

A Physiological Approach to the Assessment of Disease Activity in Rheumatoid Arthritis

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ABSTRACT A method is described for assessing the in vivo oxygen consumption and lactate production rates of human knee joints. It is based on the rate of fall of P_{O_2} and the rate of rise in lactate concentration in an intra-articular saline pool after interruption of the circulation to the joint with an arterial tourniquet. Studies in 5 control patients with degenerative joint disease and 29 patients with rheumatoid arthritis showed a 2- to 3-fold higher mean oxygen uptake rate and a 10- to 12-fold higher mean lactate appearance rate in the saline in the rheumatoid joints with severe disease compared to the control joints. These metabolic variables correlated with tissue metabolic demand as estimated in synovial biopsies. ^{133}Xe washout from the intra-articular space, which reflects joint circulatory flow, showed a 3-fold greater mean washout rate from the rheumatoid joints (48 studies) than control joints (7 studies) with extensive overlap between the two groups. ^{133}Xe washout rate correlated with knee joint inflammation estimated both clinically and histologically. After synovectomy in four patients, the operated knee showed a greater fall in lactate production than the opposite knee in three of these patients. Neither knee joint oxygen uptake nor ^{133}Xe washout rate changed significantly. Intra-articular corticosteroid injection (eight patients) resulted in decreased lactate production and a decreased ^{133}Xe washout rate in the injected knee and variable

results in the untreated knee. Oxygen uptake again was unchanged after therapy.

INTRODUCTION

A previous study has shown that the P_{O_2} of synovial fluid from joints with severe rheumatoid arthritis is lower than that of synovial fluid from joints with degenerative and some other inflammatory arthropathies (1). We proposed that the rheumatoid synovial fluid P_{O_2} was low due to an imbalance between a greatly increased oxygen consumption by joint tissues, and an increased but relatively insufficient circulatory supply of oxygen to these tissues (1).

Numerous studies employing indirect methods of dye or radioisotope washout from the synovial fluid have suggested that the circulation in the rheumatoid joint was greater than control levels (2-4). A method utilizing the washout of ^{133}Xe from the joint has overcome the problems of recirculation and biologic activity of tracers and has shown strikingly increased local circulation in the rheumatoid joint (5). Similarly, in vitro studies have shown that rheumatoid synovia have greater oxygen and glucose consumption rates, and a greater lactate production rate per mg of tissue than control synovia (6-8). It would be desirable, however, to be able to assess both metabolic and circulatory variables of synovial tissue in vivo in order to attempt to corroborate the hypothesis concerning the primary determinants of synovial fluid P_{O_2} .

This paper presents a method for assessing the in vivo aerobic and anaerobic metabolic rates of human knee joints. We also report further developments of the ^{133}Xe method and the circulatory variables that were measured

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by this technique in some of the same joints undergoing metabolic studies. Both metabolic and circulatory variables are correlated with clinical assessments and synovial biopsies of corresponding joints. The effects of synovectomy and intra-articular corticosteroids were explored using this comprehensive approach.

METHODS

Studies were performed on a total of 36 patients of whom 7 have degenerative or traumatic joint disease (DJD),¹ 8 have seronegative rheumatoid arthritis, and 21 have seropositive rheumatoid arthritis. The diagnosis of rheumatoid arthritis (RA) was based on ARA (American Rheumatism Association) criteria (9). Other requirements for inclusion in the study were: (a) over 21 years of age, (b) no evidence of pulmonary disease, (c) absence of gout or of pyogenic or tuberculous arthritis in the present or the past, (d) no prior knee surgery, and (e) for the control patients, no evidence suggesting possible rheumatoid arthritis. In all other respects, the patients represent a heterogeneous group, and in particular all were taking a variety of different anti-rheumatoid medications. All patients were hospitalized either at the Clinical Center of the National Institutes of Health or at The George Washington University Medical Center Hospital.

Dr. Goetzel evaluated each patient immediately before the studies for clinical evidence of general arthritic disease and specifically of knee arthritic disease. General arthritic severity was assessed using a system based on the criteria of Lansbury (10) as well as on semiquantitative representations of joint pain, fixed joint deformities, joint effusions, hematocrit, joint X-rays, time to walk 50 ft, and grip strength. An analogous system of seven clinical and radiological criteria was used to grade disease severity in each knee joint with an over-all score that could have a maximum value of 15. These grades for each patient were considered to be clinical indices for interpatient comparisons. Rheumatoid factor was quantitated using a titrated bentonite flocculation method (11).

24 hr before the metabolic studies described below, 22 of the 36 study patients had at least 1 evaluation of circulatory flow in each knee using the ¹³³Xe desaturation method. The general procedure of this method has been published (5). Care was taken to completely immobilize the knee, use a standard protocol for skin preparation and local anesthesia (0.2 ml 1% xylocaine [Astra Pharmaceutical Products Inc., Worcester, Mass.]), and aspirate as much synovial fluid as possible before injection of the ¹³³Xe. Air was prevented from entering the joint space by employing a three-way stopcock and flushing in the isotope dose with saline. The ¹³³Xe dose was 100 μ Ci. Immediately after mixing the knee contents, counting was begun using a sodium iodide crystal detector (Pho Dot II, wide angle flat field collimator, Nuclear-Chicago Corp., Des Plaines, Ill.) positioned at the lateral aspect of the joint at the same distance from each knee. The pulse height analyzer was set with a 20% window about the 0.070 Mev gamma photopeak for ¹³³Xe. The output was recorded for a minimum of 45 min in each knee study. At the end of this period, a gamma-scintillation camera (Pho Gamma III, Nuclear-

Chicago Corp.) scintiphoto was taken of the knee joint both in the anterior and lateral projections to determine the distribution of activity. Sequential 2 min scintiphotos were taken during several studies with the camera. The distribution of radioactivity during the first 15 min of monitoring was recorded on video tape for several other studies.

The ¹³³Xe clearance curves, which were plots of total knee radioactivity *versus* time, were transcribed to magnetic tape for computer analysis by the use of a Calma digitizer (VIP 303, Calma Co, Sunnyvale, Calif.). The data then was analyzed using least squares fitting to a two-component model. The program was NIH Nos. 22 and 23 (Division of Computer Research and Technology, National Institutes of Health), which are based on the Marquardt modification of the Gauss-Newton procedure (12).

The assessment of oxygen uptake by the knee joint tissues was based on the assumption that depriving the joints of their circulatory oxygen supply with an arterial tourniquet made the local tissue and intra-articular fluid stores the sole source of oxygen for these joint tissues. The fall in oxygen content of a previously created intra-articular saline pool then should reflect the tissue uptake of oxygen occurring in the ischemic joint. The relationship between the P_{O_2} and the oxygen content of intra-articular saline would be linear according to Henry's law. Changes in saline P_{O_2} should be directly proportional to changes in saline oxygen content. The decrements in intra-articular saline P_{O_2} were therefore considered to reflect the rate of local tissue uptake of oxygen after circulatory interruption. Similarly, the increment in lactate concentration in the intra-articular saline pool after a period of tourniquet ischemia should reflect lactate production by the joint tissues during that period. Accordingly, 22 of the 36 study patients had at least one such evaluation of local joint metabolic activity of each knee and 12 had at least one evaluation of one knee. These studies were all performed in the operating room under full sterile precautions. Joint effusions were aspirated as completely as possible through a no. 15 trochar needle which was left in place for the duration of the study. All patients then began breathing a 50% oxygen mixture. 60 ml of sterile saline was instilled into the joint, the joint contents were mixed, and the saline was aspirated and discarded. A second 60 ml portion of saline (P_{O_2} = 180) was instilled into the joint and allowed to equilibrate for 10 min. An arterial tourniquet was then inflated about the thigh to 450 mm Hg to stop the circulatory supply to the knee joint at what was designated zero time. Saline samples were collected anaerobically through a three-way stopcock in heparinized syringes before inflation of the tourniquet (baseline) and then every 4 min for 24 min with continuous mixing of the knee contents during the ischemic period. The syringes were stored in ice and the P_{O_2} and pH of each sample were subsequently measured at 37°C in an IL instrument (Instrumentation Laboratory, Inc., Lexington, Mass.) as previously described (1). The lactate concentration was measured in most of the 24-min saline samples, and in the baseline (pretourniquet) sample from 10 representative studies. Saline portions were centrifuged to remove cells and debris, and then deproteinized with trichloroacetic acid at a final concentration of 10%. The lactate concentrations were determined by a modification of the lactic acid dehydrogenase enzymatic assay (13) using Lactate Stat-Pack reagents (Calbiochem, Los Angeles, Calif.).

