THE CLEARANCE OF NA^{24} FROM THE NORMAL AND OSTEO-ARTHRITIC KNEE JOINT AND THE RESPONSE TO INTRA-ARTERIAL PRISCOLINE® [1]

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The pathogenesis of degenerative joint disease (osteoarthritis) has been the subject of debate and conjecture for many years. Because the syndrome is found so often in older subjects, it would seem logical to correlate the general arteriosclerotic vascular changes with the degenerative joint pathology. However, the weight of investigative evidence has been against such a relationship, and the factors of "wear and tear" and "stress and strain" are considered to be the major forces in the development of degenerative joint diseases (1). In many instances where pathological changes of degenerative joint disease have been discovered, no complaint of pain or disability had been made (2, 3). It would appear that arteriosclerotic changes *per se* cannot explain degenerative joint disease (4, 5), and that vasomotor changes may play a significant role. In peripheral vascular disease, intra-arterial Priscoline® was reported to produce increased blood flow and to relieve pain and disability. It was therefore reasonable to expect a comparable effect in and around a joint and such an investigation was made by one of us (S.D.) in a series of patients with degenerative joint disease of the knee (6). Priscoline® (2-benzylimidazoline hydrochloride), an adrenolytic and sympatholytic agent with a direct action upon autonomic nerve endings, was given by the intra-arterial (femoral artery) route. In view of the beneficial subjective effect, a study was then made of intra-articular temperature changes in normal knee joints (7). This investigation demonstrated that the joint temperatures increased in normal subjects following intra-arterial sympatholytic agents (Priscoline®), presumably as a result of intra-articular vasodilatation. In another series of studies by one of us, the clearance rates of radioactive sodium from skin and muscle were investigated (8, 9). A recent study of the clearance of Na^{24} from 20 normal knee joints noted 100 per cent increased clearance following local heat application, and concluded that such studies presented accurate and sensitive results in the investigation of local circulatory changes within the knee joint (10). Assuming that changes in radioactive sodium clearance from the knee joint mirror changes in the vascular bed, a study of the clearance rates of radioactive sodium from the knee joint prior to and subsequent to intra-arterial Priscoline® seemed indicated.

MATERIAL AND METHODS

All subjects rested in the supine position for a 20 to 30 minute period prior to the beginning of the experiment. The knee joint was then entered with a 1.5 inch 20 gauge needle, and 0.1 ml. of isotonic radioactive sodium chloride solution, containing 1 to 3 microcuries of Na^{24}, was injected. A light weight Geiger counter was then strapped over the side of the knee opposite to the area of injection. The radioactivity present was recorded on an automatic register at one minute intervals. After six to eight minutes, 25 milligrams of Priscoline® was injected into the ipsilateral femoral artery and recording of radioactivity continued for an additional six to eight minutes. The Geiger counter remained in place throughout the experiment. The clearance half-life (the time taken for the activity initially present to be reduced to one-half) was found by plotting the data on semilogarithmic graph paper. The clearance constant (K) was calculated from the clearance half-life from the formula: K equals natural logarithm of 2 divided by half-life in minutes. In earlier reports (8, 9) we determined standard deviation based on three studies of Na^{24} clearance from the same area in the same individual; two subsequent studies of the individual fell within the range of the average plus or minus twice the standard deviation. We also found that if a plus or minus 20 per cent error was arbitrarily assigned to a determination of Na^{24} clearance, subsequent determinations would fall within the range so established. In the present study, we determined the significance of differences between the average clearance for normal subjects and that for all the patients, between the normals and each of the two groups

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TABLE I

Na^{24} clearance from the knee of normal subjects

Subject	Age (yrs.)	Clearance constant (K) minutes^{-1}: Prior to intra-arterial Priscoline®	Clearance constant (K) minutes^{-1}: After intra-arterial Priscoline®	% change
1	42	0.0148	0.0434	+193.2
2	34	0.0242	0.0442	+ 83.5
3	47	0.0131	0.0302	+130.5
4	33	0.0273	0.0386	+ 41.4
5	42	0.0238	0.0366	+ 53.8
6	43	0.0110	0.0397	+260.9
7	27	0.0119	0.0233	+ 95.8
8	35	0.0128	0.0447	+249.2
9	28	0.0342	0.0554	+ 62.3
10	29	0.0267	0.0414	+ 55.1
11	38	0.0380	0.0231	− 39.2
12	31	0.0254	0.0254	0
13	43	0.0192	0.0616	+220.8
	Average	0.0217	0.0390	

% change of the means, 79.7

of patients, and between the two groups of patients. This was determined after finding the standard deviation of each group and comparing the observed difference to the standard error of the difference of the two groups. The formula being:

$$\sigma_\Delta = \sqrt{\frac{(\sigma_1)^2}{(n_1 - 1)} + \frac{(\sigma_2)^2}{(n_2 - 1)}},$$

where σ_Δ is the standard error of the difference, σ is the standard deviation, and n is the number of observations. The chances of the differences between the groups being on a random basis were then expressed in odds.

