these defects, as it has been seen that this process of repair may occur in "untreated" joints. Has the lactic acid, however, aggravated the pathological picture? The fact that two joints are worse than their controls would suggest such a possiblity. The introduction of 2 cc of lactic acid on eight occasions may have served to allow the irritant process to continue and to prevent natural healing. This is very difficult to compare with human osteo-arthritis, as in the human joints examined by Bennett et alia (1942) at post mortem there was never any evidence of repair present. This process of repair found in the experimental animal is therefore not analagous to human osteo-arthritis.

It has all along been felt that lactic acid is very unlikely to have any beneficial effect on the pathological process in osteo-arthritis. Its value must be a symptomatic one only. Does it however cause deterioration in the condition of the joint surfaces? Cases coming to arthrotomy

after lactic acid injections do not suggest such a possibility. It may be that the quantity injected in the animal joint which had already been exposed to an irritant might account for the resultant picture.

(b) The Effect of Intra-Articular Cortisone in the Experimental Arthritis

Only one joint (the right knee of Animal No. 462) was treated with intra-articular cortisone injections. Macroscopically there was very little difference between this joint and its control. The histology would suggest a marked difference but it may be that the defect shown in the photomicrograph was artificially produced. There is certainly nothing to indicate any beneficial effect on the pathological process, as far as intra-articular cortisone is concerned.

(c) The Effect of Hydrocortisone in the Experimental Arthritis

Four joints were "treated" with intra-articular hydrocortisone i.e. Animals Nos. 493, 494, 88 and 90 (Animal No. 494 developed the septic arthritis so will be excluded from this discussion).

The other three joints were in each case less eroded than their controls. In the case of Animal No. 493 an eroded area was evident over identical areas of each

femur. The erosion on the right i.e. the joint which received hydrocortisone, appeared shallower than the erosion on the left femoral surface. Sections were cut so as to include identical areas of these two bones. Microscopy revealed a more superficial defect on the right but both sides show evidence of repair. It cannot, therefore, be stated that the hydrocortisone accelerated or influenced the process of repair. The fact, however, that in all the joints "treated" with hydrocortisone there was less erosion than in their controls, suggests that this substance exerts a beneficial effect on the pathological process and unlike lactic acid is not only of symptomatic value in the treatment of osteo-arthritis.

CHAPTER V

THE MECHANISM OF THE NON-HORMONAL THERAPY.

In the chapter discussing the clinical investigations it was seen that lactic acid and hydrocortisone injections produced the most satisfactory results in this series. No attempt at explaining the rationale of hydrocortisone therapy will be made. The results obtained in the experimental arthritis "treated" with the hydrocortisone, however, confirm the clinical results. As far as lactic acid is concerned it was felt that it is most unlikely that the change in pH is sufficient reason to account for the relief obtained from this therapy. The experimental arthritis does not offer any explanation in the case of lactic acid.

Does lactic acid perhaps act merely by eliminating the pain and have no real therapeutic effect? Before attempting to answer this question the nerve supply of joints will be briefly considered. At the same time the possible origin of joint pain will be discussed.

The Nerve Supply of Joints

Joints are supplied by branches which reach them, either directly or indirectly, from the nerves supplying the overlying skin and the muscles which move the joints - Hilton's law. The termination of these articular nerves is not quite certain. According to Kellgren and Samuel (1950) fibrous articular ligaments are richly supplied with nerves largely

somatic in origin. Synovial membrane is less richly supplied with nerves and a large proportion of the synovial nerves appears to be autonomic in origin. Synovial membrane does, however, contain a substantial number of nerves, which are somatic in origin and terminate in nerve loops, globular endings or simple unspecialised endings. Gray and Gardner (1950) found no Pacinian corpuscles within the joint capsule, but found these complex endings adjacent to joints. They found free nerve endings in relation to blood vessels only. The fact that free nerve endings from myelinated and non-myelinated nerves are found in the vascular adventitiae suggests that perception of painful stimuli may be their functions. Bazett and McGlone (1928) performed hundreds of deep punctures in human subjects and found that when a needle entered a small artery, as it commonly did, dull, aching, not easily bearable pain resulted. Not only are free nerve endings associated with synovial vessels but they are also found in association with the vessels of the subchondral bone. This accounts for the pain experienced in bone marrow punctures (Kellgren 1939a). Kellgren and Samuel (1950) state: "There is still uncertainty as to the relative importance of bone, cartilage, ligaments and synovial membrane as sources of pain in joint disease. It is agreed that articular cartilage is devoid of nerves and gives rise to no sensation when it is stimulated. The bone ends play an important part in the

appreciation of vibratory and other mechanical stresses, and they may contribute to the pain of disease because periosteum is highly pain sensitive, and moreover cancellous bone may be sensitive though to a lesser degree".

These authors studied pressure as well as pain sensibility in the knee joints of normal human volunteers. One of them (E.P.S.) had an arthrotomy done on his own knee under local anaesthesia, and recorded his sensations when the synovial membrane was stimulated. Kellgren and Samuel (1950) conclude that the fibrous articular ligaments are richly supplied with nerves of various types and that these ligaments are densely studded with spots which give rise to sensations of pain or pressure when stimulated mechanically. The fibrous ligaments therefore play an important role in articular sensation and appear to be one of the major sources of joint pain. They found that synovial membrane, on the other hand, is less richly supplied with nerves and is a relatively insensitive structure in which only occasional spots can be found which give rise to a sensation of pain. They consequently conclude that synovial membrane is not a major source of articular sensation and probably contributes little to the symptoms of joint disease.

Kellgren (1939b) investigated 55 painful knees and divided them into three categories as follows:

a) Cases with ligamentous or muscular pain

b) Cases with synovitis and

c) Cases with a disordered joint mechanism.

The first two categories showed varying degrees of osteo-arthritis or none at all. In these cases the osteo-arthritis was always symmetrical, occurring equally in the painful and painless knees. Kellgren considers these findings coincidental. In the last category, however, they all presented considerable or gross osteo-arthritis on X-ray. In these cases the osteo-arhhritic changes were often asymmetrical and the symptoms appeared to be related to the degree and nature of the bony and cartilaginous changes present.

