Metabolic Activity of Sodium, Measured by Neutron Activation, in the Hands of Patients Suffering from Bone Diseases: Concise Communication

T. J. Spinks, D. K. Bewley, M. Paolillo, J. Vlotides, G. F. Joplin, and A. S. O. Ranicar

Medical Research Council, Cyclotron Unit, and Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom

Turnover of sodium in the human hand was studied by neutron activation. Patients suffering from various metabolic abnormalities affecting the skeleton, who were undergoing routine neutron activation for the measurement of calcium, were investigated along with a group of healthy volunteers. Neutron activation labels the sodium atoms simultaneously and with equal probability regardless of the turnover time of individual body compartments. The loss of sodium can be described either by a sum of two exponentials or by a single power function. Distinctions between patients and normal subjects were not apparent from the exponential model but were brought out by the power function. The exponent of time in the latter is a measure of clearance rate. The mean values of this parameter in (a) a group of patients suffering from acromegaly; (b) a group including Paget's disease, osteoporosis, Cushing's disease, and hyperparathyroidism; and (c) a group of healthy subjects, were found to be significantly different from each other.

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The technique of in vivo neutron activation allows labeling of atoms simultaneously regardless of the anatomical compartment in which they reside. It thus overcomes the difficulties that may occur in the study of metabolism of an element by the use of injected radiotracers because of different turnover rates in different compartments. In a previous publication (*1*) a method for measuring the turnover of sodium in the hand by neutron activation was described, together with preliminary results in patients suffering from diseases affecting the bone. Of the major body elements, only sodium (as Na-24) has a long enough half-life (15 hr), and gives enough activity, to permit metabolic processes to be followed for more than a few hours. It was shown in the earlier paper that the clearance of sodium could be fitted either by the sum of two exponential components or by a single power function. On the basis of the two-exponential model, no significant differences in clearance rate constants, or in the relative sizes of the compartments, were observed between healthy subjects and patients with metabolic bone disease. However, a significant difference between these two groups was observed in the exponent of time in the power function. The latter model thus provided a more useful as well as a simpler description of the turnover of sodium.

This work has been extended to include more patients suffering from Paget's disease, osteoporosis, and hyperparathyroidism, and also some with acromegaly and Cushing's disease. All the patients were undergoing routine measurements of total and partial body calcium by neutron activation in order to assess the effect of therapy on bone mass. We used this opportunity to monitor the hands for loss of sodium, which is activated at the same time. Analysis of the clearance by means of the two-exponential model was continued in order to observe possible differences in the new groups of patients.

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For reprints contact: T. J. Spinks, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Rd., London W12 OHS, England.

In this report we also examine the sensitivity of the parameters in the power function to the particular counting regimen.

METHOD

The methods of irradiation and counting have been described in detail previously (*1*). Briefly, the subject's left hand is exposed in a wax block to a fast-neutron beam (mean energy 7.5 MeV) from a cyclotron. The dose received by the hand is 1.5 rad and that received by the whole body due to stray radiation is less than 0.02 rad. During irradiation the right hand is shielded in a wax cylinder with cadmium lining. Counting of the induced activities is carried out by placing both hands between two pairs of vertically opposed NaI(Tl) detectors. The purpose of counting the shielded right hand is to determine simultaneously the background due both to the small activity induced in the rest of the body and to recirculation.

DESCRIPTION OF PATIENTS

The patients were suffering from the following conditions: **Paget's disease.** *Patients 1 and 2 (F) and 3 and 4 (M).* These four patients had localized disease not affecting the hands, although Patient 2 had pagetic involvement of the left distal radius. All were being treated with synthetic human calcitonin. The duration of treatment in Patient 1 was 25 mo before measurement No. 1 and 84 mo before measurement No. 2; before the single measurements in Patients 2, 3, and 4, treatment had lasted 59, 12, and 22 mo, respectively.

Osteoporosis. *Patients 5 to 7 (F), and 8 (M).* Patient 5 was treated with calcium and phosphate supplements during the year before activation analysis. Patient 6 had