57 of the 60 knees studied were biopsied during the initial evaluation using either a Parker-Pearson needle (14)

¹ Abbreviations used in this paper: DJD, degenerative joint disease; P_{O_2} , partial pressure of oxygen; RA, rheumatoid arthritis; ¹³³Xe, radioactive isotope 133 of Xenon.

(47 knees) or by an open surgical approach (10 knees). Biopsy specimens were processed as previously described (1). Histologic evaluation was performed by one pathologist without prior knowledge of the individual patients or the results of the above special studies. Increased synovial metabolic activity was assumed to be proportional to: (a) synoviocytic hyperplasia, (b) villous hypertrophy of synovial and connective tissue, and (c) the total degree of infiltration of the tissue with leukocytes (7). Each specimen was scored from "0" to "3" on an arbitrary scale of increasing severity for each of these parameters. The individual scores for categories (a)–(c) were added to arrive at a histologic grade called the "total pathology grade" which was felt to reflect the metabolic activity of each knee.

Attempts were made to standardize the conditions under which all patients were evaluated. All metabolic and isotope studies were performed with patients in the supine position, and no individual was febrile at the time of study. Each patient was being treated with salicylates in doses ranging from 1.8 to 6.0 g daily. Plasma salicylate concentrations just before the study were all in the range of 15–35 mg per 100 ml. Approximately 50% of the patients were taking oral corticosteroids which were continued during the study. No patient had received intra-articular corticoids during the month before admission to the study. Small intravenous doses of diazepam (Valium, Roche Laboratories, Nutley, N. J.), meperidine (Demerol, USV Pharmaceutical Corp., New York), and promethazine (Phenergan, Wyeth Laboratories, Philadelphia, Pa.) were routinely used to relieve discomfort produced by the arterial tourniquets. There were no significant patient complications attributable to these study procedures, and in particular there were no joint infections, no instances of intra-articular bleeding, and no neuropathy or other untoward tourniquet effects.

Red blood cell counts and white cell counts and differentials were done both on any synovial fluid aspirated before the isotope study and on a portion of the saline aspirated at 24 min during the metabolic study. The red blood cell counts in 24 min saline samples were all less than 50,000/mm³ and 70% were under 10,000/mm³, revealing that there was insignificant contamination of the saline with blood. In addition, baseline synovial fluid samples were collected anaerobically from 42 knees with patients breathing room air and before any of the special joint studies. The P_{O₂} of each was measured as described above. Portions of these fluids were also used for titrated bentonite flocculation tests for rheumatoid factor (11).

Those patients who received some form of knee joint therapy and were then restudied belonged to one of three groups. The synovectomy group had total synovectomies of one knee joint. The medically treated groups received intra-articular corticosteroids either in a soluble or a depot form as detailed in Table II. All statistical analyses comparing two groups of values were performed using the Mann-Whitney rank sum test (15).

RESULTS

Metabolic studies

It was found that the P_{O₂} levels in the intra-articular saline fell rapidly after the tourniquet was applied stopping the circulatory supply of oxygen. The rate of fall was exponential in all cases. Points were plotted on semilog paper with P_{O₂} on the log scale against time on

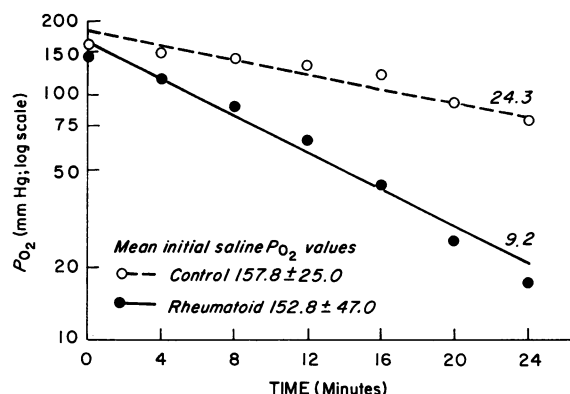


FIGURE 1 The fall of intra-articular saline P_{O₂} with time after tourniquet interruption of the circulation to the joint. The t_{1/2} O₂ value is shown on the right above each line. Mean initial P_{O₂} values in the intra-articular saline are presented ±2 SD.

the linear scale (Fig. 1). The two representative studies shown in Fig. 1 illustrate the good fit of the actual data points to the calculated least squares line which was true for all studies. The half-time for the fall in P_{O₂} along the least squares plot was called "t_{1/2} O₂" and was adopted as a standard index of joint tissue oxygen uptake.² The t_{1/2} O₂ values for both the control patient and the rheumatoid patient studies are shown on the right side of the lines in Fig. 1. The difference between the studies with high t_{1/2} O₂ and those with low t_{1/2} O₂ values was not contributed to by different baseline saline P_{O₂} levels, since the mean initial intra-articular saline P_{O₂} levels ±2 SD for the control (DJD) and rheumatoid (RA) patient populations were in the same range (Fig. 1).

The lactate levels in saline aspirated from the joint after the 10 min equilibration period were unmeasurable (under 2.5 mg per 100 ml) in nine studies and 2.5 mg per 100 ml in one study. For this reason, we felt that the lactate concentration in the saline aspirated from a joint at 24 min after circulatory interruption would reflect local lactate production. This concentration was then measured in most studies and adopted as our second standard value which is referred to as "lactate production."

The reproducibility of the t_{1/2} O₂ and the 24 min lactate concentration was evaluated by performing two or three repetitive studies on 12 knees of 8 patients (including the unoperated knees of the 4 synovectomy patients) with intervals between studies of 1–20 wk. 8 of the 12 serial studies gave values for both t_{1/2} O₂ and lactate concentration which were in the range of ±20% of the respective initial values. The other four studies, however,

² We found that pH levels in the intra-articular saline also fell after interruption of the circulation to the joint. The decrements in pH with time, however, were very erratic in most studies.

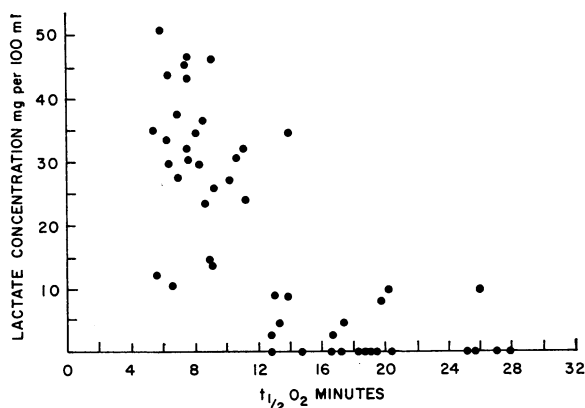


FIGURE 2 Relationship between $t_{1/2} O_2$ values and lactate concentrations in the 24-min saline samples. Each point represents a single knee joint study.

demonstrated that both $t_{1/2} O_2$ and 24-min lactate concentration could spontaneously increase by as much as 100% or decrease by as much as 50% on repeat determinations in any one joint. In this small group of patients it also is possible to state that those joints with baseline $t_{1/2} O_2$ values shorter than 16 min constituted a separate group from those with $t_{1/2} O_2$ longer than 16 min, and all patients remained within their respective group ranges during serial studies. Similarly, those 24 min lactate concentrations which were grouped under 10 mg per 100 ml and those which fell over 10 mg per 100 ml remained as separate groups on repeat studies. These results reflect both biologic variability and the precision of the methods, and so they are presented as a background on which to interpret the changes seen in these measurements after various therapeutic maneuvers.