The relief obtained from the injection of procaine into a joint must be because of its local anaesthetic on either synovial or subchondral nerve endings, when the latter are exposed. This relief is often very temporary. Is it possible that lactic acid has had an anaesthetic effect as well?

In the hopes of providing an answer to this question the following experiments were done:

Two frog nerve muscle preparations were set up simultaneously, using the sciatic nerve and the gastrocnemius

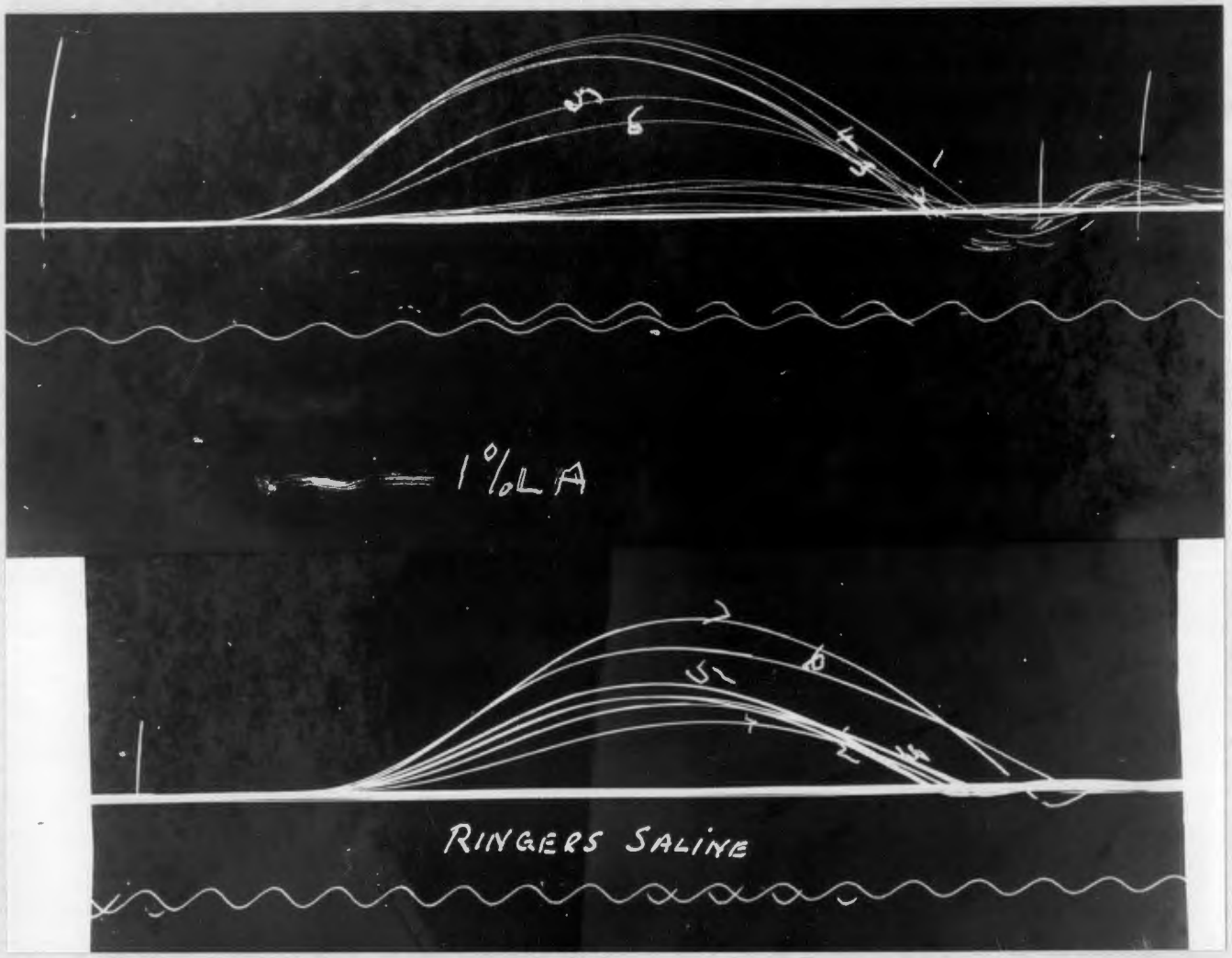


FIG. 3: NOTE THE PROLONGED LATENT PERIOD IN THE TRACING OF THE NERVE BATHED IN 1% LACTIC ACID.

