EFFECT OF SYNOVECTOMY ON THE CLEARANCE OF RADIOACTIVE XENON (^{133}Xe) FROM THE KNEE JOINT OF PATIENTS WITH RHEUMATOID ARTHRITIS

W. CARSON DICK, A. SHENKIN, P. FREEMAN, G. NUKI, K. WHALEY and W. W. BUCHANAN,
GLASGOW, SCOTLAND

The rate of clearance of radioactive xenon (^{133}Xe) from a joint (St Onge, Dick, Bell and Boyle 1968*a*; Dick, Whaley, St Onge, Downie, Boyle, Nuki, Gillespie and Buchanan 1970*b*) has been shown to reflect the degree of inflammatory involvement of the joint at the time of study, and has been used to measure synovial blood flow in the human knee (St Onge, Dick, Boyle, Jasani, Whaley, Pack and Buchanan 1968*b*; Dick, St Onge, Gillespie, Downie, Nuki, Gordon, Whaley, Boyle and Buchanan 1970*a*). We have investigated the effect of synovectomy on the synovial blood flow measured by the rate of clearance of ^{133}Xe from the human knee.

CLINICAL MATERIAL

Two groups of patients were studied. The first group, comprising eight patients with "classical" rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox and Jessar 1956) had ^{133}Xe studies performed before synovectomy of the knee, at one to three months after synovectomy, and at one year after operation. The mean age of these patients was 52.4 years (range thirty-three to sixty-one years) and five were male.

The second group, comprising twenty-one patients with "definite" or "classical" rheumatoid arthritis (Ropes and colleagues 1956), had ^{133}Xe studies performed between two and three years (mean 2.9 years) after synovectomy of the knee. All these patients had positive sheep cell agglutination tests (Ziff 1957) and in all, radiographs of the knees showed articular erosions. Sixteen were women and the mean age was 54.6 years (range twenty-six to seventy-one years). All the women were post menopausal.

TECHNIQUE OF OPERATION

Synovectomy was carried out with pneumatic tourniquet control through an elongated medial parapatellar incision. The synovium and menisci were removed, and the cruciate and collateral ligaments and the popliteus tendon were cleared of granulation tissue. Synovium from the back of the joint was removed with the knee fully flexed. The patella was left intact in all cases. The joint was closed in two layers with a suction drain and a plaster was applied. The knee was manipulated at two weeks under general anaesthesia.

CLINICAL ASSESSMENT OF THE KNEE JOINT

The degree of inflammatory involvement of the joint at the time of the study was estimated before the ^{133}Xe studies. A history of pain and of stiffness was elicited and graded. The knee was then subjected to firm pressure over the joint margin and the response graded. Finally, the degree of swelling was estimated subjectively and graded. Grading in all cases was on a 0 to 3 basis, where 0="absent", 1="slight", 2="moderate" and 3="severe". All clinical examinations were performed by one observer (C. D.).

Each patient was asked whether the result of the operation was "excellent", "satisfactory", "poor" or "bad".

¹³³Xe STUDIES

With full aseptic precautions approximately 10 μ Ci of ¹³³Xe in 1 millilitre of sterile saline were injected into the knee joint by a lateral infrapatellar approach. Precautions were taken to avoid the presence of air bubbles in the syringe since ¹³³Xe is highly soluble in air, and before the introduction of the isotope into the joint cavity an attempt was made to aspirate the joint completely.

After the injection the patient lay supine with the knee extended and immobilised with sandbags. A collimated sodium iodide scintillation crystal (3.75 $\times$ 2.5 centimetres) connected to an ECHO scaler (type H530G) was positioned six inches from the medial aspect of the joint using the upper border of the patella as a reference point. Counts per minute were recorded manually from five to thirty-five minutes following the injection and the background, which was of the order of 5 per cent of the count rate, was subtracted. The results were then plotted on semi-logarithmic graph paper as a function of time. In all cases the results could be described by a single exponential function. Throughout these studies the room temperature remained between 18 and 21 degrees Centigrade and an extraction fan was in operation to reduce the concentration in the air of the radioactive gas exhaled by the patient.

SYNOVIAL BLOOD FLOW

The method of expressing the results in terms of blood flow (millilitre per 100 millilitres per minute) (St Onge and colleagues 1968*b*, Dick and colleagues 1970*a*) is based on the work of Kety (1949) which was subsequently modified to apply to ¹³³Xe by Lassen, Lindbjerg and Munck (1964) who measured muscle blood flow in this way. The method employs the relationship:

$$\text{S.B.F.} = \kappa \cdot \lambda \cdot 100 \text{ millilitres per 100 millilitres per minute}$$

where S.B.F. = synovial blood flow

λ = the partition coefficient of ¹³³Xe for synovial tissue with respect to blood

and κ = the clearance constant.

