RADIOSODIUM CLEARANCE FROM THE KNEE JOINT IN RHEUMATOID ARTHRITIS

BY

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The rate of removal of radioactive sodium from a tissue has been shown by Kety (1949) to be a quantitative measure of the local circulation. This technique has been used extensively to study circulation in skin, subcutaneous tissue, and muscle (McGirr, 1952), and it has been applied to the study of the normal human knee joint (Jacox, Johnson, and Koontz, 1952; Harris and Millard, 1956). In our previous study, simple exponential curves were consistently found. When the counting rate was plotted semi-logarithmically against time, straight lines were obtained for periods up to 60 minutes (Fig. 1). For a series of 23 normal knees, the clearance constant ranged between 0.025-0.080, with a mean value of 0.050 (S.D. 0.021). The effects of manoeuvres likely to affect circulation in the joint (arterial and venous occlusion, deep heating with diathermy, and exercise) were studied. In ten subjects the measurement was repeated at an interval varying from 1 to 14 weeks, and these findings showed a close comparison in distribution values for the two groups, although individual knees showed a difference of as much as 100 per cent. on different occasions. The groups had similar mean values (0.050; S.D. 0.017; 0.054; S.D. 0.019).

From this experiment it was concluded that the method could be used usefully in studying circulation in the knee joint, and that in the normal knee the results are reasonably reliable and reproducible.

We have now applied the technique to the study of the knee joint in patients suffering from rheumatoid arthritis, by which we mean polyarthritis affecting three or more joints for at least 3 months without other discernible cause.

Method

The subjects were all in-patients in the rehabilitation unit, with an age range of 20 to 68 years.

The degree of disease activity in the knee joint was graded on a clinical assessment, from 0-3, as follows:

0 = No involvement.

1 = Minor involvement (Tenderness +; pain on use ±; thickening ±; effusion ±).

2 = Moderate involvement (Heat +; tenderness +; or ++; pain at rest ±; pain on use + or ++; thickening +; effusion −, +, or ++).

3 = Severe involvement (Heat +; tenderness ++; pain at rest +, or +++; pain on use + or +++; thickening +; effusion + or ++).

Fig. 1.—Clearance curve from the knee joint of a normal subject showing a straight line for over 50 min.
The degree of effusion present was also graded 0-3, as follows (modified from Millard and Parry, 1953):

- 0 = No effusion or thickening.
- 1 = Just perceptible trace of fluid; or thickening.
- 2 = Clearly visible effusion.
- 3 = Moderate or large effusion.

The erythrocyte sedimentation rate (Westergren) was also noted.

The subject rested on a couch for 30 minutes with the legs horizontal, comfortably supported in plaster back splints. The room temperature remained constant during each observation, but varied on different days between 19-22°C. Between 0.2-0.5 ml. isotonic saline, containing 5-10 microcuries 24 Na was injected rapidly into the knee joint through a 2-in. long, 26-gauge hypodermic needle, with the usual aseptic precautions. The approach was retropatellar, from behind the medial border. No local anaesthetic was used. In the presence of an effusion the injection was technically very simple. No pain was experienced and in only two out of about 100 injections was it considered that the injection had not been placed intra-articularly. Fluid was not aspirated. Two unshielded scintillation counters were arranged at either side of the knee joint, to give a wide-field view of the joint. Each was connected to a rate-meter. The initial counting rate was about 1,000 per second. The counting rate of each counter was recorded at minute intervals to background level. The sum of each pair of readings, less the background count, was plotted semi-logarithmically against time. The purpose of the double counting system was to compensate for any movement of the joint or sodium shift within the joint, and the composite count gave a smoother curve than either of its components (Harris and Millard, 1956). This plot gives a fairly straight line. From the graph, the clearance constant, K, was found where

\[
K = \frac{\log C_1 - \log C_2}{0.4343(t_1 - t_2)},
\]

where \(C_1\) and \(C_2\) are counting rates at times \(t_1\) and \(t_2\) respectively.

In addition to single clearance studies, the sodium clearance measurements were repeated after an interval in some knees, and also at a certain interval after intra-articular hydrocortisone injections.