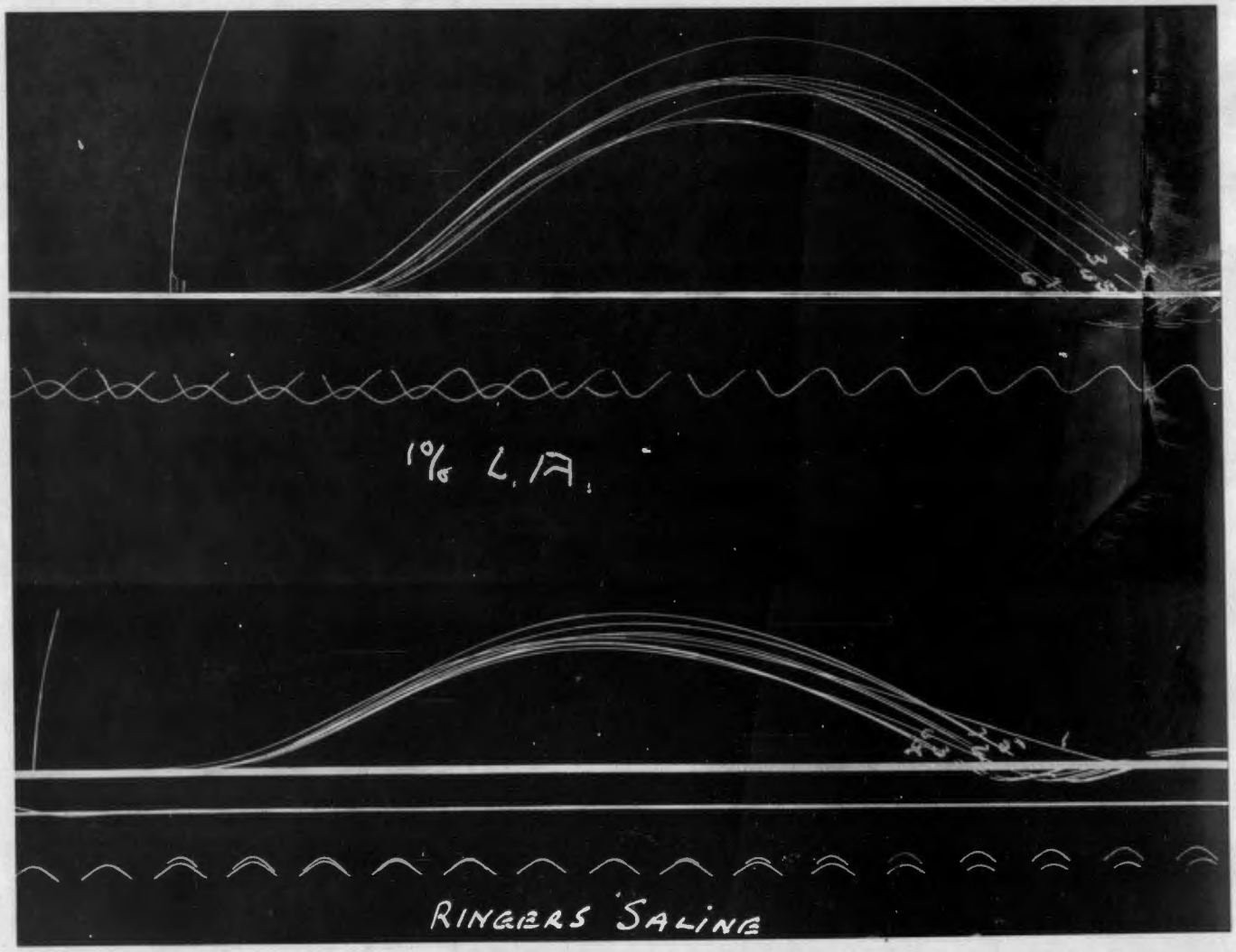


FIG. 4.

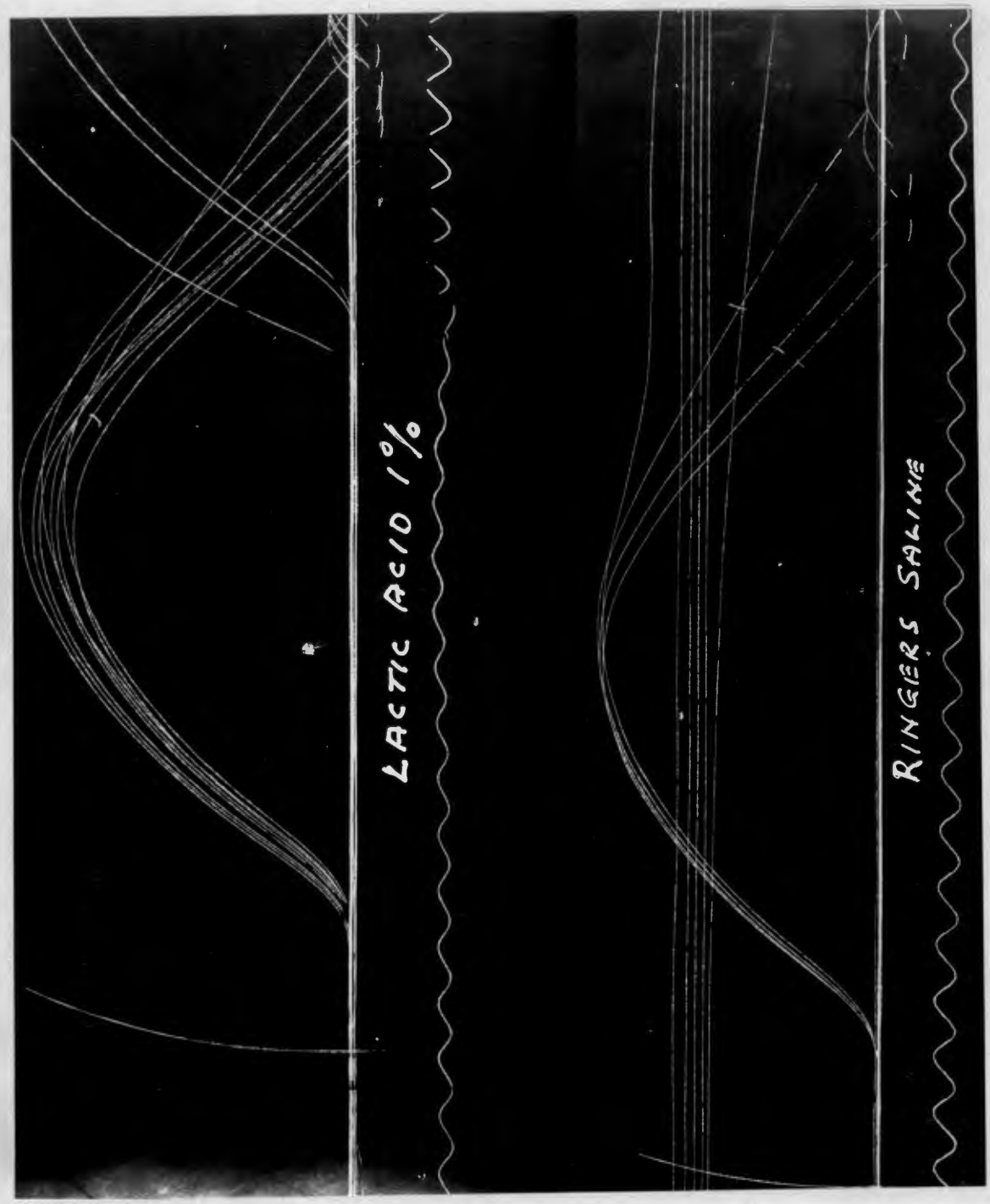


FIG. 5.

muscle in each case. The one sciatic nerve was placed in a small bath containing Ringer's saline, while the second was conducted via a bath containing 1% lactic acid. The rest of the nerve and the muscle was in each case kept moist with Ringer's saline. Electrical stimuli were then sent through each preparation at three minute intervals and recorded on drums revolving at the same speed. These stimuli were continued until fatigue became evident. In the case of the nerve muscle preparation in which only Ringer's saline was used there was no prolongation of the latent period. In the preparation where the nerve was conducted via the bath of lactic acid the latent period showed signs of a gradual but repeated increase. This can be seen by consulting fig. 3.