Fig. 2 shows a plot of $t_{1/2} O_2$ vs lactate concentration for those knee joints which had both studies. Each point represents results from a single joint during an initial study or during a repeat study if it did not follow some therapeutic procedure. For $t_{1/2} O_2$ values longer than 16 min, all lactate concentrations were under 10 mg per 100 ml and 11 of 16 were unmeasurable. For $t_{1/2} O_2$ values shorter than 16 min, 24 of 30 lactate concentrations were over 10 mg per 100 ml, and there is a suggestion of a steep inverse relationship between $t_{1/2} O_2$ and lactate concentration in this range. This distribution of data and the reproducibility studies above led us to analyze most of the subsequent results in two arbitrary groups for $t_{1/2} O_2$ (shorter than 16 min, and longer than 16 min) and lactate concentrations (under 10 mg per 100 ml, and over 10 mg per 100 ml).

Fig. 3 shows all $t_{1/2} O_2$ values for initial knee studies only. These results are arranged in three diagnostic groups: 6 studies in 5 control (DJD) patients, 13 studies in 8 seronegative RA patients, and 37 stud-

ies in 21 seropositive RA patients. The seronegative RA group almost completely overlaps the group A seropositive RA range. The control values are significantly different from those in the seronegative and lower (group A) seropositive RA groups (P less than 0.01). The four group B RA patients are segregated because they were a stable group with low oxygen uptake when three of them were studied on multiple occasions over 16 wk time. When restudied at 20 wk, however, one patient showed a dramatic decrease in $t_{1/2} O_2$ from the 18–28 min range to 5–6 min symmetrically for both knees. This patient had severely deforming nodular disease of 16 yr duration and may simply represent an example of fluctuation in local metabolic rate, but is unusual also because the lactate concentrations for all three of her serial studies were much higher (15–17 mg per 100 ml) than those of the other group B patients which ranged 0–9.5 mg per 100 ml. A discrepancy between our assessments of aerobic and anaerobic metabolism cannot be explained by any of our data, and therefore we have left the results of the studies of this unusual patient out of Fig. 2. The other three group B patients had mild disease of less than 2 yr duration and without any joint deformities or limitation of range of motion. All of the group A RA patients had severe deforming disease with duration ranging from 5 to 28 yr.

We have attempted to investigate the metabolic compartment which is responsible for the oxygen consumption and lactate production being measured in our studies. The first approach was to compare the white blood cell counts (white cells/mm³) in the aspirated native synovial fluid and the 24 min intra-articular saline with the corresponding $t_{1/2} O_2$ values. Figs. 4 and 5 show results from initial studies and repeat measurements where there was no interim therapy. There appears to be no correlation between $t_{1/2} O_2$ values and either synovial fluid

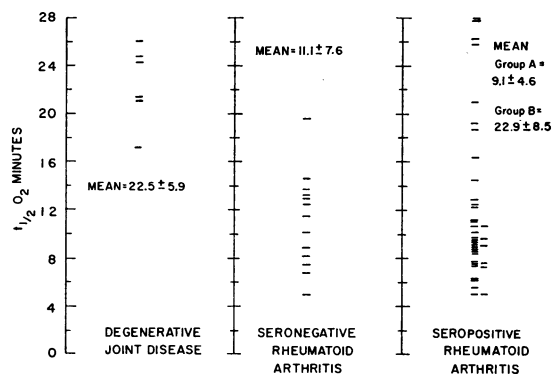


FIGURE 3 Distribution of $t_{1/2} O_2$ values by clinical diagnosis. Each dash represents one knee study. The mean ± 2 sd is given for all values in each group. Group B is composed of those eight studies with $t_{1/2} O_2$ longer than 16 min, and group A contains all studies with $t_{1/2} O_2$ shorter than 16 min.

white blood cell counts (Fig. 4) or saline white blood cell counts (Fig. 5). Correlation of leukocyte counts with lactate concentrations showed a similarly random relationship. It would be more meaningful to relate $t_{1/2} O_2$ and lactate levels to the total number of white blood cells in the intra-articular saline instead of to the number of cells/mm³. However, the joints were all flushed with saline and aspirated completely before each study, and the initial volume of saline was identical in all cases. This uniformity of intra-articular volume was further reinforced by the fact that we were always able to recover essentially the same total saline volume (42–45 ml.) from each joint in the course of the metabolic study. For inter-joint comparisons then the total number of leukocytes in the saline during the metabolic measurements is very well approximated by the number of white cells/mm³ of saline. We concluded therefore that neither the white cells in any residual synovial fluid present after the joint flushing procedure nor the white cells in the saline were primary determinants of the measured oxygen uptake rates or lactate production rates.

Our second approach was to grade synovial tissue biopsies on a semiquantitative scale for histologic evidence of metabolic activity. 63 biopsies were obtained from knees undergoing initial studies and repeat studies where there was no change in therapy. Of these, 54 were considered adequate for grading by the pathologist and were assigned a "total pathology grade" which reflects both synoviocytic hyperplasia and tissue inflammatory cell density. These are plotted in two groups against the corresponding $t_{1/2} O_2$ values and the lactate concentrations from some of the same knee studies (Fig. 6). The two groups of biopsies in each correlative analysis are significantly different (P less than 0.01), but the difference is slightly greater between the two lactate groups.

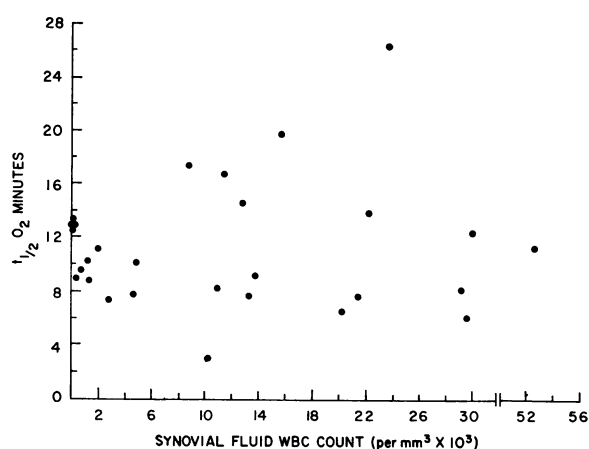


FIGURE 4 Lack of correlation between $t_{1/2} O_2$ values and corresponding synovial fluid white blood cell counts. Each data point represents a single knee joint study.

