Synovial perfusion of clinically normal knee joints in patients with rheumatoid arthritis

An isotope study

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In recent studies on the pathogenesis of rheumatoid joint inflammation, Hollander and his co-workers have injected immune gamma globulin molecules or IgG fragments isolated from serum into the clinically uninvolved knees of patients with definite rheumatoid arthritis (Restifo, Lussier, Rawson, Rockey, and Hollander, 1965; Hollander, Fudenberg, Rawson, Abelson and Torralba, 1966; Quismorio, Owen, Rawson, Abelson, and Hollander, 1968; Hollander and Rawson, 1968). Definite inflammatory reactions occurred after the injections, and the suggestion was made that fragments related to the IgG molecule might form the antigen which induces rheumatoid factor antibody and reacts with it in rheumatoid arthritis.

The question may be posed whether a knee 'not clinically involved' is also a joint unaffected by rheumatoid pathology. Sokoloff and Gleason (1954) demonstrated, in a small series of necropsy examinations of rheumatoid patients, that the sterno-clavicular joint showed histological changes characteristic of rheumatoid arthritis, although in no case was there a record of the joint having been involved clinically. However, it was not indicated that evidence of rheumatoid activity had been specifically sought in the sterno-clavicular joints during life and, as suggested by the authors themselves, casual clinical examination is unlikely to elicit involvement of these joints when arthritis of other larger and more mobile joints is attracting attention.

It was, therefore, thought of interest to investigate patients with 'classical' rheumatoid arthritis in whom the knee joints, on careful clinical examination, did not appear to be affected by the rheumatoid process.

Several workers (*e.g.* Sokoloff and Bunim, 1957; Bränemark, Lindström, Jonsson, Laine, and Vainio, 1963; Kulka, 1964) have presented evidence which suggests that an early feature of the pathology in rheumatoid arthritis is an abnormality of the small

blood vessels. It thus seemed appropriate to employ a method applicable to the study of small blood vessels.

The method used was an isotope clearance technique using radioactive xenon (^{133}Xe). The rate of disappearance of radioactivity from the knee after intra-articular injection of ^{133}Xe is believed to provide a reproducible method of measuring perfusion of synovial tissues (Dick, Whaley, St. Onge, Downie, Boyle, Nuki, Gillespie, and Buchanan, 1970).

Patients studied

22 patients were studied. All had 'classical' (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) sero-positive rheumatoid arthritis with erosions present on radiographs of several joints, and all had had peripheral symmetrical polyarthritis for more than 6 months. There were sixteen female and six male patients and their ages ranged from 35 to 66 years.

The joints studied were considered to be 'not involved' clinically. None of the patients had had symptoms referable to their knees at any time. On careful examination of the knees, there was no evidence of synovial thickening or abnormal warmth of the overlying skin, and there was no joint tenderness or restriction of joint movements. All the patients had normal radiographs of the knees.

Method of measuring ^{133}Xe clearance

In each patient xenon studies were carried out on one knee. The patient rested on a couch in a room at a fairly constant temperature (18° to $24^{\circ}\text{C}.$). Approximately $10\ \mu\text{Ci}$ of ^{133}Xe in 1 ml. 0.9 per cent. sterile sodium chloride solution were introduced into the knee joint by a medial parapatellar injection. Routine aseptic technique was observed for the articular injection: infiltration of local anaesthetic was not employed. The knee was rested in the extended position and supported on each side by sandbags to ensure immobility.

A detector head with collimated sodium iodide scintillation crystal and photomultiplier (Ekco H.R. gamma detector Type M5400 A/1) was placed over the joint and connected to an amplifier, pulse height analyser Ekco M5010 (suitably adjusted for ¹³³Xe), and digital rate-meter Ekco M5183A.

Counts per unit time were graphed by a direct writing pen recorder for from 5 to 40 minutes after the injection. The background count amounted to approximately 1 per cent. of the count rate. The results were then plotted on semi-logarithmic graph paper as a function of time, and the halving-time (T_½) of the ¹³³Xe clearance from the knee obtained from the graph, which was mono-exponential.

Derivation of synovial perfusion

In the times required for clearance of the xenon from the knee, the diffusion of ¹³³Xe into the synovial blood vessels should not be a limiting factor in the clearance rate (Kety, 1949; Perl, 1962). Experiments in dogs with the limb isolated from the body except for the femoral artery and vein have suggested that the clearance of xenon occurs primarily by venous channels, and in studies on patients, a tourniquet inflated around the thigh was shown to arrest the clearance of ¹³³Xe from the knee, indicating that routes through bone were not important (Dick, St. Onge, Gillespie, Downie, Nuki, Gordon, Whaley, Boyle, and Buchanan, 1970).