Figures 4 and 5 show repetition of the same experiment with identical results, indicating that the lactic acid had a retarding effect on the conduction of the nerve impulses.

The above experiment has, however, one serious drawback in that the nerve used was not a free or complex nerve ending. To, try and overcome this difficulty the following experiment was done:

I immersed my lower lip in a 1% lactic acid solution for 30 minutes, and then asked someone to test my sensation to pinprick, comparing the sensation of the lower with that of the upper lip. The lower lip was definitely hypoalgesic in comparison with the upper.

It was decided to see what effect lactic acid would have on an exposed dental nerve. A non-European female presented with a large cavity in her left second lower molar and complained of severe toothache, which had been present for more than a week. A pledget of cotton wool was soaked in 1% lactic acid and inserted into the cavity. After a few minutes the patient stated that her toothache was better. The lactic acid was re-applied at frequent intervals throughout the day. After eight hours the effect of a jet of cold air directed into the cavity produced no pain. The following day there was still no recurrence of the toothache.

In order to investigate the hypothesis further three cases of osteo-arthritis of the knee joint with pain as the prominent symptom were selected. Without using any local anaesthetic an injection needle was inserted into the affected knee joint in each case. After this 0.2 cc absolute alcohol was injected. In each case the patient immediately complained of intense pain which he or she likened to the pain experienced from the disordered joint. These patients were then given a course of lactic acid injections with moderate response in the case of two of them and a marked response in the third. (See Appendix Cases No. 37, 38 and 40). Cases No. 37 and 38 have no pain at present, whereas Case No. 40 has slight pain on twisting the knee which may be ligamentous in origin, and is therefore classed as a moderate response.

The response in Case No. 37 has been considered moderate because the range of movements only increased by 20°. No preliminary procaine was employed to give these injections of lactic acid. A week after each course had been completed 0.2 cc absolute alcohol was again injected into each of the affected knees without using a local anaesthetic. On these occasions the pain experienced was very mild and had to be elicited by asking leading questions. 0.2 cc absolute alcohol was also injected into the knee joint of a case after having received intra-articular lactic acid injections in the Orthopaedic Department of Groote Schuur Hospital and not included in this series. This patient also experienced very mild pain, and as no preliminary alcohol had been given it seems reasonable to assume that it could not be the preliminary alcohol which provided the analgesic effect.

It would seem therefore that lactic acid exerts an anaesthetic effect on the synovial and also the subchondral nerve endings, when these are exposed. Lactic acid has for many years been advocated as a good caustic for mucous membranes because it has a low toxicity. In the mouth it is valuable for gingivitis and aphthous ulceration; it is also employed to cauterise tuberculous ulcers of the pharynx or larynx and, diluted to remove diphtheritic membrane (Dilling, 1951).

Caustics kill the protoplasm of all tissue and in so doing kill the exposed nerve endings. They have no specific

action on nerve endings but destroy them altogether with all surrounding tissues. Procaine and other local anaesthetics, on the other hand, produce a temporary interruption of nervous conduction and the process is a reversible one. They also have a selective action on nerve tissue (Clark 1952).

The concentration of lactic acid employed in intra-articular injections is a very dilute one. Consequently, the noxious effect on the tissues is probably very mild. Repeated injections may, however, damage specialised tissue like nerve endings sufficiently to impede their function as pain perceptors. The more prolonged, if not permanent, relief obtained from the use of lactic acid can therefore possibly be explained on this basis. Ammonium sulphate presumably acts similarly but is likely to be more irritating.

CHAPTER VI

GENERAL DISCUSSION

When the literature on intra-articular lactic acid injections for osteo-arthritis is consulted, it is found that most authors are of the opinion that this type of therapy has a beneficial effect on the symptoms of the disease. The question as to whether there is objective improvement is not, however, always specificically stated. Crowe (1944) using acid potassium phosphate found subjective improvement in all cases, but only 56 out of 93 cases were objectively improved. Baker and Chayen (1948) are the only authors who have endeavoured to compare the results of lactic acid therapy with those of procaine. They, however, do not give specific follow-up figures; nor do they distinguish between subjective and objective improvement. Half the cases which received lactic acid therapy in their series either improved markedly or moderately whilst the remaining half did not change or only improved slightly. The group which received procaine in saline (with a neutral pH) behaved similarly. Their series included cases with various joints involved and they do not separate their cases according to the joint affected. Waugh, who was responsible for the introduction of this form of therapy in osteo-arthritis gives his results in 18 cases affecting the hip joint. He makes no distinction between objective and subjective improvement. The group of patients which was given lactic acid injections by the interns in the Orthopaedic Department of the Groote Schuur Hospital showed on the whole a satisfactory response

especially if the temporary remissions are included.

In this series the objective and subjective improvement has been noted separately. In addition the functional performance of each patient has been assessed. The results in the group of patients which received lactic acid injections in this series were better than those of Baker and Chayen (1948) These authors, however, included cases with osteo-arthritis of the hip joint for example and it is known that injections into this joint may quite easily not be intra-articular. The results in this series are also slightly better than in the group which received their injections from the interns at Groote Schuur Hospital. Once again the possibility that all their injections were not definitely intra-articular exists. As far as the procaine injections are concerned this series behaved similarly to the series of Baker and Chayen. The results in the group which received ammonium sulphate injections were not as good as those for the lactic acid series when compared by Mood's likelihood ratio method.