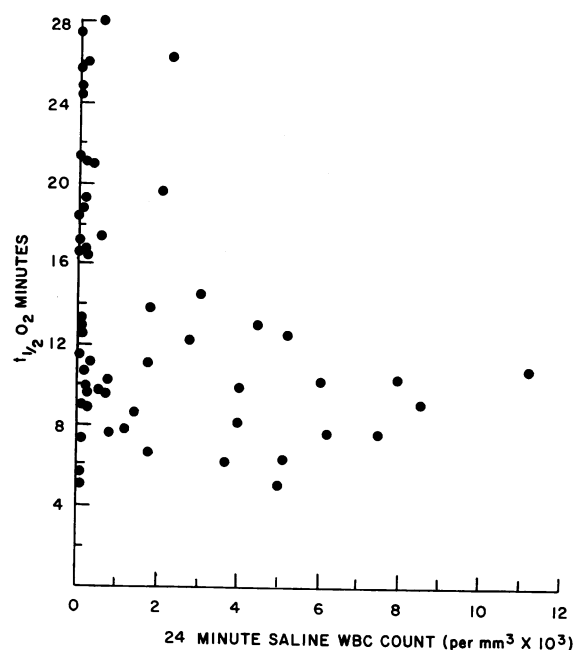


FIGURE 5 Lack of correlation between $t_{1/2} O_2$ values and corresponding 24-min saline white blood cell counts. Each point represents a single knee joint study.

For all biopsy grades, the subscores for synoviocytic hyperplasia and those for total inflammatory cell infiltration were essentially equivalent. We therefore could not distinguish between the tissue white blood cells and the synovial fixed cells as to which cell type was primarily responsible for the measured metabolic rates. Most certainly, the over-all cellularity of the tissue in the joint is a primary determinant of local metabolic activity based on the above results. There is also a suggestion (Fig. 6) that seronegative patients (open circles) require denser tissue cellularity than seropositive patients (closed circles) in order to produce as much lactate in knee joints. Any serologic differentiation among the biopsy grades in the two $t_{1/2} O_2$ groups does not appear justified.

The knee clinical grades, a crude index of local disease severity, show an obvious correlation with corresponding $t_{1/2} O_2$ values and lactate concentrations from the same knee joints (Fig. 7). The two groups of clinical grades are significantly different in both plots (P less than 0.01 and P less than 0.02 respectively), but the difference is greater between the $t_{1/2} O_2$ groups. There does not appear to be any serologic differentiation within the clinical grades.

¹³³Xe Desaturation studies

External monitoring of the rate of decrease of radioactivity in knee joints following the intra-articular in-

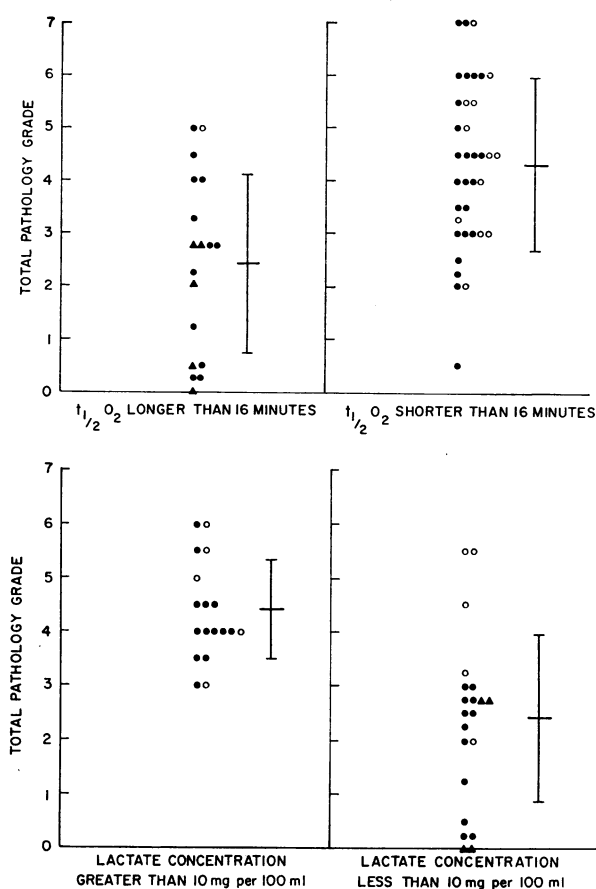


FIGURE 6 Distribution of synovial biopsy pathology grades in the two $t_{1/2} O_2$ and lactate concentration groups. Each point represents the biopsy from a single knee joint study. The bars depict the mean pathology grade ± 1 sd for each group. Seropositive RA = \bullet , seronegative RA = \circ , and DJD = \blacktriangle .

jection of ^{133}Xe in saline was employed as a measure of regional blood flow in these joints. The fact that ^{133}Xe is removed from the knee joint solely by circulation has been shown (16), and was confirmed in four patients by demonstrating that there was no fall in radioactivity over a 10–15 min period when an arterial tourniquet was inflated about the thigh before injection of the isotope. The following procedures were carried out to rule out significant differences in distribution of ^{133}Xe within the knee joints which might enter into the interpretation of subsequent results. Eight knees of six patients were studied by sequential 2 min gamma-scintiphotos of the joint in both the lateral and anteroposterior projections from 1 to 60 min after isotope injection. In addition, five knees in four patients were studied by continuous video tape recording of the ^{133}Xe radioactivity distribution in the lateral projection from 0 to 20 min. Radioactivity was found primarily in the

suprapatellar pouch with much less activity in the knee joint space proper. None of these studies showed any significant redistribution of ^{133}Xe radioactivity from the earliest time at which sufficient radioactivity was present to allow an image to be recorded (5–10 sec after injection) up to 60 min. ^{133}Xe seems, therefore, to be instantaneously distributed into the joint and suprapatellar pouch and a distribution steady state is maintained throughout the study. To check for inhomogeneity of distribution due to faulty injection or unusual anatomical conditions, all patients had lateral and anterior scintiphotos immediately after each desaturation study. These scans generally revealed only minor differences in distribution of ^{133}Xe among the patients undergoing their initial studies. However, 3 of the 80 scans showed local “hot spots” or accumulations of radioactivity in a small area of the suprapatellar pouch. In addition, three of the four postsynovectomy knees (I, II, and III in Table I) had smaller areas of ^{133}Xe distribution than

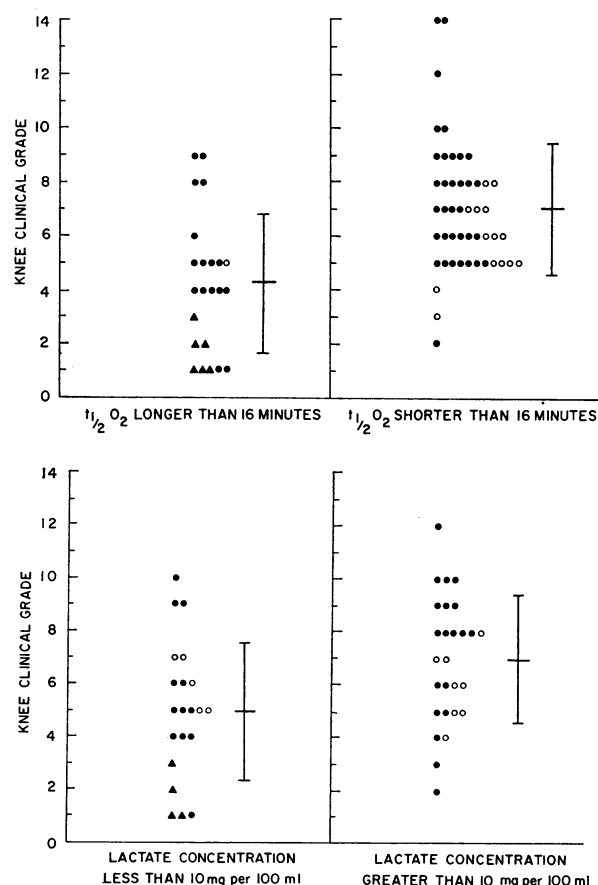


FIGURE 7 Clinical grades of knee disease in the two $t_{1/2} O_2$ and lactate concentration groups. Each point represents the clinical evaluation of one knee joint. The bars show the mean knee clinical grade ± 1 sd for each group. Refer to Fig. 6 for the meaning of the symbols.