**Results**

Radiosodium clearance measurements were made on 69 different knees. This includes five pairs of knees which were studied simultaneously by a single-counter technique. In 63 of the 69, a good single straight line was found. The six others showed a more complex curve which consisted of two dissimilar gradients. In five of the six, the gradient of the curve suddenly slowed between 14 to 22 minutes after injection, by about 50 per cent. The sixth subject showed a double curve with an increase in gradient of nearly 100 per cent. at 16 minutes. There was no obvious correlation of the double curve with either local disease activity or the grade of effusion present. (The initial portion of the curve has been used in calculating the clearance constant in these subjects.) We have not seen this complex curve in over 100 observations in a control group of fifty subjects who were either normal or suffering from a variety of non-rheumatoid diseases (ankylosing spondylitis, osteo-arthritis, neuropathic joints).

The clearance constant for the whole group varied considerably with a range between 0.020 and 0.191 (mean value 0.070, S.D. 0.040). This is much beyond the range for the normal non-arthritic knee.

**Correlation with Local Disease Activity.**—Table 1 shows clearly a close relation between the clearance rate and the degree of local activity of the disease—the more active the knee the higher the clearance rate of the group. However, individual knees may not show this and five out of the twelve knees graded as "severely involved" had values within the normal range. On the other hand no knees in rheumatoid subjects had abnormal values at Grades 0 and 1 (i.e. without clinical signs, or with only minor involvement). In Grade 2, 33 per cent. had clearance values higher than the range found in normal knee joints. These findings are brought out more clearly in Fig. 2 (opposite), which also includes the findings for fifty normal knees, from a control group of "non-rheumatic" subjects.

**Correlation with Effusion.**—By definition of our method of assessment, no subject with Grade 0 activity had an effusion, and all subjects with Grade 3 activity had effusions. Thus the likelihood of an effusion being present increased with the local

<table>
<thead>
<tr>
<th>State of Knee</th>
<th>Normal Controls</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>50</td>
<td>19</td>
<td>11</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>0.02-0.090</td>
<td>0.02-0.093</td>
<td>0.032-0.090</td>
<td>0.025-0.178</td>
<td>0.048-0.191</td>
</tr>
</tbody>
</table>

**Table 1**

CLEARANCE VALUES OF NORMAL AND RHEUMATOID KNEE JOINTS (GRADED 0-3 ACCORDING TO LOCAL DISEASE ACTIVITY)
activity grading. The only large effusions present were found in activity Groups 2 and 3. Fig. 3 correlates clearance value and effusion grading. When no effusion was present over 90 per cent. of the clearance constants fell within the normal range, and in Groups 1 and 3 approximately 20 to 25 per cent. of the clearance values were abnormally high. In Group 2 (moderate effusion), on the other hand, approximately 50 per cent. of the clearance constants were beyond the range of normal knees. It is therefore clear that the very large effusions are not associated with very high clearance values (Table II).

In considering the distribution of effusions in the disease activity groups, using the χ² formula, no significant correlation was found between the clearance constant and the grade of effusion except in disease activity Grade 2. In this group, of the eighteen subjects who had clearance constants within the range of normal (<0·090), ten had Grade 3 effusions, and four had Grade 2 effusions, whilst in the nine subjects with clearance values outside the range of normal, none had Grade 3 effusions and six had Grade 2 effusions. This difference is statistically significant (P>0·02).

These findings indicate that the presence of a large effusion may modify the rate of sodium clearance from the joint, or that the circulation of active joints with large effusions is reduced by comparison with similar joints with smaller effusions. The presence of a large or chronic effusion may also affect synovial permeability. It is probable also that the size of the effusion unduly influenced our clinical grading of the knee, the tendency being to give them too high an activity grading. In retrospect we consider that our activity index would have been more reliable had "effusion" been omitted.
Table III
CLEARANCE CONSTANT, K, OF FIVE PAIRS OF KNEES

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Measurement No.</th>
<th>Right K</th>
<th>Grade of Disease</th>
<th>Left K</th>
<th>Grade of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>0.065</td>
<td>0</td>
<td>0.060</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>0.065</td>
<td>0</td>
<td>0.093</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>0.102</td>
<td>3</td>
<td>0.117</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>0.185</td>
<td>3</td>
<td>0.059</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>0.048</td>
<td>0</td>
<td>0.034</td>
<td>0</td>
</tr>
</tbody>
</table>

Pairs of Knees.—The clearance from pairs of knees was measured simultaneously in five subjects by a single counter technique. Table III shows a clear correlation between local disease activity and clearance rate in the pairs of knees; where both knees were at the same clinical stage, clearance values were fairly symmetrical and within the appropriate range for the stage of activity. In pairs where one knee was more actively involved, that knee had the higher clearance constant.