Studies were made in 13 normal subjects between the ages of 29 and 47 years; and in 53 cases selected at random from the Arthritis Clinic with degenerative knee joint disease. The latter were between the ages of 44 and 81 years. Thirty-one of the 53 patients revealed moderate to advanced roentgenological changes typical of degenerative joint disease and 22 had normal findings or minimal X-ray changes.

In the 22 patients where distinct X-ray changes were absent, all were in the older age group and complained of pain following exercise, stiffness after resting, and local tenderness of one or both knees, with no relation to other disease or trauma. They were presumably suffering from degenerative joint disease.

RESULTS

The clearance rates for 13 normal subjects were determined. The most rapid rate was 0.0380 minute^{-1}, and the slowest was 0.0110 minute^{-1}. The average was 0.0217 minute^{-1}. Eleven of the normal subjects showed a significant increase in clearance rate following intra-arterial Priscoline®; one showed a decrease, and in one instance there was no change. The increase in mean clearance following Priscoline® for this group was 79.7 per cent (see Table I).

The mean clearance constant for all 53 patients was 0.0511 minute^{-1} and the odds against the difference from the mean clearance of the normal group being on a random basis were more than 500,000,000 to 1. The response to Priscoline® for all the patients showed an increase in mean clearance of 5.0 per cent.

Of the 53 patients, 31 had roentgenological changes in the knee joints. The average clearance rate for all the cases with X-ray changes was 0.0587 minute^{-1}. Following injection of Priscoline® 10 patients showed a significant (more than 20 per cent) increase in clearance, 11 showed a

TABLE II

Na^{24} clearance from the knee of arthritis clinic patients with X-ray evidence of osteoarthritis

Patient	Age (yrs.)	Clearance constant (K) minutes^{-1}: Prior to intra-arterial Priscoline®	Clearance constant (K) minutes^{-1}: After intra-arterial Priscoline®	% change
O. J.	53	0.0990	0.0440	− 55.6
A. L.	66	0.0408	0.0631	+ 54.6
R. M.	76	0.0257	0.0578	+124.9
I. F.	71	0.0291	0.0420	+ 44.5
E. M.	65	0.1510	0.0481	− 68.0
S. M.	71	0.0401	0.0199	− 50.4
M. E.	73	0.0630	0.0221	− 64.9
T. F.	69	0.0774	0.0448	− 42.2
M. C.	65	0.0531	0.0593	+ 11.7
S. T.	61	0.0961	0.1020	+ 6.1
A. S.	61	0.0842	0.0387	− 54.0
A. G.	65	0.0924	0.0714	− 22.7
S. G.	60	0.0953	0.0537	− 43.6
C. M.	65	0.0730	0.0676	− 7.3
M. B.	67	0.0693	0.0953	+ 37.5
E. B.	81	0.0440	0.0631	+ 43.3
H. Y.	50	0.0774	0.0457	− 41.0
B. G.	66	0.0194	0.0315	+ 62.4
K. S.	70	0.0540	0.0867	+ 60.6
R. S.	55	0.0346	0.0346	0.0
M. T.	65	0.0536	0.0495	− 7.6
B. H.	65	0.0434	0.0332	− 23.5
A. A.	64	0.0447	0.0504	+ 12.8
E. K.	80	0.0693	0.0793	+ 14.4
A. B.	75	0.0361	0.0793	+119.7
G. L.	72	0.0774	0.0660	− 14.7
C. F.	60	0.0163	0.0267	+ 63.8
L. M.	55	0.0447	0.0447	0.0
P. M.	45	0.0447	0.0321	− 28.2
D. S.	67	0.0504	0.0566	+ 12.2
A. M.	70	0.0215	0.0385	+ 79.0
Average		0.0587	0.0564	

% change of the means, −4.2

significant decrease, and 10 showed no significant change in clearance. The overall change in mean clearance following Priscoline® for this group was 4.2 per cent (Table II). The odds against the observed differences of the mean clearance from the normal being on a random basis were 500,000,000 to 1.