TABLE I
Effects of Synovectomy

Patient	Procedure	Lactate concentration		t _{1/2} O ₂		Po ₂ †		¹³³ Xe t _{1/2} II		Knee clinical grade	
		R*	L	R	L	R	L	R	L	R	L
		mg per 100 ml		min		mm Hg		min			
I	Left knee synovectomy										
	Baseline	—§	—	9.7	10.2	—	—	78.5	485.3	5	5
	1 month after surgery	—	—	10.3	13.1	20	15	—	—	6	8
	4½ months after surgery	34.5	36.5	8.1	8.5	9	18	74.0	67.7	9	10
II	Right knee synovectomy										
	Baseline	31.5	34.5	7.3	5.0	24.5	27	50.4	39.0	7	7
	1 month after surgery	19.5	37.4	17.4	6.9	—	—	—	—	6	3
	4½ months after surgery	10.2	43.3	11.0	7.6	30	7	61.9	49.9	8	6
III	Right knee synovectomy										
	Baseline	—	—	12.3	11.2	—	—	102.8	28.2	7	6
	1 month after surgery	24.0	26.5	11.2	10.6	16.5	—	59.0	21.9	7	7
	5 months after surgery	13.0	51.3	7.7	5.9	27	6	53.5	55.0	5	5
IV	Left knee synovectomy										
	Baseline	19.8	28.0	5.0	6.8	21.5	19	39.9	30.5	5	5
	1 month after surgery	26.8	16.5	9.2	7.7	—	—	—	—	6	7
	5 months after surgery	23.5	6.3	8.6	8.0	25	32	97.8	31.4	4	5

* R, right knee; L, left knee.

† Po₂, oxygen partial pressure in synovial fluid sampled from the knee joint with the patient breathing room air.

§ A dash indicates that the particular study was not performed.

the preoperative scans, whereas serial studies in non-operated knees showed no such changes. Except for the reservations stated for these six knees, the other desaturation curves seemed amenable to computer analysis using a two component model as previously described (17, 18).

The computer program was able to define a significant first and second component and derive half-times for these components in 60 out of 80 studies performed on three control (DJD) and 19 RA patients. In the remaining 20 studies, only the second (slow) component could be defined with a standard error within $\pm 10\%$ of the t_{1/2} value. Half-times for the first (fast) component, t_{1/2} I, showed wide fluctuations when measured several times over intervals of 2–25 wk in 11 knees of 8 patients. They were often shorter than 1 min and therefore greatly influenced by artifacts of the recording equipment. Half-times for the slow component, t_{1/2} II, and the t_{1/2} values for the 20 studies with one component, in contrast, fell in a convenient working range (21.9–865.0 min) where they would not be influenced by technical artifacts. For this reason we used the t_{1/2} II value as a standard number for each desaturation curve for interpatient and serial patient comparisons.

The t_{1/2} II data are grouped by clinical diagnoses in Fig. 8, including 44 initial studies and 11 studies with

no interval change in medical regimen or over-all condition of the patient. The seropositive rheumatoid patients were divided arbitrarily as for the metabolic studies into two groups: B containing the three patients with mild nondeforming disease of under two yr duration, and A for the other 11 patients with destructive arthritis of longer duration (5–28 yr). These t_{1/2} II values show considerable scatter indicating that as for the metabolic studies this test has no differential diagnostic value. Unlike the metabolic measurements, however, the differences between the group mean values are statistically insignificant. Group A and group B also show extensive overlap in t_{1/2} II values. Some correlation is seen between the t_{1/2} II and the corresponding metabolic variables, however. All seven of the control joint studies and six of the eight group B seropositive RA joint studies which all demonstrate low oxygen uptake, had t_{1/2} II levels longer than 100 min. 22 of 27 group A studies and 12 of 13 seronegative RA studies, where oxygen uptake is high, had t_{1/2} II levels shorter than 100 min. Since seronegative patients are not distinguished from group A seropositive patients by t_{1/2} II values, we did not attempt to separate rheumatoid joint studies by serology in further analyses.

We attempted to correlate t_{1/2} II values with both clinical and histologic estimates of joint inflammation.

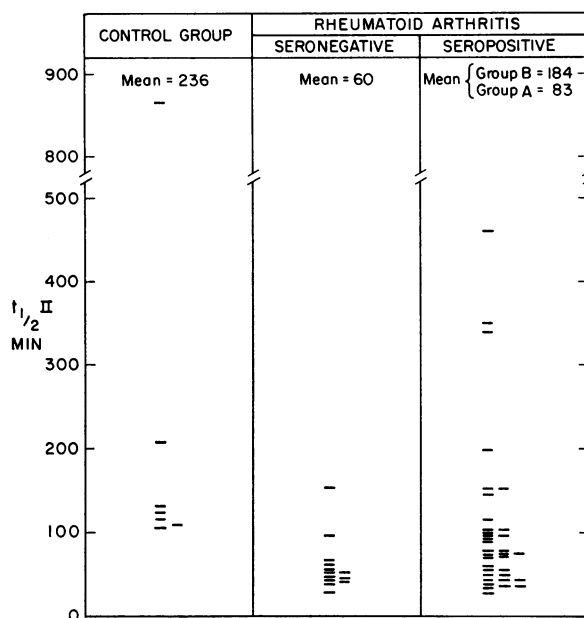


FIGURE 8 Distribution of ^{133}Xe $t_{1/2}$ II values by clinical diagnosis. Each dash represents one knee joint study. Group mean values (min) were: control 235.9 (SEM 40.7), seronegative RA 60.4 (SEM 9.0), and seropositive RA 105.8 (SEM 51.4) with group A 82.6 (SEM 16.5) and group B 184.3 (SEM 37.1). The eight studies for the group B patients are not separated symbolically, but six of the eight had $t_{1/2}$ II values over 100 min.

Fig. 9 shows the data in three groups of increasing clinical severity from mild (0-4) to severe (9-15) disease. Again marked scatter is seen in each group, but there is a significant difference (P less than 0.01) between the $t_{1/2}$ II values in the group with mild local disease (0-4) and those in the group with severe (9-15) local disease. It seemed that comparison of the two knees in any one patient might show better clinical correlations than interpatient comparisons. In fact, in all patients where the two knee clinical grades differed by two numbers or more (six patient studies), the $t_{1/2}$ II was significantly shorter in the knee with more severe disease. However, since the clinical estimates include several factors not related to the immediate degree of inflammation in the joint, it is not surprising that only two of nine patients with symmetrical clinical grades showed $t_{1/2}$ II values within $\pm 20\%$ for their two knees. On the other hand, in each of 11 knees studied serially, changes in clinical grades and in $t_{1/2}$ II levels showed a striking inverse relationship. It would seem therefore that the $t_{1/2}$ II values and clinical grades correlate well only in serial studies of the same knee or when comparing two knees with gross clinical differences in disease activity.

Fig. 9 shows the $t_{1/2}$ II values grouped according to synovial biopsy histologic grades from mild inflammation (0-1) to severe inflammation (3). Inflammation here refers to total cellular infiltrate estimated from multiple synovial fragments sampled from several areas of the joint. These data also show marked scatter, but there is a significant difference (P less than 0.01) between the $t_{1/2}$ II values of the group with minor pathology (0-1) and those of the group at the other extreme with severe pathology (3). For seven of nine patients with at least one full grade difference in biopsy inflammation, the knee with more severe histologic disease had a significantly shorter $t_{1/2}$ II. The ^{133}Xe washout therefore appears to be an index of local knee circulation which is in part related to local inflammation as estimated either histologically or clinically. There are, however, numerous other variables which may play a part in determining the $t_{1/2}$ II values for any joint and this makes interpatient or even interknee comparisons hazardous.