Fig. 4 shows the clearance curves simultaneously recorded from the two knees of a single subject, each knee being at a different stage of clinical activity. The clearance constants are markedly different, being much higher in the more severely involved knee.

Repetition of Clearance Estimation.—The clearance was measured at intervals varying from 1 to 12 weeks in nine subjects. Table IV shows that the clearance constant varied considerably in three subjects who showed no obvious changes in the grade of local disease activity. Both large increases and large decreases were found (e.g. 0.178-0.105, and 0.026-0.126). Two subjects showed no major changes.

In the five subjects in whom clinical improvement of the joint was observed, sharp decreases in clearance were found. One of these subjects was followed over a longer period and the clearance was measured again when the knee was deteriorating; on this occasion the clearance constant was found to be markedly increased (Patient 6 in Table IV). As might be expected over this period (1 to 12 weeks)
RADIO SODIUM CLEARANCE FROM THE KNEE JOINT

the patients improved, and this is shown by a fall in the mean local activity grading in Table IV, from 1·9 to 1·44. In the same period there was a comparable fall in the mean clearance constant, from 0·106 to 0·074.

Intra-Articular Hydrocortisone.—In thirteen subjects the effect of hydrocortisone injections into the joint was studied. The clearance from the knee joint was first measured (and these values included in the main series), and immediately afterwards 50 mg. hydrocortisone acetate acid free was injected into the joint without a local anaesthetic. In four subjects 1,000 units "hyalase" were given at the same time. The clearance was measured again in one week. In one subject the measurement was made after 24 hours, and in this case a major fall in clearance from 0·178 to 0·048 coincided with a good clinical response (Fig. 5).

On the whole the second clearance constant was decreased in comparison with the initial value, although one subject showed a rise of over 100 per cent. (0·050 to 0·119) with no evidence of clinical deterioration in the knee; in fact the joint was clinically improved. Eight subjects showed changes of less than ±20 per cent., and the other four showed major decreases.

Table V shows, however, that in the three subjects who did not improve with the local hydrocortisone there were only small increases in the clearance constants. By contrast, the two subjects who were "much improved", both show major decreases in clearance.

General Activity of the Disease.—The erythrocyte sedimentation rate was recorded in all patients within one week of the sodium clearance measurement. This can be considered as a very approximate index of the general activity of the disease. Plotting erythrocyte sedimentation rate against the clearance constant gave a randomly scattered graph, with no

**TABLE V**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Measurement No.</th>
<th>Initial K</th>
<th>Interval (wks)</th>
<th>Second K</th>
<th>Clinical Result</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
<td>Grade of Activity</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>1</td>
<td>221</td>
<td>224</td>
<td>2</td>
<td>0·105</td>
<td>0·119</td>
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<tr>
<td>2</td>
<td>225</td>
<td>226</td>
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<td>0·048</td>
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<tr>
<td>3</td>
<td>228</td>
<td>231</td>
<td>3</td>
<td>0·076</td>
<td>0·068</td>
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<tr>
<td>4</td>
<td>229</td>
<td>230</td>
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<td>0·050</td>
<td>0·119</td>
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<td>6</td>
<td>227</td>
<td>233</td>
<td>2</td>
<td>0·045</td>
<td>0·039</td>
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<tr>
<td>7</td>
<td>236</td>
<td>241</td>
<td>3</td>
<td>0·090</td>
<td>0·047</td>
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<td>8</td>
<td>239</td>
<td>243</td>
<td>3</td>
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<td>0·045</td>
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<td>9</td>
<td>240</td>
<td>244</td>
<td>0</td>
<td>0·059</td>
<td>0·073</td>
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<tr>
<td>10</td>
<td>245*</td>
<td>247</td>
<td>3</td>
<td>0·067</td>
<td>0·025</td>
</tr>
<tr>
<td>11</td>
<td>246*</td>
<td>249</td>
<td>2</td>
<td>0·067</td>
<td>0·073</td>
</tr>
<tr>
<td>12</td>
<td>256*</td>
<td>253</td>
<td>2</td>
<td>0·039</td>
<td>0·033</td>
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<tr>
<td>13</td>
<td>251*</td>
<td>252</td>
<td>2</td>
<td>0·042</td>
<td>0·044</td>
</tr>
<tr>
<td>Mean</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0·076</td>
<td>0·058</td>
</tr>
</tbody>
</table>

* 1,000 units "hyalase" given simultaneously with the hydrocortisone.
statistically significant correlation, which suggests that the clearance depends on local factors in the joint and not on the general disease activity.