TABLE 1. PARAMETERS OF TWO-EXPONENTIAL FUNCTION

Patient's number*	A_1†	A_2†	$\frac{A_1}{A_1 + A_2}$	λ_1† (hr^{-1})	λ_2† (hr^{-1})
Paget's					
1′	87 ± 6	25 ± 7	0.78	0.7 ± 0.1	0.02 ± 0.02
4	100 ± 2	50 ± 2	0.67	1.2 ± 0.1	0.02 ± 0.01
Osteoporosis					
5	99 ± 18	41 ± 16	0.71	1.0 ± 0.4	0.03 ± 0.06
6	98 ± 21	28 ± 20	0.78	1.1 ± 0.5	0.00 ± 0.05
7″	100 ± 14	36 ± 13	0.74	1.4 ± 0.4	0.01 ± 0.03
8	117 ± 49	27 ± 27	0.81	0.2 ± 0.1	0.00 ± 0.05
Hyperparathyroidism					
10	111 ± 13	75 ± 13	0.60	0.9 ± 0.2	0.03 ± 0.02
11	119 ± 15	42 ± 14	0.74	1.2 ± 0.3	0.03 ± 0.05
12	90 ± 14	46 ± 12	0.66	2.1 ± 0.7	0.08 ± 0.08
Acromegaly					
13	126 ± 17	38 ± 14	0.77	1.6 ± 0.5	0.02 ± 0.06
14	85 ± 34	108 ± 27	0.44	4.3 ± 3.6	0.30 ± 0.17
15	110 ± 16	25 ± 15	0.81	1.4 ± 0.4	0.01 ± 0.09
17	168 ± 47	17 ± 50	0.91	1.2 ± 0.5	0.00 ± 0.37
19	177 ± 13	40 ± 11	0.82	1.8 ± 0.3	0.01 ± 0.03
Normals					
20′	58 ± 9	31 ± 8	0.65	0.8 ± 0.3	0.01 ± 0.02
20″	85 ± 25	59 ± 26	0.59	1.9 ± 1.5	0.05 ± 0.09
21	87 ± 16	56 ± 14	0.61	0.9 ± 0.3	0.01 ± 0.02
22	101 ± 9	40 ± 7	0.72	1.2 ± 0.2	0.00 ± 0.08
23	71 ± 16	63 ± 18	0.53	0.8 ± 0.4	0.02 ± 0.02

* Where the activation procedure was carried out twice, the run concerned is indicated by attaching ′ or ″ to the subject's number.

† Errors given are approximate 95% confidence limits, see ref. *2*.

received only calcium supplements for 2 yr, and Patient 8 for 4 yr, before measurement. Patient 7 was untreated.

Cushing's disease. *Patient 9* (*F*). This patient had been treated by pituitary implant of Au-198 rods 3 yr previously; she was in clinical and biochemical remission, and not on replacement therapy.

Primary hyperparathyroidism. *Patients 10 to 12* (*F*). Patient 10 had presented with acromegaly and was in full clinical and biochemical remission following pituitary implantation of Y-90 rods. Nevertheless hypercalcemia persisted. Patient 11 had mild and untreated disease, and Patient 12, also with mild disease, had been treated with phosphate supplements for 18 mo.

Acromegaly. *Patients 13–18* (*6 F*), *and 19* (*M*). All patients in this group had been suffering from the disease for 6 yr or more before measurement, and all had been treated by pituitary implant or external radiation. Patient 17 had been on thyroxine and prednisone for 4 yr before measurement. The others were not on replacement therapy. Growth-hormone levels were based on the means of the 60-, 90-, and 120-min levels during an oral glucose-tolerance test. In order of ascending patient number, the levels were 212, 36, 130, 20, 54, 79, and 100 mIU/l. The upper limit of normal is 10 mIU/l.

COUNTING PROCEDURES AND DATA ANALYSIS

Counting was continued for up to 2 days after irradiation, beyond which time it was not possible to detect the Na-24 activity. Each count lasted 20 min, the first being started about 3 min after irradiation. In some cases the data for each 5-min section of the first three 20-min periods were stored separately in an attempt to delineate more clearly the faster component of clearance.

Data were analyzed by use of the following two mathematical models:

$$C(t) = A_1\exp(-\lambda_1 t) + A_2\exp(-\lambda_2 t) \quad (1)$$

$$C(t) = Bt^{-x} \quad (2)$$

Where C(t) is the decay-corrected Na-24 count rate, t the time between the middle of the irradiation and counting periods, and A_1, A_2, λ_1, λ_2, B, and x are positive constants. The parameters in Eq. 1 were obtained by weighted least-squares analysis using the computer routine GAUSHAUS (*2*). The inverse variances of each point were used as weighting factors. The parameters in Eq. 2 were obtained by simple linear least-squares analysis after log transformation.

RESULTS

Two-exponential model. The values of the parameters in Eq. 1 obtained from subjects for whom counts were made through more than 20 hr, are shown in Table 1. Also included are values of $A_1/(A_1 + A_2)$, which measure the relative sizes of the two compartments. The data from three runs (Patients 2, 7′, and 16) did not permit the iterative computer program to produce convergent solutions. The mean of $A_1/(A_1 + A_2)$ for all subjects (0.70) was the same as that for the smaller group presented in the earlier paper (*1*), although the range in the present case was slightly wider. By Student's t-test, the means of $A_1/(A_1 + A_2)$ for patients (0.73) and normal subjects (0.62) did not differ significantly at the 5% level; neither did those for $A_2/(A_1 + A_2)$. There was also no difference between mean λ_1 for the patients (1.4 hr^{-1}, or $T_{1/2}$ = 30 min) and that for the normals (1.1 hr^{-1}, $t_{1/2}$ = 38 min). The same was true for λ_2, which had a mean value of 0.040 hr^{-1} ($t_{1/2}$ = 17 hr) for patients and 0.019 hr^{-1} ($t_{1/2}$ = 36 hr) for normals. Individually, considering the confidence limits, most values of λ_2 were indistinguishable from zero.