Effects of therapy

Synovectomy. Four patients who had a synovectomy of one knee were studied before surgery (baseline) and at 1 month and 4½ or 5 months after surgery (Table I). The $t_{1/2}$ O₂ values show no significant changes in any patient except for the temporary increase seen in the operated knee of patient II at 1 month. Lactate concentrations show a progressive fall in the operated knee relative to the unoperated side in the two patients fully studied (II and IV). In one patient (III) there is a decrease in the synovectomy knee lactate concentration from months 1 to 5 despite a rise on the control side. Patient I has no serial values but the lactate concentrations are symmetrical at 4½ months. In two instances (patients II and IV) the synovial fluid P_{O₂} has risen more in the operated knee than the control side at 4½ or 5 months. Patient III shows a greater increase in the 5 month P_{O₂} on the operated side than the control knee, but no baseline P_{O₂} is available. The results of patient I are inconclusive. Thus, increases in the P_{O₂} levels parallel decreases in the saline lactate concentrations. The $t_{1/2}$ II values after synovectomy show no consistent changes. The knee clinical grades do not correlate with any of the physiological variables.

Intra-articular corticosteroid therapy. Five patients received a soluble corticosteroid in one knee and three received a depot steroid which gives slow sustained release of corticoid locally in one knee (Table II). The knee clinical grades showed bilateral improvement in all soluble corticoid patients (group 1), and in one depot corticoid patient (VI in group 2). The other two patients in group 2 (VII and VIII) showed improvement in only the corticoid injected knee. The $t_{1/2}$ O₂

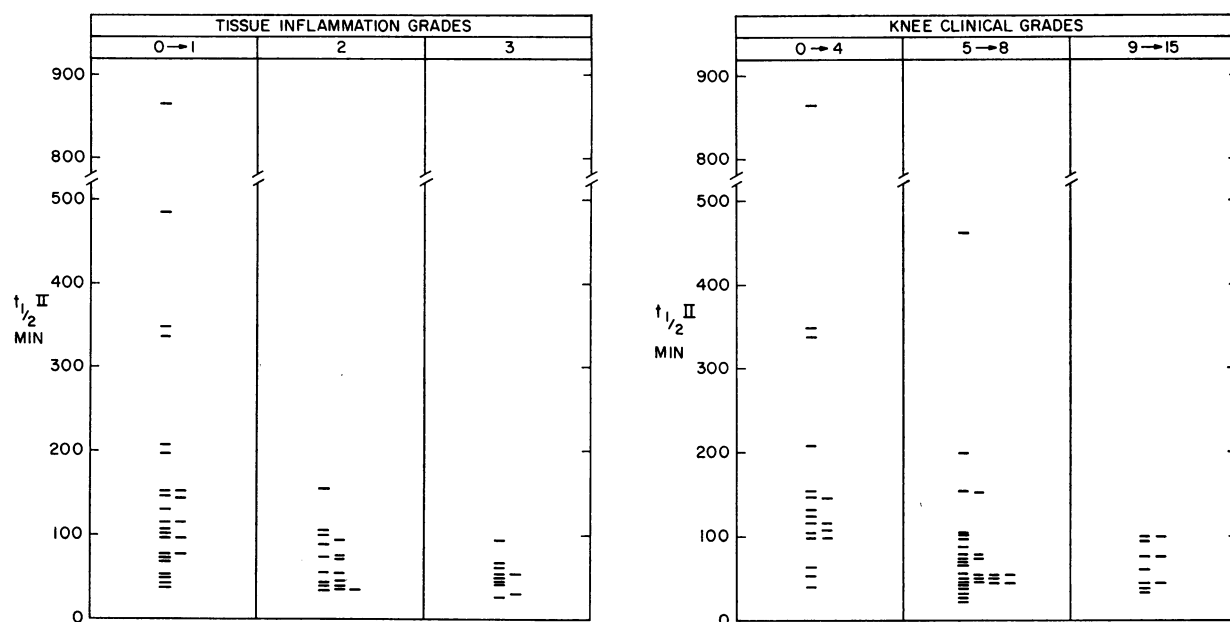


FIGURE 9 Correlation of ^{133}Xe $t_{1/2}$ II values with synovial biopsy inflammation grades and knee clinical grades. Each dash indicates the evaluation of one joint. Mean biopsy values were: 0-1 = 173.6 (SEM 41.2), 2 = 72.2 (SEM 7.6), and 3 = 49.3 (SEM 6.2). Mean clinical values were: 0-4 = 180.2 (SEM 41.1), 5-8 = 85.4 (SEM 16.1), and 9-15 = 66.2 (SEM 8.1).

values showed no significant changes in any patient (Table II).

Decreases in saline lactate concentrations were associated with increases in synovial fluid P_{O_2} levels, as in the synovectomy group. Lactate concentrations fell symmetrically in the three patients (III, IV, V) in group 1 where values are available, suggesting that possibly the corticoid escaped from the injected joint and had contralateral knee effects. This is supported by the bilateral increase in room air synovial fluid P_{O_2} values in the two patients in this group (II and IV) where there are data. The $t_{1/2}$ II values also are seen to rise in both knees in two group 1 patients (I, II), but not in the other three.

The lactate concentrations fell and the synovial fluid P_{O_2} values rose only in the injected knee in two patients in group 2 (VI and VII). In the other patient (VIII) lactate levels were initially low and no synovial fluid P_{O_2} was obtained. The ^{133}Xe $t_{1/2}$ II values showed a strikingly asymmetric increase in the injected knees of patients VI and VII, but the $t_{1/2}$ II values rose for both knees of patient VIII. These results taken together suggest that depot corticoid action is confined to the treated knee.

In summary, the $t_{1/2}$ O_2 values showed no significant fluctuations in either therapy group. Decrements in lactate concentration correlated with increments in syno-

vial fluid P_{O_2} in both therapy groups. Changes in the ^{133}Xe $t_{1/2}$ II values and the knee clinical grades were related to changes in the metabolic variables only for the intra-articular corticoid group.

In addition, we found that baseline synovial fluid P_{O_2} levels did not show any relation to $t_{1/2}$ O_2 values in corresponding joints. We also found that neither the metabolic results nor the ^{133}Xe $t_{1/2}$ II values showed any consistent relationship with serum or synovial fluid titers of rheumatoid factor in the seropositive RA patients. Finally, none of the metabolic or circulatory variables correlated with the general clinical grades of over-all disease severity.

DISCUSSION

The results of the metabolic studies indicate that knee joints of patients with long-standing rheumatoid arthritis use more oxygen and produce more lactate in vivo than control knee joints. In vitro studies have shown similarly that the oxygen consumption of rheumatoid synovium is 10-20 times that of normal synovium per mgN of tissue (7). This difference is a minimum value limited by the inability to accurately quantitate the very low in vitro oxygen uptake of normal synovium. The in vitro lactate production by rheumatoid synovium has been found to be between three and six times that of normal synovium per mgN of tissue (7,