The partition coefficient of ¹³³Xe for synovial tissue with respect to blood has been measured in several excised homogenised samples of rheumatoid synovial tissue obtained at synovectomy and gave a mean value of 1 (Dick and colleagues 1970*a*). The clearance constant

(κ) = $\frac{0.693}{T_{\frac{1}{2}}}$ where $T_{\frac{1}{2}}$ is the halving time of the disappearance of ¹³³Xe from the joint. Since the semilog plots of the results were monoexponential, $T_{\frac{1}{2}}$ values could be readily obtained from the graph.

RESULTS

Group 1—Figure 1 shows the synovial blood flow values obtained in eight patients with rheumatoid arthritis before, one to three months after, and one year after synovectomy. It can be seen that the values one to three months after operation (mean $0.87 \pm \text{S.E.M. } 0.09 \text{ ml./100 ml./min.}$) are significantly lower ($p < 0.05$) than the values obtained before operation (mean $1.41 \pm \text{S.E.M. } 0.25 \text{ ml./100 ml./min.}$). However, the values obtained one year after operation (mean $1.27 \pm \text{S.E.M. } 0.34 \text{ ml./100 ml./min.}$) did not differ significantly ($p < 0.4$) from the values obtained before operation. There was no significant difference between the values obtained one to three months and one year after operation. The test of significance employed was the paired student *t*-test. All eight patients reported the results of their operation as being "satisfactory".

Group 2—Figure 2 shows the synovial blood flow values obtained when ¹³³Xe studies were performed two to three years after synovectomy in twenty-one patients with rheumatoid arthritis. Included for comparison are the synovial blood flow values obtained previously (Dick and colleagues 1970*b*) in a group of twelve healthy male volunteers (aged twenty-two to twenty-six years) and the synovial blood flow values, also obtained previously (Dick and

colleagues 1970b) in a group of forty-three patients with rheumatoid arthritis. These forty-three patients had "definite" or "classical" rheumatoid arthritis and all had active inflammatory involvement of the knee joint with articular erosions at the time of study. None had been subjected to synovectomy. It can be seen that the synovial blood flow values obtained in the twenty-one operated knees (mean $1.97 \pm \text{S.E.M. } 0.23 \text{ ml./100 ml./min.}$) were similar to those obtained in the group of forty-three patients with rheumatoid arthritis (mean $1.56 \pm \text{S.E.M. } 0.12 \text{ ml./100 ml./min.}$) and differ markedly from the values obtained in healthy subjects (mean $0.46 \pm \text{S.E.M. } 0.08 \text{ ml./100 ml./min.}$). More refined statistical evaluation is not justified because these groups of patients are not matched for clinical involvement of the knee (knee score), although both groups satisfy the criteria for "definite" or "classical" rheumatoid arthritis.

FIG. 1
Synovial blood flow before and after synovectomy (eight patients).

FIG. 2
Comparison between synovial blood flows in healthy patients, in patients with rheumatoid arthritis and in patients with rheumatoid arthritis after synovectomy.

The relationship between the clinical index of inflammatory involvement of the knee and the relevant $T\frac{1}{2}$ value was analysed. The correlation coefficient ($r=0.32$) shows that there was no significant correlation between these parameters.

Four of these patients considered that the result of their operation was "poor", the remaining seventeen recording the result as being "satisfactory".

DISCUSSION

"As long as this proof is lacking we shall, in my opinion, have to regard this treatment (synovectomy) like all others in rheumatoid arthritis as an empirical one, and we shall have to

discuss the best way to obtain evidence of the influence of this procedure on the natural history of the disease" (Goslings 1969).

The clinical results of synovectomy of the knee are well documented (Steindler 1925; Wolcott 1927; Heyman 1928; Inge 1938; Ghormley and Cameron 1941; London 1955; Carruthers 1960; Aidem and Baker 1964; Gariépy, Demers and Laurin 1966; Marmor 1966; Stevens and Whitefield 1966; Vainio 1966; Barnes and Mason 1967; Brånemark, Ekholm, Goldie and Lindström 1967; Lembo 1967; Mikkelsen 1967; Ramadier, Achach and Courbon 1967) and have been recently reviewed by Paradies (1969). Most series record a "satisfactory" figure of over 80 per cent in terms of pain relief, although a variable degree of reduction in range of motion is recorded in a significant percentage of cases. Paradies (1969) recorded a progressive diminution in the percentage of "satisfactory" results as the length of follow-up increased. Thus, at two years, 65 per cent of results in his series were "satisfactory", but at three years only 40 per cent remained so. The results in a series which included long-term follow-ups (London 1955) also seem to demonstrate a similar tendency to recurrence of disease activity with increasing time after operation. Thus, there is some evidence to suggest recurrence of disease activity following synovectomy of the knee.