It is consequently concluded that intra-articular lactic acid injections do produce clinical improvement in cases with osteo-arthritis, if it can be certain that the injections do are truly intra-articular. There is more likelihood of subjective improvements occurring but many cases show objective improvement as well. The duration of the improvement varies from case to

case.

With regard to the mechanism of the relief obtained it seems most unlikely that the alteration of the pH of the synovial fluid is responsible for the improvement. Such a change can only be a very temporary one as has been shown by Ramamurthi (1947) and again during these investigations The fact that procaine with a neutral pH and ammonium sulphate with a pH of 7.0 have afforded relief also detracts from such a likelihood. Waugh's original estimations of the pH of the synovial fluid in chronic arthritis are also open to criticism.

From the observations in the experimental animals there is nothing to suggest that lactic acid has an advantageous effect on the pathology of osteo-arthritis. The results in this series indicate that in two out of three joints in which an arthritis had been induced lactic acid "therapy" actually aggravated the induced arthritis. The lactic acid appears to have increased the irritant effect of the silver lactate used to induce the arthritis.

The most feasible explanation of the mechanism of the action of lactic acid therapy is that the lactic acid acts as a local anaesthetic and thereby relieves the symptoms The objective improvement is probably a completely secondary effect. It is felt that lactic acid acts by destroying the

nerve endings responsible for the pain in osteo-arthritis, whereas procaine only paralyses them. This would account for the more prolonged relief obtained after lactic acid therapy when compared with procaine. As these nerve-endings regenerate after lactic acid therapy so the symptoms may recur.

The solution of lactic acid used therapeutically is a very dilute one, therefore, it is felt that the noxious effect of such a solution is not likely to be marked. Arthrotomies done after lactic acid therapy have not revealed any obvious deleterious effects, but the changes present in the experimental animals in this series indicate that such a possibility does exist.

As far as the hormonal intra-articular injections are concerned hydrocortisone seems to have replaced cortisone. The cortisone injections when given intra-articularly are more likely to be irritating as judged by the patient's reaction. In addition the cortisone is more liable to produce systemic side effects. Hydrocortisone in the majority of cases gives dramatic relief which may be temporary although a few cases have now been symptom free for several months. The findings in the experimental animals suggest that hydrocortisone may exert a beneficial effect on the pathological process. Three out of three animals with induced arthritis showed less departure from the normal in the knees which received hydrocortisone when

compared with the control knees.

In conclusion it may be stated that intra-articular lactic acid provides symptomatic relief in osteo-arthritics but that there is a possibility that the resultant effect on the articular surfaces may be harmful. It is felt that in many cases procaine, when given intra-articularly, will provide similar relief but of a less permanent nature. Hydrocortisone affords dramatic relief and in addtion there is evidence to suggest that the condition of the articular surfaces is improved. It is consequently suggested that hydrocortisone be given a very thorough trial as this form of therapy seems to offer the best hope for the crippled osteo-arthritic.

S U M M A R Y

1. The available literature on intra-articular injections in osteo-arthritis has been reviewed.

2. Forty-two cases of osteo-arthritis of the knee were treated with various intra-articular injections. The injections used were procaine in saline, lactic acid in a procaine base, saturated ammonium sulphate solution, cortisone acetate and hydrocortisone acetate.

The results of these investigations suggest that lactic acid and hydrocortisone were more constant in providing symptomatic relief than the other types of injection. There were, however, favourable results in each group of patients.

3. In vitro studies on synovial fluid were performed. These investigations, however, did not afford a suitable explanation as to the possible mechanism whereby intra-articular injections provide relief in osteoarthritis.

4. In vivo experiments were done on animal joints. These demonstrated the fact that intra-articular therapy is not devoid of risks. It was not possible to demonstrate any advantageous effect from the use of lactic acid in the

experimentally induced arthritis. On the contrary, the results after lactic acid "therapy" in the induced arthritis suggested a deleterious effect. The use of hydrocortisone on the other hand revealed an improvement in the condition of the articular surfaces when compared with the controls.

5. It is suggested that the mechanism of the action of intra-articular lactic acid is purely an anaesthetic one. Various procedures were performed in an attempt to substantiate this hypothesis. It is felt that ammonium sulphate probably acts in a similar way.

6. The conclusion is therefore reached that lactic acid provides symptomatic relief in osteo-arthritis but does not improve the pathological process present. Because of the dilute solution used it is unlikely but not impossible that a noxious effect may result from its clinical use intra-articularly. The hypothesis that its mechanism of action is via the altered pH is not substantiated.

7. Hydrocortisone may, on the other hand, improve the pathological process and not only afford symptomatic relief. The relief is, however, often temporary and repeated injections may be required. A longer follow-up will permit of a better appraisal of these results.

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APPENDIX

BRIEF CASE RECORDS

CASE NO. 1 (M.M.)

European female aged 60
Ostee-arthritis left knee

Chief complaints

Severe pain both on movement and at rest for one year
Marked stiffness.

On Examination

Active movements:

These will be described as permanent flexion deformity (P.F.D.) if there is limitation of extension and full flexion (F.F.)

	Right Knee	Left Knee
P.F.D.	0°	10°
F.F.	160°	90°

Marked limp with much walking difficulty.

Treatments

Received 6 injections of procaine
No response
Movements after procaine - left knee
P.F.D. 30°
F.F. 90°

Received 6 injections of ammonium sulphate
some improvement
Movements:
P.F.D. 5°
F.F. 120°

Two months later relapsed
Movements:
P.F.D. 15°
F.F. 90°

Follow - up: 1 year.

CASE NO. 2 (S. M.)

Non-European female aged 45

Osteo-arthritis Right Knee

Chief Complaints:

Severe pain and stiffness - 6 months

On Examination:

Active movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	90°	150°

Marked limp

Treatment:

3 injections procaine with no response subsequently

5 injections lactic acid.

Marked response.

Movements: (Right Knee)

P.F.D. 0°

F.F. 140°

Follow - up: 6 months.

CASE NO. 3 (B. F.)