TABLE II
Effects of Intra-Articular Corticosteroids

Patient	Procedure	Lactate concentration		$t\frac{1}{2} O_2$		$PO_2\ddagger$		$^{133}Xe\ t\frac{1}{2} II$		Knee clinical grade	
		R*	L	R	L	R	L	R	L	R	L
		<i>mg per 100 ml</i>		<i>min</i>		<i>mm Hg</i>		<i>min</i>			
1. Soluble corticosteroid											
I	Control	—	—	10.1	8.8	—	—	88.6	98.4	8	9
	After right knee injection	—	—	14.5	7.3	—	—	323.9	147.8	6	7
II	Control	—	—	9.5	5.0	18	18	43.0	60.0	14	14
	After left knee injection	—	—	5.6	6.2	29	31	146.5	81.3	10	10
III	Control	27.2	21.8	7.7	8.6	24.5	—	57.2	101.4§	8	6
	After right knee injection	2.1	2.0	11.4	13.8	29	—	186.5	62.5	4	4
IV	Control	30.5	36.5	7.6	6.2	27	23.5	44.0	35.9	10	10
	After left knee injection	0	7.5	14.3	11.8	31	33	32.9	87.0	8	8
V	Control	27.0	9.0	10.2	13.0	—	—	152.9§	40.9	6	6
	After right knee injection	5.0	8.0	8.7	14.3	—	—	60.2	41.8	2	3
2. Depot corticosteroid											
VI	Control	46.0	29.5	7.5	8.2	6	23	51.7	54.7	8	7
	After right knee injection	20.5	27.0	6.7	6.9	27	25.5	174.9	53.6	3	4
VII	Control	2.7	32.2	12.8	11.1	28	26	73.9	38.2	10	12
	After left knee injection	7.0	10.0	11.7	10.0	28	31	47.6	53.5	10	9
VIII	Control	5.0	7.5	7.3	9.7	—	—	69.4	151.5	6	5
	After right knee injection	4.0	6.0	14.5	8.3	—	—	125.1	338.8	4	5

* R, right knee; L, left knee.

† PO_2 , partial pressure of oxygen in synovial fluid sampled from the knee joint with the patient breathing room air.

§ The ^{133}Xe scintiphotos of these knees showed anomalous local concentration of radioactivity (see text).

|| In both corticoid groups, the more symptomatic knee was treated and the control knee was injected with 1 ml of sterile saline. Group 1 patients received two intra-articular injections of 40 mg each of methyl prednisolone (Medrol, The Upjohn Company, Kalamazoo, Mich.) at weekly intervals with repeat studies one week after the last injection. Group 2 patients received one intra-articular injection of 24 mg of triamcinolone hexacetonide (Aristospan, Lederle Laboratories, Pearl River, N. Y.) with repeat studies 10 days after the injection.

8). It would be expected that these striking in vitro differences between control and rheumatoid joint oxygen uptake and lactate production per mgN of tissue might be amplified in vivo by the presence of greater tissue mass in the rheumatoid knee. This was found to be the case for 24 min saline lactate concentrations where the mean value for the group A rheumatoid patients was 30 mg per 100 ml and the mean value in control knees was 2.5 mg per 100 ml. On the other hand, the $t_{\frac{1}{2}} O_2$ values, which reflect local oxygen uptake, show less than a 3-fold difference between the means of these rheumatoid and control groups. We anticipated that the rate of fall in intra-articular saline PO_2 would be proportional to the rate of total oxygen uptake by the knee joint. Since the volume of intra-articular saline was the same in all knees studied, the rate of fall in PO_2 might be a comparable measure of oxygen uptake from knee to knee. However, we have not studied such other possibly important factors in determining the rate of

fall in saline PO_2 as the oxygen diffusion rate or the oxygen reservoir in the static blood pools of the joint which may vary for different knees. The thickened, often fibrin coated, membrane of rheumatoid synovium may act to decrease the rate of fall of the intra-articular saline PO_2 by limiting oxygen diffusion. In addition, regardless of the over-all thickness of the synovial membrane, only that small fraction of the rheumatoid synovium closest to the joint space might be effectively utilizing all of the saline oxygen. The increased vascular engorgement of rheumatoid synovium might also tend to minimize the rate of fall of saline PO_2 by providing other oxygen sources for the deprived synovium.

We must also consider the possibility that the factors responsible for the exponential shape of the intra-articular PO_2 decay curve might affect the calculated $t_{\frac{1}{2}} O_2$. These include: (a) decreasing metabolic consumption of oxygen by the synovial tissue with the falling ambient PO_2 level, and (b) decreasing gradient in PO_2 be-

tween the saline and the synovial tissue resulting in a progressively falling rate of diffusion. The rheumatoid joints with their high rate of oxygen consumption cause the intra-articular saline P_{O_2} to fall to low levels very early in the study period. Therefore, both the metabolic consumption of intra-articular oxygen and the diffusion of oxygen out of the saline would decrease earlier in rheumatoid joint studies, resulting in a leveling off of P_{O_2} values sooner than in the control joint studies. The net result might be an aberrantly high calculated $t_{1/2} O_2$ relative to the true oxygen uptake rate of the rheumatoid joint. All of the above considerations would make the measured oxygen uptake rate an underestimate of the true knee joint oxygen consumption. Similar factors may also operate to decrease the rate of rise of the intra-articular saline lactate concentrations in rheumatoid joints during tourniquet occlusion. However, we have less information about this variable since no kinetic studies were performed.

In addition to these factors which could minimize the measured oxygen uptake of rheumatoid joints for reasons inherent in the testing system, rheumatoid synovium has metabolic properties which would tend to make the lactate production much more prominent than the oxygen consumption. A type of feedback control related to ambient P_{O_2} levels has been found for lactate production in normal synovium in vitro (7, 8). Incubating normal synovium in a nitrogen atmosphere increased lactate production by 50–75%. In contrast, rheumatoid synovium produced lactate at a high rate which was unchanged by decreasing atmospheric P_{O_2} (7, 8). Thus, rheumatoid synovium would produce lactate during the entire 24 min study interval, but normal or control synovium would only produce significant amounts of lactate when ambient P_{O_2} fell late in the 24 min period. Another metabolic reason for the high in vivo lactate production by rheumatoid joints may be the lack of substrate limitation for local lactate production. Synovial glycogen is readily available and about 50% of the total store can be converted to glucose and utilized during a 1 hr in vitro incubation (19). For all of the above reasons we would anticipate that lactate production would be more prominent than oxygen consumption. The failure of $t_{1/2} O_2$ to increase after therapeutic maneuvers was probably also due in part to the technical inadequacies of our assessment of this variable. It is possible that oxygen uptake could decrease without a significant increase in $t_{1/2} O_2$.

We have assumed that only joint tissues and leukocytes infiltrating joint tissues are responsible for the measured differences in oxygen uptake and lactate production. For this reason any metabolic role of leukocytes in the intra-articular fluid must be excluded. This is particularly important since the polymorphonuclear

leukocytes could have a significant metabolism in the joint, especially if involved in phagocytosis of antigen-antibody complexes (20). The joints in the study were carefully flushed with saline after all synovial fluid had been aspirated, so that any remaining leukocytes would be very few in number compared to those infiltrating the tissue. Secondly, rheumatoid synovial fluid leukocytes have been found to have a very low basal rate of oxygen consumption with levels 20–60% of those for peripheral polymorphonuclear leukocytes from the same patient (21). Thirdly, there was no correlation between $t_{1/2} O_2$ values and saline white blood cell counts. These leukocyte counts as discussed above, should generally reflect the total number of leukocytes in the intra-articular fluid during the study. In addition, it has been previously shown that the P_{O_2} of a synovial fluid sample does not fall significantly when stored in ice regardless of the leukocyte count (1). Our measurement of P_{O_2} in saline therefore should be very close to the intra-articular P_{O_2} at the time the saline was aspirated. For these reasons, we believe that the fluid phase leukocytes are not contributing significantly to the metabolic rates measured in this study.