**Discussion**

The methods available for studying circulatory changes in joints are complicated and subject to criticism. The venous occlusion plethysmograph, with adrenaline iontophoresis to suppress skin circulation, is fairly satisfactory, but complicated in use (Bonney, Hughes, and Janus, 1952), and is difficult to use on painful joints. Extensive use has been made of intra-articular temperature measurements to study and compare changes in the knee joint in rheumatoid arthritis and osteo-arthritis (Hollander, Stoner, Brown, and De Moor, 1951; Hollander and Moore, 1956), and also to study the effect of intra-articular hydrocortisone in these conditions. The authors recognize the limitations of the method and the difficulty in interpreting results, and it has been shown by plethysmography (Bonney, Hughes, and Janus, 1952) that large alterations in blood flow can occur with only small changes in deep temperature, because of the stabilizing effect of the increased circulation at higher temperatures.

The radioactive sodium clearance technique is relatively convenient and simple, and we have shown in our earlier work (Harris and Millard, 1956) that the removal of sodium from the normal joint is influenced by factors which affect the blood supply of the joint. Ahlström, Gedda, and Hedberg (1956) have used the clearance of radioactive iodine-labelled serum albumin to study the difference between clinically normal and affected rheumatoid knee joints. Their results, using this large molecule, agree generally with ours, and, though the clearance values they found are much less than ours, the difference they found between active and inactive joints was similar to ours. They studied ten polyarthritics of varying degrees of activity, seven with and three without clinical changes in the knees. Between 2 and 22 mg. albumin, labelled with I\(^{131}\) and containing the equivalent of 15 to 20 microcuries, were injected intra-articularly and followed by a scintillation-counter and scaler. The clearance rate from the active knees was higher than that for normal knees. The highest clearance rate was found in a thickened knee without effusion in a subject with only a moderately raised erythrocyte sedimentation rate. They also studied the effects of intra-articular hydrocortisone in three subjects, and all showed a tendency to slow down towards normal values.

Our experiments clearly show that local factors in the joint itself, in contrast to the general state of the disease, are the major influences on the sodium clearance.

In the pairs of knees studied simultaneously when the knees were at different stages of local activity, the more severely involved knees showed the greater clearance values. Intra-articular hydrocortisone, which produces only localized clinical effects, usually reduced the sodium clearance. However, we have shown that the local sodium clearance may vary after an interval without any obvious change in the joint, and there is also a wide variation in clearance from joints at the same stage of clinical activity. Also three subjects showed a complex curve for which we can offer no explanation. These are important factors limiting the value of the method.

The results in general were much as expected. It is well known that the active rheumatoid joint has a hyperaemic synovial membrane and that after the intra-articular injection of hydrocortisone both this and the intra-articular temperature return towards normal levels. These facts, with our observations of the local as opposed to the systemic factors involved, indicate that the sodium clearance technique is chiefly useful in measuring the total circulation and blood supply of the joint.

**Summary**

(1) The rate of removal of radioactive sodium from the knee joint has been studied in 69 knees of patients with rheumatoid arthritis, defined as polyarthritis affecting three or more joints for at least 3 months without other discernible cause.

(2) The results show that, as in normal controls, the clearance from the joint is exponential; a single straight clearance line was obtained in 63 out of 69 experiments when the counting rate was plotted semi-logarithmically against time.

(3) The clearance rate was found to vary widely, the range in rheumatoid knees with little local disease activity or none being the same as in normal control knees.

- **Normal knees:** Mean K=0.051 (range 0.02 to 0.090).
- **Knees showing only minor disease activity:** Mean K=0.057 (range 0.032 to 0.090).