Obese Non-European female aged 64

Osteo-arthritis both knees

Chief Complaints:

Severe stiffness and moderate pain for 12 years

On Examination:

Active movements:	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	110°	110°

Treatment:

6 injections procaine into Right Knee

6 injections lactic acid into left knee

Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	120°	130°

Follow - up: 6 months.

CASE NO. 4 (E.L.)

Obese Non-European female aged 50

Osteo-arthritis both knees especially right

Chief Complaints

Severe pain and stiffness - 2 years

On Examination

Active Movements	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	90°	100°

Treatment

2 procaine injections right knee

2 lactic acid injections left knee

Both knees improved markedly. One year later right relapsed. Then given five lactic acid injections into right knee with marked improvement.

Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	150°	150°

Follow - up: 22 months left knee

7 months since lactic acid to right knee.

CASE NO. 5 (J.P.)

European male aged 82

Osteo-arthritis both knees

Chief Complaints:

Severe pain and stiffness, especially right knee for two months.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	10°	5°
F.F.	90°	120°

Walking very difficult and painful.

Treatment:

6 procaine injections into right knee

6 ammonium sulphate injections into left knee

Moderate improvement right knee for 4 months

Marked improvement left knee

Subsequently 4 injections lactic acid right knee with marked response

Active Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	140°	140°

Follow - up: 14 months left knee

9 months since lactic acid injections right knee.

CASE NO. 6 (M. D.)

European male aged 32

Early ostee-arthritis both knees

Chief Complaints:

Moderate pain and stiffness for 3 years

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	5°	5°
F.F.	120°	120°

Treatment:

4 procaine injections into left knee

4 lactic acid injections into right knee

Satisfactory response. Movements full.

Has some pain in left knee on occasions.

Follow - Up: 22 months.

CASE NO. 7 (E. G.)

European female aged 40

Osteo-arthritis both knees.

Chief Complaints:

Pain and stiffness of both knees - 18 months

Also osteo-arthritic changes in spine and hips.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	90°	60°

Treatment:

6 procaine injections into left knee

6 ammonium sulphate injections into right knee

Subjectively no change

Objectively Right Knee unchanged

Left Knee movements increased by 30°

Subsequently right knee given 4 injections of lactic acid with again no subjective improvement but with an increase in the range of active movements of 20°

Follow - up: 11 months.

CASE NO. 8 (E.C.)

European female aged 35

Early ostee - arthritis right knee

Chief Complaints:

Pain and stiffness right knee for several months

On Examination:

Active movements limited

Treatment:

6 lactic acid injections with marked response.

Follow - up:

2 years.

CASE NO. 9 (H. S.)

European male aged 68

Osteo-arthritis both knees, especially right

Chief Complaints:

Moderate degree of pain with marked stiffness for six months.

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	100°	110°

Treatment:

6 lactic acid injections into each knee with marked response

Movements normal.

Follow - Up:

7 months.

CASE NO. 10 (M. F.)

Obese Non-European female aged 69

Osteo-arthritis both knees.

Chief Complaints:

Severe pain and stiffness both knees for several years.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	10°	0°
F.F.	80°	70°

Treatment:

6 injections heparin sodium (10,000 units each) into right knee

6 lactic acid injections into left knee

Left knee satisfactory response - active flexion 130°

Right knee no response

Subsequently 6 lactic acid injections into right knee with marked response.

Movement: P.F.D. 30°

F.F. 130°

Follow - up: 19 months.

CASE NO. 11 (P. S.)

European male aged 57

Osteo-arthritis both knees

Chief Complaints:

Severe pain and stiffness both knees for 4 years

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	5°
F.F.	100°	100°

Treatment:

2 lactic acid injections into each knee with satisfactory response. Letter received from patient, but because he lives in the country have not been able to re-examine him.

Follow - Up:

6 months.

CASE NO. 12 (M.T.)

European female aged 64

Osteo-arthritis left knee.

Chief Complaints:

Severe pain and stiffness left knee for four months.

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	5°
F.F.	150°	120°

Treatment:

4 lactic acid injections into left knee

Still has occasional pain in knee but movements are full.

Follow - Up:

8 months.

CASE NO. 13 (M.S.)

Obese Non-European female aged 60

Osteo-arthritis Right Knee

Chief Complaints:

Severe pain and stiffness right knee for 1 year

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	30°	150°

Treatment:

5 lactic acid injections with marked improvement

Active movements Right Knee P.F.D. 0°

F.F. 100°

Follow - Up:

1 year.

CASE NO. 14 (L. D.)

Non European female aged 54

Osteo-arthritis both knees

Chief Complaints:

Severe pain and stiffness of knees for 1 year

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	5°
F.F.	130°	100°

Treatment:

6 lactic acid injections into each knee with indifferent response. Still complains of rest pain but objectively has improved

Active Movements Now:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	140°	140°

Follow - Up:

3 months.

CASE NO. 15 (A. Y)

Asiatic female aged 60

Osteo-arthritis both knees

Chief Complaints:

Pain and stiffness both knees for two months

On Examination:

Very little restriction of active movements

Treatment:

6 lactic acid injections into right knee

6 ammonium sulphate injections into left knee

Still has occasional episodes of pain in right knee

Follow - Up:

10 months.

CASE NO. 16 (E. B.)

European female aged 47

Very obese and build disproportional

Osteo-arthritis both knees but only left producing symptoms

Chief Complaints:

Severe pain and stiffness left knee for two years

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	5°
F.F.	140°	100°

Treatment:

6 lactic acid injections.

Marked improvement.

Follow - Up:

6 months.

This is one of the cases on which the electro-phoretic estimation of synovial fluid proteins was done, also pH of fluid before lactic acid injections was 7.0 and after injections pH uncharged.

CASE NO. 17 - (L. A.)

Non-European female aged 58

Osteo-arthritis left knee.

Chief Complaints:

Severe pain and stiffness left knee for few months.

On Examination:

Active Movements:	Left Knee
P.F.D.	0°
F.F.	70°

Treatment:

6 ammonium sulphate injections with moderate subjective response but marked objective response: Active Movements: F.F. 110°.