Experimental synovectomy (Key 1925) has been less intensively studied. Suleimanov (1964) showed that granulation tissue, with disturbed vascularity, grew after synovectomy in experimental animals. Lindström (1966) showed that after "atraumatic" synovectomy in rabbits complete regeneration of normal tissue could occur but in "traumatic" cases granulation tissue with wide tortuous blood vessels grew in. The caloric response in traumatic cases was abnormal. Brånemark and colleagues (1967) demonstrated abnormal tissue after synovectomy and Mitchell and Cruess (1967), using tritiated thymidine, showed that metaplasia of existing mesenchyme, rather than hyperplasia of remaining synovial tissue, contributed to the regrowth of villi in a period of thirty days after synovectomy in rabbits.

However, some workers (Marmor 1966) have presented evidence that regenerated synovium and its vasculature may be normal in human subjects. Thus it seemed reasonable to study the effect of synovectomy on the clearance of ^{133}Xe which provides a measure of blood flow.

That the clearance of intra-articularly administered ^{133}Xe from the joint is a function of effluent blood flow in healthy subjects and in patients with various arthritides has been demonstrated (Dick and colleagues 1970a, St Onge and colleagues 1968b). Is this so in the knee after synovectomy? In the patients whom we studied the pattern of clearance could be described by a single exponential function, indicating that the isotope was still being cleared from the joint. An experiment performed during five ^{133}Xe studies demonstrated that the isotope was not clearing from the synovial epiphysial system (Davies and Edwards 1948) to the nutrient vessels of bone (Fig. 3). After fifteen minutes, by which time the rate of clearance had been established, a narrow tourniquet placed immediately above the knee was inflated to a pressure midway between the systolic and diastolic blood pressures of the patient. At that point the clearance of the isotope stopped and, when the tourniquet was released five minutes later, the clearance recommenced at the initial rate. The $T_{\frac{1}{2}}$ values before and after the application of the tourniquet were similar (the standard error of the difference was 0.18 minutes). Thus the isotope was not being cleared through the nutrient vessels of bone in these patients, since drainage by these vessels would not have been affected by the application of the tourniquet. The fibrous capsule of the joint has a blood supply separate from that of the synovial tissue (Brånemark and Goldie 1969) and therefore it is difficult to escape the conclusion that the ^{133}Xe is being cleared by blood vessels in the regenerated "synovial tissue".

The results of this study are of some interest. The blood flow values one to three months after synovectomy were significantly lower than the values before operation, presumably indicating a reduction in vascularity of the regenerated tissue after operation. However, the results one year after operation had returned to a level which did not differ significantly from

the values before operation. This may indicate that synovial regeneration with abnormal vessels had occurred by that time although it is interesting to note that all these patients reported the result of their operation as being "satisfactory". Unfortunately the number studied is small, and firm conclusions are not justified.

The values obtained for blood flow in the second group of patients are clearly different from those obtained in healthy joints. It is interesting to note how well they accord with values obtained for patients with rheumatoid arthritis who had not been subjected to synovectomy. The forty-three values for patients with rheumatoid arthritis were obtained

FIG. 3
Effect of tourniquet on clearance of ^{133}Xe from the knee.

simply by studying every patient suffering from "classical" or "definite" rheumatoid arthritis with clinical involvement of the knee joint who came to the out-patient department of this hospital between September 1967 and February 1968. The clinical knee score was estimated in all these cases in the same manner and by the same physician (C. D.) who examined clinically the knee joints of the twenty-one patients who had a synovectomy of the knee. In the case of forty-three patients the correlation coefficient between the clinical knee score and the relevant $T_{1/2}$ values was 0.76 (Dick and colleagues 1970b). However, in the case of the twenty-one knees subjected to synovectomy (Fig. 3) the correlation coefficient was 0.32. Although for the reasons mentioned above refined statistical analysis of these two figures is not valid, the difference between a good correlation in the one case and none at all in the other is sufficient to suggest that a meaningful difference does exist. However, the reason for this discrepancy is obscure. It may be that abnormalities in the regrowth of the nerve supply after synovectomy may have an effect on the clinical score after operation. However, there is insufficient evidence on this point at present.