The synovial perfusion can be calculated by the methods described by Kety (1949), Thorburn, Kopald, Hert, Hollenberg, O'Morchoe, and Barger (1963), and Lassen, Lindbjerg, and Munck (1964) for blood flow measurements, and is given by the formula:

Synovial perfusion = $\frac{69 \cdot 3 \lambda \text{ ml.}}{T_{\frac{1}{2}}} / 100 \text{ ml. synovial tissue/min.,}$

where T_½ is the halving time of the ¹³³Xe clearance in minutes, and λ is the partition coefficient (Conn, 1961) of ¹³³Xe between synovial tissue and blood, which is approximately 1·0 (Dick, St. Onge, and others, 1970).

Results (Table 1)

In seven patients the synovial perfusion exceeded 1 ml./100 ml./min. (T_½ values < 70 min.). In a further five patients the values obtained were between 0·5 and 1 ml./100 ml./min. (T_½ values from 82 to 106 min.).

The Figure shows the distribution of the T_½ values obtained in the clinically 'not involved' joints of rheumatoid patients and also the T_½ values for two other groups, namely an unselected series of 82 patients suffering from 'classical' or 'definite' rheumatoid arthritis attending the Centre for Rheumatic Diseases, and a series of 40 volunteers who had no evidence of joint disease.

Table I *The T_½ values and synovial perfusions recorded, using ¹³³Xe, in 22 knees not clinically involved in patients with rheumatoid arthritis. Also shown are the mean values and ranges obtained in forty knees of normal subjects and 82 clinically involved knees of rheumatoid patients.*

Patient no.	T _½ value (min.)	Synovial perfusion (ml./100 ml./min.)
1	35	1·98
2	38	1·82
3	46	1·51
4	50	1·39
5	52	1·33
6	56	1·24
7	68	1·02
8	82	0·85
9	92	0·75
10	95	0·73
11	105	0·66
12	106	0·65
13	150	0·46
14	160	0·43
15	180	0·39
16	190	0·36
17	240	0·29
18	260	0·27
19	320	0·22
20	325	0·21
21	360	0·19
22	465	0·15
Forty normal subjects	Mean 252 Range 95-630	Mean 0·28 Range 0·11-0·73
82 rheumatoid patients (knees clinically involved)	Mean 43 Range 10-134	Mean 1·61 Range 0·52-6·93

FIGURE Distribution of $T_{1/2}$ values of ^{133}Xe clearance from the knee in three groups of subjects.

The range of $T_{1/2}$ values in the rheumatoid patients was 10 to 134 min. (synovial perfusion 0.52 to 6.93 ml./100 ml./min.). The range in the normal joints was 95 to 630 min. (synovial perfusion 0.11 to 0.73 ml./100 ml./min.). In the rheumatoid group only two patients out of 82 had a $T_{1/2}$ value in excess of 100 minutes, and in the normal group only one knee out of forty had a $T_{1/2}$ of less than 100 minutes.

Discussion

Rheumatoid arthritis is a polyarthritis and the distribution of clinically involved joints in any particular patient appears to be quite random, although certain joints are affected more frequently than others. Joints which do not appear to be inflamed at one examination may often be involved at a later date and, though perhaps less commonly, joints obviously inflamed on one occasion may subsequently appear to be quiescent and indeed quite normal. The question, therefore, arises whether any joint lined by synovium can be considered to be 'not involved' in rheumatoid arthritis. No histological information on this point is known to the authors.

The results obtained in the clinically normal joints of patients with 'classical' rheumatoid arthritis show that, in seven out of the 22 knees examined, the synovial perfusion was markedly abnormal, the levels being similar to those found in a series of clinically affected joints in rheumatoid patients. In a further five knees, the synovial perfusion was greater than the values commonly found in normal subjects.

All our patients with 'classical' rheumatoid arthritis and clinically uninvolved knees were not studied in this investigation; the 22 who were examined were not chosen for any reason other than convenience and availability. In selecting only

patients with 'classical' rheumatoid arthritis, however, there was likely to be a bias in favour of more advanced and generalized joint involvement.

Dick, Whaley, and others (1970) demonstrated a correlation between a clinical index of inflammation of knee joints and the rate of ^{133}Xe clearance ($r = 0.75$). The present study shows, however, that a joint which appears to be normal clinically may show evidence of an abnormally high synovial perfusion. It cannot, therefore, be assumed that such joints are not involved by rheumatoid inflammation. Histological studies, which would no doubt provide further information, have not been performed as synovial biopsy of these symptomless joints was considered to be unjustifiable.

Summary

22 clinically normal knee joints in patients with sero-positive rheumatoid arthritis have been investigated by radioactive xenon clearance methods. The synovial perfusions in seven knees was found to be in the range usually associated with clinically involved joints in rheumatoid arthritis, and in a further five cases the perfusion exceeded the usual values previously found to be associated with normal joints. The conclusion drawn is that care must be exercised in considering any particular joint to be 'not involved' in rheumatoid arthritis; those that appear not to be involved by clinical and radiological criteria may yet show abnormal vascular function, which may be an early feature of the disease process.

The authors wish to thank Miss Charlotte McShane for preparing the typescript and the Medical Illustration Department of the Western Infirmary, Glasgow, for the preparation of the Figure.

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