X-ray changes were absent in 22 cases and the average clearance constant for this group was 0.0404 $minute^{-1}$. The odds against the observed difference of the means as compared to the controls being random were 3,142 to 1. Ten of the patients showed a significant increase, 4 showed a significant decrease, and 8 showed no significant change in clearance rate following intra-arterial Priscoline®. The overall increase in clearance following administration of Priscoline® for this entire group was 26.2 per cent (see Table III).

In comparing the mean clearance rates for the two groups of patients we found that the odds against the observed differences being on a random basis were 99 to 1.

TABLE III

Na^{24} clearance from the knee of arthritis clinic patients without X-ray evidence of osteoarthritis

Patient	Age (yrs.)	Clearance constant (K) $minutes^{-1}$: Prior to intra-arterial Priscoline®	Clearance constant (K) $minutes^{-1}$: After intra-arterial Priscoline®	% change
S. R.	65	0.0250	0.0536	+114.4
M. P.	64	0.0231	0.0514	+122.5
J. B.	44	0.0322	0.0447	+ 38.8
I. K.	77	0.0552	0.0858	+ 55.4
C. I.	72	0.0612	0.0513	− 16.2
J. V.	67	0.0514	0.0303	− 60.1
R. Z.	60	0.0236	0.0236	0.0
B. L.	56	0.0900	0.0489	− 45.7
R. T.	60	0.0178	0.0178	0.0
J. G.	72	0.0536	0.0457	− 14.7
L. M.	57	0.0457	0.0299	− 34.6
H. T.	56	0.0223	0.0227	+ 1.8
P. G.	60	0.0284	0.0284	0.0
D. M.	50	0.0185	0.0618	+234.0
P. S.	57	0.0631	0.1460	+131.4
G. S.	54	0.0514	0.0351	− 31.7
R. L.	68	0.0346	0.0346	0.0
O. I.	66	0.0261	0.0693	+165.5
M. K.	68	0.0215	0.0447	+108.0
D. D.	45	0.0326	0.0565	+ 73.5
M. G.	60	0.0361	0.0651	+ 80.5
P. J.	50	0.0770	0.0636	− 17.4
Average		0.0405	0.0505	
		% change of the means, 26.2		

DISCUSSION

We have divided the clinical subjects in this investigation into two main groups, those with and those without X-ray changes. In the group with X-ray changes, rapid resting clearance rates as compared to the normals were demonstrated in 77.4 per cent. Also, the average response to Priscoline® injected intra-arterially as measured by the clearance of Na^{24} from the knee joint differed considerably in this group (− 4.2 per cent, as contrasted with the normals' average of + 79.7 per cent). The most logical explanation is that in joints in which osteoarthritis has been present long enough for roentgen alterations to appear, a marked degree of vasodilatation already exists and further stimulation by vasodilating agents is without effect. This hypothesis is supported by a recent study which demonstrated that the intra-articular temperature in osteoarthritis is elevated as compared to normals (11). Unpublished data of our own corroborate this report. In fact, in this group there were many studies in which the clearance rate became slower than the rate prior to the administration of Priscoline®. Since the arterioles and capillaries in the skin and muscle of the thigh and leg are in the resting state and can respond to the vasodilating drug (as evidenced by the pilomotor response, the flush and the increased skin temperature), there is an increase in blood flow to tissues other than those of the joint. This may result in a decrease of flow through the already markedly dilated vessels of the synovia subsequent to the dilatation of vessels elsewhere. We cannot account for the seven instances in which X-ray changes existed and the clearance rate was within normal range. However, as has been noted above, the odds against the average differences for the entire group as compared with the normals being on a random basis are extremely wide and indicate a high degree of probability that the differences in clearance rate are significant.

The 22 cases without X-ray change revealed a more widely scattered pattern of findings. However, when comparing the average clearance constant for this group with the average for the normal controls, statistical analysis reveals that the difference is significant. This indicates that even patients who lack X-ray changes but have symp-

toms of degenerative joint disease also have a higher degree of vasodilatation than normal.

The older age of the clinical subjects as compared to the observed normals, and, therefore, presumably the extent of arteriosclerosis present, could be considered as a factor producing the findings noted in this study. Therefore we examined for the presence of dorsalis pedis and posterior tibial pulses in all our patients. They were easily palpable except in eight instances, and a correlation could not be established between the status of the peripheral pulses and the results of our studies. If arteriosclerosis with its implied reduction in available blood flow was primarily involved, there should be an associated slower clearance of Na^{24} in the resting state in the patient with degenerative joint disease and it should follow that a subject without arteriosclerosis should evince a more rapid initial Na^{24} clearance. We have found the opposite to be true and this is not surprising since arteriosclerosis is not implicated in the pathogenesis of degenerative joint disease (4, 5). Consequently we do not consider arteriosclerosis to play a conspicuous role in the clearance of Na^{24} from the knee joint.