Thus in this paper we report ^{133}Xe clearance studies as a measure of blood flow in two groups of patients. In the first group blood flow fell significantly one to three months after synovectomy but returned to its former level after a year. These patients considered the results of their operation to be "satisfactory". In the second group of patients blood flow values were measured two to three years after synovectomy. These values were noted to be markedly different from values obtained in normal subjects and to fall within the range of values found

in patients with rheumatoid arthritis. Seventeen of these patients considered that the result of their operation was "satisfactory" and four recorded the result as "poor".

These isotope studies suggest that the operation of synovectomy has a limited "life span". This is in accord with the clinical findings of Paradies (1969) and of London (1955). It is likely that the regrowth of synovium with abnormal vessels occurs early, but that clinical deterioration takes rather longer. It will be interesting to see, in long-term follow-up studies, whether the timing and severity of clinical deterioration is predictable from the blood flow values.

SUMMARY

1. ^{133}Xe clearance rates as a measure of blood flow were determined in the knees of two groups of patients.
2. In the first group eight patients with rheumatoid arthritis were studied before, three months after and one year after synovectomy. Blood flow values were significantly lower three months after operation but the values recorded one year after operation did not differ significantly from those before operation.
3. In the second group (twenty-one patients with rheumatoid arthritis) blood flow values were determined two to three years after synovectomy. The values obtained differed from those obtained in normal joints and fell within the range of values obtained in forty-three patients with rheumatoid arthritis who did not have synovectomy.

This work would not have been possible without the support of the Arthritis and Rheumatism Council for Research in Great Britain. The isotope counting equipment was provided by the National Fund for Research into Crippling Diseases. One of us (G. N.) is a Ciba Research Fellow.

REFERENCES

- AIDEM, H. P., and BAKER, L. D. (1964): Synovectomy of the Knee Joint in Rheumatoid Arthritis. *Journal of the American Medical Association*, **187**, 4.
- BARNES, C. G., and MASON, R. M. (1967): Synovectomy of the Knee Joint in Rheumatoid Arthritis. *Annals of Physical Medicine*, **9**, 83.
- BRÄNEMARK, P.-I., EKHOLM, R., GOLDIE, I., and LINDSTRÖM, J. (1967): Synovectomy in Rheumatoid Arthritis—Experimental Biological and Clinical Aspects. *Acta Rheumatologica Scandinavica*, **13**, 161.
- BRÄNEMARK, P.-I., and GOLDIE, I. (1969): Physiologic Aspects on the Timing of Synovectomy in Rheumatoid Arthritis. In *Early Synovectomy in Rheumatoid Arthritis*, p. 11. *Proceedings of the Symposium on Early Synovectomy in Rheumatoid Arthritis*. Amsterdam, The Netherlands, April 1967. Edited by W. Hijmans, W. D. Paul and H. Herschel. Amsterdam: Excerpta Medica Foundation.
- CARRUTHERS, F. W. (1960): Debridement and Synovectomy Knee Joint. *Western Journal of Surgery, Obstetrics and Gynecology*, **68**, 382.
- DAVIES, D. V., and EDWARDS, D. A. W. (1948): The Blood Supply of the Synovial Membrane and Intra-articular Structures. *Annals of the Royal College of Surgeons of England*, **2**, 142.
- DICK, C., ST ONGE, R. A., GILLESPIE, F. C., DOWNIE, W. W., NUKI, G., GORDON, I., WHALEY, K., BOYLE, J. A., and BUCHANAN, W. W. (1970a): Measurement of Synovial Blood Flow in Man using Xenon (^{133}Xe). *Annals of the Rheumatic Diseases*, **29**, No. 2, March.
- DICK, C., WHALEY, K., ST ONGE, R. A., DOWNIE, W. W., BOYLE, J. A., NUKI, G., GILLESPIE, F. C., and BUCHANAN, W. W. (1970b): Clinical Studies on Inflammation in Human Knee Joints: Xenon (^{133}Xe) Clearances Correlated with Clinical Assessment in Various Arthritides and Studies on the Effect of Intra-articularly Administered Hydro-cortisone in Rheumatoid Arthritis. *Clinical Science*, **38**, 123.
- GARIÉPY, R., DEMERS, R., and LAURIN, C. A. (1966): The Prophylactic Effect of Synovectomy of the Knee in Rheumatoid Arthritis. *Canadian Medical Association Journal*, **94**, 1349.
- GHORMLEY, R. K., and CAMERON, D. M. (1941): End Results of Synovectomy of the Knee Joint. *American Journal of Surgery*, N.S. **53**, 455.
- GOSLINGS, J. (1969): In *Early Synovectomy in Rheumatoid Arthritis*, p. 13. *Proceedings of the Symposium on Early Synovectomy in Rheumatoid Arthritis*. Amsterdam, The Netherlands, April 1967. Edited by W. Hijmans, W. D. Paul and H. Herschel. Amsterdam: Excerpta Medica Foundation.
- HEYMAN, C. H. (1928): Synovectomy of the Knee Joint. *Surgery, Gynecology and Obstetrics*, **46**, 127.
- INGE, G. A. L. (1938): Eighty-six Cases of Chronic Synovitis of Knee Joint Treated by Synovectomy. *Journal of the American Medical Association*, **111**, 2451.
- KETY, S. S. (1949): Measurement of Regional Circulation by the Local Clearance of Radioactive Sodium. *American Heart Journal*, **38**, 321.