(4) The clearance rate for knees showing more severe local disease activity varied more widely and was generally higher.

- **Knees severely involved:** Mean K=0.106 (range 0.048 to 0.191).

(5) In subjects in whom the two knees were at different stages of disease activity, the sodium clearance was higher in the knee which was more severely involved.
The effect of intra-articular hydrocortisone on sodium clearance was studied in thirteen knees at intervals of from 1 to 14 days; in general a reduction in the clearance rate towards normal values was found.

The technique seems to be useful in studying circulatory changes in the knee joint, and could be used for screening potentially active drugs.

We wish to acknowledge the technical help given by Dr. Gilbert of the Christie Hospital, Manchester, the valuable criticism of Professor J. H. Kellgren, and the statistical advice given by Miss F. Bier of the Rheumatism Research Unit, University of Manchester.

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REFERENCES


Elimination of the radioactivity of sodium in the knee joint

**RÉSUMÉ**

1. Le taux d’élimination du sodium radioactif de l’articulation du genou fut étudié dans 69 genoux des maladies atteints d’arthrite rhumatismale, définie comme polyarthrite impliquant trois articulations ou plus, existant depuis au moins 3 mois et ne connaissant pas de cause apparente.

2. Les résultats montrent que l’élimination articulaire suit une courbe exponentielle, comme chez des témoins normaux; une seule ligne droite d’élimination fut obtenue dans 63 sur 69 épreuves par un tracé semi-logarithmique de la fréquence numérique en fonction du temps.

3. On a trouvé de grandes variations dans le taux d’élimination, les chiffres pour les genoux rhumatismes manifestant peu ou pas d’activité morbide étant les mêmes que ceux pour les genoux normaux.

4. Le taux d’élimination pour les genoux manifestant une activité morbide locale plus sévère était plus variable et généralement plus élevé.

Genoux sévèrement impliqués: Moyenne K = 0,0106, (étendue: 0,048-0,191).

5. Chez des sujets chez qui l’un des deux genoux était plus atteint que l’autre, l’élimination du sodium était plus intense dans l’articulation plus sévèrement impliquée.

6. On a étudié l’effet d’hédrocortisona intra-articulaire sur l’élimination du sodium dans treize genoux par intervalles de un a 14 jours; on a trouvé qu’en général le taux d’élimination tendait à diminuer et à revenir à des chiffres normaux.

7. Ce procédé paraît être utile dans l’étude des altérations de la circulation dans l’articulation du genou et pourrait être employé pour essayer des médicaments potentiellement actifs.

Eliminación del sodio radioactivo de la articulación de la rodilla en la artritis reumaatoide

**SUMARIO**

1. La tasa de eliminación del sodio radioactivo de la articulación de la rodilla fue estudiada en 69 rodillas de enfermos con artritis reumaatoide, definida como poliartritis implicando tres articulaciones o más, en existencia desde 3 meses al menos y no manifestando causa aparente.

2. Los resultados muestran que la eliminación articular sigue una curva exponencial, como en los testigos normales; se obtuvo una sola línea recta en 63 de los 69 experimentos por un trazado semi-logarítmico de la frecuencia numérica en función del tiempo.

3. Se encontraron grandes variaciones en la tasa de eliminación; las cifras para rodillas reumáticas con poca o ninguna actividad morbida fueron las mismas que para rodillas normales.

Rodillas normales: Media K = 0,051 (extensión: 0,02-0,090). Rodillas con poca actividad morbida: Media K = 0,057 (extensión: 0,032-0,090).

4. La tasa de eliminación para las rodillas manifestando una actividad morbida local severa fue más variable y generalmente mayor.

Rodillas severamente implicadas: Media K = 0,106 (extensión: 0,048-0,191).

5. En sujetos en que las rodillas se encontraban en etapas diferentes de actividad morbida, la tasa de eliminación fue mayor en la rodilla más severamente implicada.

6. Se estudió el efecto de hidrocortisona intra-articular sobre la eliminación del sodio en trece rodillas a intervalos de uno a 14 días; generalmente hubo reducción y retorno a lo normal de la tasa de eliminación.

7. Este procedimiento parece útil en el estudio de las alteraciones circulatorias de la articulación de la rodilla y se puede emplear para ensayar medicamentos potencialmente activos.
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