Normal synovial tissue, though pale in color, contains a rich capillary bed which is not fully dilated (12). In this quiescent state, Na^{24} clears slowly, but when vasodilatation is produced by the intra-arterial Priscoline®, the Na^{24} clearance rate increases.

In degenerative joint disease, histological examination of the synovia reveals diffuse collagenous fibrosis, reduced vascularity and endarteritis obliterans of some of the more deeply situated arteries, but the small delicate villi contain engorged capillaries (12). This is an indication that, *in vivo,* whatever local blood supply remains in the synovia in patients with degenerative joint disease is in a state of dilatation. This is further indicated by the initial rapid clearance rates, and lack of ability of this already markedly vasodilated vascular bed to respond to further stimulation by Priscoline® intra-arterially.

That a truly inflammatory synovitis is not responsible for these results is shown by studies (12) of synovial fluid and synovia in degenerative joint disease which reveal no evidence of inflammatory changes (no leucocytic infiltration and synovial fluid cell counts well below 5,000 per cubic millimeter, and a maximum of 15 to 20 per cent polymorphonuclear cells).

We are of the opinion that our results indicate that "wear and tear" phenomena are not alone significant in the evaluation and clinical status of degenerative joint disease, but that local vascular factors play a role as well. These local vascular factors probably are of significance in the response of a joint to noxious influences. Conceivably some degree of pain in degenerative joint disease can be considered a consequence of poor or altered absorption (*i.e.,* clearance) of metabolites from the joint following exercise. Hitherto most inquiries relating to circulation and degenerative joint disease have been along purely anatomical and pathological lines. We are of the opinion that the studies herein described indicate the need for investigation into the circulatory physiology of joints.

SUMMARY

Sixty-six studies were performed to determine the rate of clearance of radioactive sodium from the knee joint before and after the injection of Priscoline® into the ipsolateral femoral artery. In 13 normal subjects the findings indicate that in a normal joint stimulation by Priscoline® produces vasodilatation as evidenced by more rapid clearance of the Na^{24}.

Fifty-three patients considered to have degenerative joint disease were studied. Where distinct roentgen changes were present there was a rapid initial clearance of sodium from the knee joint in the majority of instances, as compared with the normals. There was no increase in clearance following Priscoline®.

In the group without X-ray changes, the average clearance constant was rapid as compared with the normal group. The response to Priscoline® was moderate.

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REFERENCES

1. Bennett, G. A., Waine, H., and Bauer, W. Changes in the Knee Joint at Various Ages. New York, The Commonwealth Fund, 1942.

2. Bauer, W. Studies pertaining to the origin and nature of hypertrophic arthritis. Trans. Stud. Coll. Phycns Philad. 1939, **7**, 1.
3. Amprino, R., and Bairati, A. Studi sulle trasformozioni delle cartilagini dell' uomo nell' accrescimento e nella senescenza. Z. Zellforsch. 1934, **20**, 489.
4. Heine, J. Uber die Arthritis deformans. Virchows Arch. path. Anat. 1926, **260**, 521.
5. Kling, D. H. Significance of peripheral circulatory disturbances for development of osteo-arthritis. Amer. J. med. Sci. 1939, **197**, 358.
6. Davison, S., and Wolf, M. Palliative treatment of osteoarthritis (degenerative joint disease) by the intra-arterial injection of Priscoline. N. Y. St. J. Med. 1952, **52**, 2025.
7. Davison, S., Borken, N., and Wolf, M. Elevations in temperature of joint muscle and skin following injection of Priscoline intra-arterially. J. Mt. Sinai Hosp. 1954, **21**, 98.
8. Wisham, L. H., and Yalow, R. S. Some factors affecting the clearance of Na^{24} from human muscle. Amer. Heart J. 1952, **43**, 67.
9. Wisham, L. H., Yalow, R. S., and Freund, A. J. Consistency of clearance of radioactive sodium from human muscle. Amer. Heart J. 1951, **41**, 810.
10. Harris, R., and Millard, J. B. Clearance of radioactive sodium from the knee joint. Clin. Sci. 1956, **15**, 9.
11. Hollander, J. L., and Moore, R. Studies in osteoarthritis using intra-articular temperature response to injection of hydrocortisone acetate and prednisone. Ann. rheum. Dis. 1956, **15**, 4.
12. Collins, D. H. The Pathology of Articular and Spinal Diseases. Baltimore, The Williams and Wilkins Co., 1949.