- KEY, J. A. (1925): The Reformation of Synovial Membrane in the Knees of Rabbits after Synovectomy. *Journal of Bone and Joint Surgery*, **7**, 793.
- LASSEN, N. A., LINDBJERG, J., and MUNCK, O. (1964): Measurement of Blood-Flow through Skeletal Muscle by the Intramuscular Injection of Xenon-133. *Lancet*, **i**, 686.
- LEMBO, E. J. A. (1967): Sinovectomia en la artritis reumatoidea de rodilla. *Boletines y trabajos de la Sociedad argentina de ortopedia y traumatologia*, **32**, 194.
- LINDSTRÖM, J. (1966): Studies in Experimental Synovectomy. *Acta Rheumatologica Scandinavica*, **12**, 175.
- LONDON, P. S. (1955): Synovectomy of the Knee in Rheumatoid Arthritis. *Journal of Bone and Joint Surgery*, **37-B**, 392.
- MARMOR, L. (1966): Surgery of the Rheumatoid Knee. *American Journal of Surgery*, **111**, 211.
- MIKKELSEN, O. A. (1967): Residiv etter knesynovectomi ved rheumatoid arthritt. *Nordisk Medicin*, **78**, 1483.
- MITCHELL, N. S., and CRUESS, R. L. (1967): Synovial Regeneration after Synovectomy. *Canadian Journal of Surgery*, **10**, 234.
- PARADIES, L. H. (1969): Synovectomy of the Knee. In *Early Synovectomy in Rheumatoid Arthritis*, p. 129. *Proceedings of the Symposium on Early Synovectomy in Rheumatoid Arthritis*. Amsterdam, The Netherlands, April 1967. Edited by W. Hijmans, W. D. Paul and H. Herschel. Amsterdam: Excerpta Medica Foundation.
- RAMADIER, J. O., ACHACH, P., and COURBON, S. (1967): La synovectomie du genou dans le rhumatisme inflammatoire technique opératoire—évolution post-opératoire. *Revue du Rhumatisme*, **34**, 413.
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., and JESSAR, R. A. (1956): Proposed Diagnostic Criteria for Rheumatoid Arthritis. *Bulletin on Rheumatic Diseases*, **7**, 121.
- ST ONGE, R. A., DICK, W. C., BELL, G., and BOYLE, J. A. (1968a): Radioactive Xenon (¹³³Xe) Disappearance Rates from the Synovial Cavity of the Human Knee Joint in Normal and Arthritic Subjects. *Annals of the Rheumatic Diseases*, **27**, 163.
- ST ONGE, R. A., DICK, W. C., BOYLE, J. A., JASANI, M. K., WALEY, K., PACK, A. I., and BUCHANAN, W. W. (1968b): Measurement of Synovial Blood Flow in the Human Knee Joint. *Arthritis and Rheumatism*, **11**, 508.
- STEINDLER, A. (1925): Synovectomy and Fat Pad Removal in the Knee. *Journal of the American Medical Association*, **84**, 16.
- STEVENS, J., and WHITEFIELD, G. A. (1966): Synovectomy of the Knee in Rheumatoid Arthritis. *Annals of the Rheumatic Diseases*, **25**, 214.
- SULEIMANOV, I. (1964): Vosstanovlenie sinovial'noi obolochki i osobennostee vaskuliarizatsii posle sinovéktomii kolennogo sustava v eksperimente. *Ortopediia, Travmatologiya i Protezirovaniye*, **25**, 43.
- VAINIO, K. (1966): Synovectomie du genou dans les arthrites rhumatismales. *Médecine et Hygiène*, **24**, 616.
- WOLCOTT, W. E. (1927): Regeneration of the Synovial Membrane following Typical Synovectomy. *Journal of Bone and Joint Surgery*, **9**, 67.
- ZIFF, M. (1957): The Agglutination Reaction in Rheumatoid Arthritis. *Journal of Chronic Diseases*, **5**, 644.