Subsequently 6 lactic acid injections with slight further improvement subjectively.

Follow - Up:

11 months after ammonium sulphate injections.

CASE NO. 18 (G. W.)

European male aged 47

Osteo-arthritis both knees, only right producing symptoms

Chief Complaints:

Marked stiffness and moderate pain right knee for 2 years

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	90°	150°

Treatment:

6 ammonium sulphate injections into right knee

Active movements increased by 20°. Moderate response

Follow - Up:

15 months

CASE NO. 19 (C. P.)

Obese Non-European Male aged 55

Ostee-arthritis left knee

Chief Complaints:

Severe pain and stiffness left knee for 1 year

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	10°
F.F.	150°	40°

Treatment:

6 ammonium sulphate injections with marked subjective improvement. Active movements now P.F.D. 0° F.F. 40° but painless.

Follow - Up:

13 months.

CASE NO. 20 (W. M.)

Non-European male aged 65

Osteo-arthritis both knees, left producing symptoms

Chief Complaints:

Complete inability to move left knee for 2 months

Severe pain.

On Examination:

Nil active movements left knee

Passive movements produced much pain

Treatment:

Unsuccessful arthrotomy for loose body.

Subsequently 4 ammonium sulphate injections

into left knee with dramatic response.

Active movements : full

Follow - Up:

21 months.

CASE NO. 21 (C. C.)

Non-European female aged 47

Osteo-arthritis right knee

Chief Complaints:

Severe pain and stiffness right knee for a few years

On Examination:

Active movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	50°	140°

Treatment:

6 ammonium sulphate injections with marked response. Has full movements now.

Follow - Up:

1 year.

CASE NO. 22 (H. L.)

European male aged 40

Post Traumatic Arthritis left knee.

Complaints: Fractured left patella 1935 - fifteen years later had grossly arthritic patella excised and subsequently failed to achieve much movement because of severe pain. Especially painful for 6 months.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	Artificial limb	5°
F.F.		90°

Treatment:

6 ammonium sulphate injections into left knee.

Marked response.

Active movements now: P.F.D. 0°
F.F. 140°

Follow - up:

16 months.

CASE NO. 23 (F. M.)

Non European female aged 60

Osteo-arthritis left knee

Chief Complaints:

Pain left knee for one month

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	10°
F.F.	150°	90°

Treatment:

2 injections ammonium sulphate into left knee with marked improvement

Active movements now P.F.D. 0° F.F. 150°

Follow- up:

10 months

CASE NO. 24 (H. T. L.)

European Male aged 75

Osteo-arthritis both knees, left producing symptoms.

Chief Complaints:

Severe pain and stiffness left knee for 1 month

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	5°
F.F.	150°	110°

Treatment:

2 ammonium sulphate injections into left knee

Active movements left knee P.F.D. 0° F.F. 140°

Still has pain, however.

Follow - Up:

1 year.

CASE NO. 26 (H. P.)

Non-European female aged 48

Osteo-arthritis both knees.

Chief Complaints:

Severe stiffness with some pain both knees for 4 months

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	90°	90°

Walks with marked limp.

Treatment:

6 bi-weekly injections of cortisone acetate into each knee. Response evident after the fourth injection. After this 5 weekly injections of 50 mg. cortisone. Marked response. Active flexion is now 120° in each knee. Experiences slight pain on kneeling but it is intermittent.

Follow - Up:

11 months.

CASE NO. 27 (L. B.)

Non-European female aged 64

Osteo-arthritis both knees

Chief Complaints:

Severe pain left knee for 5 years and right knee for 1 year

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	110°	110°

Marked limp.

Treatment:

7 weekly injections of 50 mg. cortisone into each knee. Subjectively marked improvement. Also marked increase in functional performance. Objectively active movement increased by 20°.

Follow - Up:

3 months.

CASE NO. 28 (E. L. R.)

Non-European female aged 76

Osteo-arthritis both knees, only right producing symptoms

Chief Complaints:

Severe pain and stiffness at varying times during the past 12 years, particularly severe for last 5 months.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	110°	150°

Treatment:

3 weekly injections of 50 mg. cortisone into right knee. Marked response active movements now P.F.D. 0° F.F. 140°. Slight pain after 6 months.

Follow - Up:

7½ months.

CASE NO. 29 (J. K.)

European female aged 56

Bilateral estee-arthritis of knees.

Chief Complaints:

Severe pain and stiffness, especially right knee for one month.

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	5°	0°
F.F.	90°	120°

Marked limp.

Treatment:

4 bi-weekly injections of 100 mg. cortisone into each knee. Some irritation after injections but response evident after the third injection. Injections changed to 50 mg. cortisone bi-weekly and subsequently weekly Received 12 injections with marked improvement, 4 weeks later had relapse and was given a single injection of 50 mg. cortisone into each knee. Now occasional pain right knee and active movements are as follows:

	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	140°	140°

Follow-Up: 7 months.

CASE NO. 30 (E. K.)

European female aged 77

Osteo-arthritis left knee

Chief complaints:

Severe pain and some stiffness left knee intermittently for 8 years. Exacerbation present for one month.

On Examination:

Active Movement	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	150°	120°

Treatment:

7 weekly injections of cortisone acetate with slight subjective improvement. Subsequently 13 injections of hydrocortisone. Has had remissions varying from 14 to 28 days. Quadriceps weak and this limited her functional performance. Consequently quadriceps exercises started. With marked improvement. Now receives injections of hydrocortisone at 3 to 4 weekly intervals.

CASE NO. 31 (H. P.)

European male aged 74

Osteo-arthritis left knee

Chief Complaints:

Marked stiffness with moderate pain left knee for 3 years

On Examination:

Active movement	Right Knee	Left Knee
P.F.D.	0°	10°
F.F.	140°	60°

Marked limp.

Treatment:

3 weekly injections 50 mg. cortisone. Remission after first injection lasting 6 days. After this no change Then hydrocortisone injections starting with 25 mg. and increasing to 50 mg. weekly.

Marked remission but longest duration 6 days.

Treatment discontinued.