The correlation found between the $t_{1/2} O_2$ and lactate concentration values and the total pathology grades of corresponding synovial biopsies (Fig. 6) is significant. These variables which assess local metabolic rates therefore must be determined in part by the over-all cellularity of the synovial tissue, including infiltrating leukocytes as well as fixed tissue cells. This good correlation also suggests that the cell density in the synovium, as estimated by the histologic grades, parallels the metabolic activity of individual cells and the total bulk of synovial tissue in the joints. However, the sampling error of needle biopsies in a disease with such variable and focal pathology must be considered. This is critical because it has been shown for rheumatoid synovium that oxygen consumption for villi is almost six times that of membranous areas per mgN of tissue and that lactate production has a similar ratio for villi over membranous synovium (6). Our method of sampling tissue from several areas for each joint biopsy was intended to minimize this type of error, and within the limits of the other determinants above, it appears to have been successful.

The results of our ^{133}Xe desaturation studies agreed with previous work in several respects. The mean values for our $t_{1/2} \text{II}$ results are close to those in the literature. W. C. Dick and his colleagues (22) found a mean $t_{1/2} \text{II}$ for osteoarthritic patients of 139.6 min and for normals of 248.8 min which approximates the mean of 235.9 min for our control group composed of patients with degenerative and mild traumatic arthropathy. In this same series, the rheumatoid mean $t_{1/2} \text{II}$ was 61.2 for 43

patients compared with 60.4 for our seronegative rheumatoid group and 82.6 for our group A seropositive rheumatoid group. These workers found a significant overlap between the rheumatoid and degenerative arthropathy groups much as was revealed by our study. A significant relationship between ^{133}Xe $t_{1/2}$ II values and clinical estimates of knee inflammation has been reported (22). We have confirmed these results and also demonstrated a relationship between the ^{133}Xe desaturation rates and the histologic estimates of total synovial inflammation in the needle biopsies.

The above data relate the rate of desaturation of intra-articular ^{133}Xe with clinical and histologic assessments of local joint inflammation and therefore indirectly with local circulatory flow. Direct evidence that ^{133}Xe washout rate from intra-articular saline is related to human joint regional blood flow has been reported previously (16) and was confirmed in this study by arterial tourniquet tests. Other evidence directly relating ^{133}Xe washout with regional circulation is available from studies of dog joints (23) and also muscle (17) and skin (18).

We have chosen to use the t value from the slow component of all of our ^{133}Xe desaturation curves ($t_{1/2}$ II or $t_{1/2}$ when only one component was found) as a reflection of joint blood flow for the following reasons: (a) A monoexponential curve would be expected if ^{133}Xe distribution in the joint was essentially instantaneous and the synovial tissue was both homogeneous and not close to saturation with ^{133}Xe . Our serial ^{133}Xe scintiphotos and continuous video tape recordings indicated that the distribution of ^{133}Xe was complete by the time enough activity could be recorded for an image (or a reading on the rate-meter). In addition, no redistributions were seen within the limits of the resolution of scanning which suggests that diffusion equilibrium was maintained. Tissue solubility studies (24) indicate that our ^{133}Xe dose was under 10% of that required to saturate tissue with ^{133}Xe . Therefore, ^{133}Xe counter-current recycling could begin immediately and might not change appreciably during the course of most of our studies. (b) Most $t_{1/2}$ II values were much faster than that for fat alone which has been measured to be over 200 min (25), so that it is unlikely that all of the ^{133}Xe instantaneously dissolved in fat around the joint with subsequent washout reflecting adipose circulation only. The $t_{1/2}$ II may however represent two or more washout rates from synovial tissue and inflamed subsynovial tissue. (c) This component could be accurately defined and represented over 85% of the total curve in 70 of our 80 studies. (d) The $t_{1/2}$ II was predictably reproducible as has previously been shown for 24-hr repeat studies (22). It correlated with meaningful clinical and pathologic variables. (e) The

first component half-time ($t_{1/2}$ I) when it could be defined was more erratic. It is possible that this results from variable trauma inducing either direct passage of ^{133}Xe to blood or transient reactive hyperemia as has been suggested (18, 26).

Our studies show that there are significant differences between the control and rheumatoid group mean values for either $t_{1/2}$ O_2 or saline lactate concentration. However, the overlap between the metabolic measurements in either rheumatoid group and those in the control group clearly demonstrates that they have no diagnostic value in routine clinical work. These tests also have no known prognostic or therapeutic implications, with the possible exception of the high $t_{1/2}$ O_2 and low lactate levels of the patients with early mild rheumatoid arthritis. The ^{133}Xe $t_{1/2}$ II values do not even show significant differences between diagnostic group means, and the scatter is greater than for the metabolic measurements. Seropositive and seronegative rheumatoid groups showed no definite differences for any of the variables. There was also marked scatter when any of these variables were grouped on clinical or pathologic grounds, and again the scatter was greater for the ^{133}Xe $t_{1/2}$ II values. The use of a single set of physiological measurements in the evaluation of an arthritic patient therefore cannot be recommended at the present time.

In the therapy groups where there were serial determinations, the importance of the physiologic approach was evident. Of all the variables followed after synovectomy, only the saline lactate concentrations and synovial fluid P_{O_2} levels showed asymmetric changes in the operated knees. After intra-articular corticosteroids, these same two variables showed significant changes, and also the ^{133}Xe $t_{1/2}$ II lengthened in the injected knee and occasionally the contralateral knee. Clinical improvement, however, as reflected in the knee grades, paralleled these physiological changes only in the corticosteroid group. The in vivo effects of corticoids on some of the above variables are consistent with previous results of corticoid effect on synovial metabolism in vitro and synovial circulation in vivo. Corticoids have been shown at physiologic concentration to decrease lactate production and oxygen consumption by rheumatoid synovium in vitro (6), and lactate production but not oxygen consumption by human peripheral leukocytes in vitro (27). Previous studies of ^{133}Xe washout after intra-articular corticoids showed an increase in $t_{1/2}$ II in 19 of 26 joints of the same order of magnitude as reported here (22). Unfortunately, only the injected knee was restudied. Our results show contralateral knee changes especially when the soluble preparation was used possibly due to direct steroid effects. The failure of synovectomy to reduce the oxygen uptake of rheumatoid knee joints may be due to high oxygen uptake

either by regenerating synovial tissue or by the few fragments of residual rheumatoid synovium not removed at operation. Repeat needle biopsies did show inflamed synovial tissue present already 1 month after surgery. The failure of corticosteroids to raise t_1 O_2 remains unexplained. It is possible however that the corticoids affect primarily the leukocytes infiltrating the synovium, in which case we might expect to see changes in lactate production but not in oxygen consumption (27).

The value of this combined clinical and physiological approach to document alterations in the over-all state of diseased joints after therapeutic maneuvers is clear. The relationship of any of the physiological alterations to progressive joint destruction however is not clear and can only be determined by long term follow-ups.

The results of these studies demonstrate that both local metabolic rate and regional circulatory flow are increased in the rheumatoid joint. Although both variables are increased, an imbalance between the two may be a more significant factor in the severity of joint disease and the response to various therapies. Local oxygen consumption and circulatory oxygen supply must by definition determine the steady state P_{O_2} measured in synovial fluid (1). Thus the slight increases in intra-articular P_{O_2} seen after synovectomy or local corticosteroid therapy represent an alteration in the ratio of these two determinants. Our relatively crude methods for evaluating either independent variable, however, preclude any statement concerning which determinate has been disproportionately altered to account for the observed change in ratio. In addition, it was not possible to correctly predict other steady state intra-articular P_{O_2} values from the respective t_1 II and t_1 O_2 levels. These levels then must be considered as only reflections of the true joint regional circulatory flow and oxygen consumption rates.

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Note added in proof: A recent study (28) has been published which confirms our findings (1) of very low P_{O_2} levels in the synovial fluid from joints of patients with severe rheumatoid arthritis. Although no detailed clinical data or synovial biopsies are presented, 16 of the 48 rheumatoid fluids and none of the control fluids had P_{O_2} levels under 20 mm Hg.

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