CASE NO. 32 (E. E.)

European male aged 45

Post traumatic arthritis right knee

Chief Complaints:

Injury to right knee 3 years ago and again 8 months ago. Severe stiffness with moderate pain.

On Examination:

Marked effusion right knee

Active Movements	Right knee	Left Knee
P.F.D.	5°	0°
F.F.	120°	160°

Marked limp.

Sedimentation rate 26 mm. Westergren

Treatments:

Hydrocortisone injections ranging from 25 mg to 37.5 mg. Marked remissions lasting 14 days. Now symptom free for 6 months. This case provided the other specimen of synovial fluid for the electrophoretic estimation of the proteins.

CASE NO. 33 (M.S.)

European female aged 55

Osteo-arthritis both knees, associated with possible Paget's disease of left femur.

Chief Complaints:

Severe pain and stiffness of knees especially left for 4 years.

On Examination:

Active movements	Right knee	Left knee
P.F.D.	0°	5°
F.F.	110°	90°

Treatment:

5 weekly injections of hydrocortisone ranging from doses of 25 to 37.5 mg. into each knee.

No response.

Discontinued treatment.

CASE NO. 34 (H. H.)

European female aged 66

Bilateral osteo-arthritis of knees

Chief Complaint:

Severe pain both knees for 6 years.

On Examination:

Active movements	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	100°	100°

Treatment:

Total of 7 hydrocortisone injections ranging from 25 to 37.5 mg. per injection into each knee.

Marked remissions - longest duration 21 days.

Last injection 26th September, 1952.

After cessation of treatment pain has been minimal although stiffness still troubles her. Movements as before therapy.

Follow - Up:

6 months.

CASE NO. 35 (D. G.)

European female aged 54

Post-traumatic arthritis left knee

Chief Complaints:

Severe pain and marked stiffness following compound fracture upper end left tibia in 1949. Fracture involved articular surface.

On Examination:

Active Movement	Right Knee	Left Knee
P.F.D.	0°	10°
F.F.	140°	80°

Treatment:

7 weekly injections of 25 mg. hydrocortisone with slight remissions lasting 3 to 4 days. On the whole poor response.

CASE NO. 36 (J. S.)

Obese Non-European female aged 65

Bilateral estee-arthritis knees

Chief Complaint:

Severe pain and stiffness of knees for past 3 years and inability to walk.

On Examination:

Active Movements:	Right Knee	Left Knee
P.F.D.	15°	10°
F.F.	35°	90°

Treatment:

Has had long courses of physio- and X-ray therapy without relief.

9 injections of 25 mg. hydrocortisone into each knee, with marked remissions. Longest duration of remission was one week. Is able to walk without the aid of a stick during remission. After remission no change Has asked to stop treatment.

CASE NO. 37 (M. V.)

Non-European female aged 53

Bilateral osteo-arthritis of knees, only left symptomatic.

Chief Complaints:

Severe pain and stiffness left knee for several years

On Examination:

Active Movements:	Right Knee	Left Knee	
P.F.D.	0°	5°	very painful
F.F.	120°	90°	very painful

Treatment:

No local anaesthetic employed.

0.2 cc absolute alcohol introduced into left knee with intensive stabbing pain.

Then given 7 injections lactic acid. Subsequently 0.2 cc absolute alcohol injected again with severe pain. After this tried to inject lactic acid but resistance encountered suggesting needle was not in the joint. The needle was then re-inserted and 0.2 cc absolute alcohol was injected again and on this occasion only very slight pain was felt. 10 cc. lactic acid was then injected. One week later 0.2 cc absolute alcohol injected with very slight pain. This had to be elicited by asking a leading question, whereas on the very first occasion the pain was immediately obvious from the reaction exhibited by the patient. Pain is no longer present and active movements have increased by 20°

Follow - up: few weeks

CASE NO. 38 (D. J.)

Non-European Male aged 60

Osteo-arthritis left knee

Chief Complaints:

Severe pain and stiffness left knee for 4 months

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	8°
F.F.	130°	80°

Treatment:

3 cc. fluid aspirated from left knee pH - 7.0

0.2 cc absolute alcohol injected intra-articularly resulting in severe pain.

Six injections lactic acid given

Marked response Movements: P.F.D. 0° F.F. 130°

0.2 cc absolute alcohol injected subsequently. Very mild pain experienced which once again had to be ascertained by asking a leading question.

pH of fluid after 4 lactic acid injections unchanged.

Follow-up: Few weeks.

CASE NO. 39 (H. H.)

Non-European female aged 45

Osteo-arthritis right knee

Chief Complaints:

Severe pain right knee 3 years

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	110°	130°

Treatment:

4 injections lactic acid with marked improvement.

Follow - Up: 6 weeks.

CASE NO. 40 (B. B.)

European female aged 55

Osteo-arthritis right knee

Chief Complaint:

Severe pain right knee for 14 months. Also mild effusion.

On Examination:

Movements only slightly impaired. Pain on extreme flexion.

Treatment:

0.2 cc. Absolute alcohol introduced into right knee joint with severe pain.

8 injections lactic acid

0.2 cc absolute alcohol injected again with hardly any pain.

Response to treatment moderate - still has very occasional pain on twisting knee whilst in bed ? ligamentous pain.

Follow - Up:

Few weeks.

CASE NO. 41 (F. S.)

European male aged 52

Traumatic osteo-arthritis right knee

Chief Complaint:

Severe pain right knee 1 year before treatment

On Examination:

Active Movements	Right Knee	Left Knee
P.F.D.	0°	0°
F.F.	90°	130°

Treatment:

9 weekly injections hydrocortisone with marked response. Movements full. No pain.

Follow - up:

2 months.

CASE NO. 42 (M. K.)

European female aged 70

Osteo-arthritis left knee

Chief Complaint:

Severe pain left knee for 4 months before treatment was started.

On Examination:

Movements not impaired.

Treatment:

3 injections lactic acid with marked improvement for 11 months. Then pain gradually returned again. 6 weekly injections hydrocortisone with once again marked improvement.

Follow - Up:

1 month.