Power-function model. The parameters of Eq. 2, obtained by lease-squares analysis, are slightly different when the Na-24 counting rates for the first three 20-min periods are used raw (Method A) and when each is subdivided into 5-min sections (Method B). By method A the value of x for 19 patients is 0.40 (range 0.27–0.59), whereas by Method B it is 0.36 (range 0.22–0.45). The two lines fitting the data are shown in Fig. 1, a log-log plot of Na-24 count rate against time for the patient showing the largest difference in x. It is observed that the points for the 5-min counting periods suggest a flattening off at times earlier than about 0.05 hr. This is expected theoretically since Eq. 2 is meaningless at t = 0. However, it provides an adequate description of sodium clearance over the period of interest. Five subjects were measured periodically for the first 10 hr only, whereas

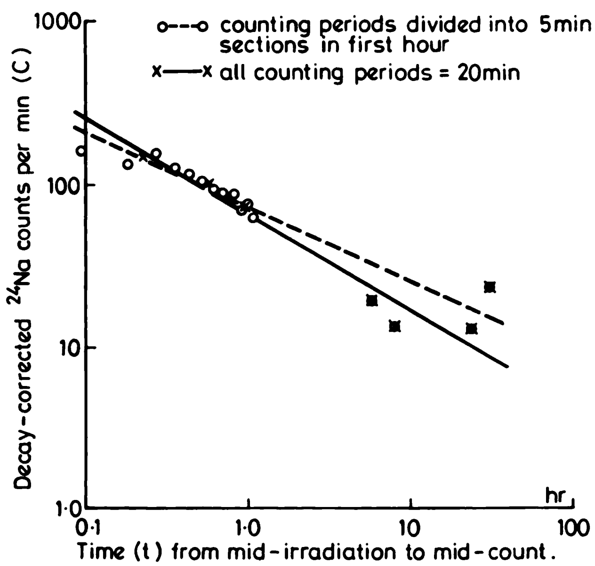

FIG. 1. Comparison between clearance rates of sodium, calculated by least-squares analysis, in Patient 16 when the first three 20-min counts are plotted (log-log) in 5-min sections and as continuous 20-min periods.

for the rest of the series it was continued up to 48 hr. The values of x for the latter group were recalculated using only the data accumulated in the first 10 hr after irradiation. The mean value of x in 21 patients for the first 10 hr (20-min counting periods) was 0.38 (range 0.24–0.60), and for 48 hr 0.37 (range 0.26–0.59). In general, the differences are small because the accuracy of later points is lower, so they are given less weight in the mathematical analysis.

In order to make a valid comparison between all subjects, only data obtained within the 10 hr after irradiation were used, with counting periods of 20 min. Table 2 gives individual values of B per rad and x, together with the means for each group. B is proportional to the mass of sodium in the hand, and there is no significant difference between the means of B per rad for any group. However, there are considerable differences in the mean values of x. For the Paget's, osteoporosis, Cushing's, and hyperparathyroid groups these means are similar, the combined mean being 0.37. A t-test reveals that the mean x for this combined group is significantly different from those of the normal subjects ($P < 0.01$) and the acromegalics ($P < 0.001$). The difference between the acromegalic and normal groups is similarly significant ($P < 0.001$). Figure 2 presents these findings graphically. A comparison between the log-log plots for an acrome-

TABLE 2. PARAMETERS OF POWER FUNCTION

Patient's number*	Sex	Age	B/rad ± s.e.	Mean B/rad ± s.e.m.	x ± s.e.	Mean x ± s.e.m.
Paget's						
1′	F	58	25 ± 2		0.41 ± 0.03	
1″		64	25 ± 2		0.43 ± 0.04	
2	F	62	29 ± 4	30 ± 2	0.30 ± 0.06	0.37 ± 0.03
3	M	71	32 ± 1		0.41 ± 0.02	
4	M	64	35 ± 2		0.33 ± 0.02	
Osteoporosis						
5	F	64	30 ± 3		0.40 ± 0.04	
6	F	74	26 ± 2		0.42 ± 0.04	
7′	F	54	25 ± 2	33 ± 5	0.34 ± 0.03	0.36 ± 0.04
7″		56	27 ± 1		0.40 ± 0.02	
8	M	72	49 ± 5		0.24 ± 0.05	
Cushing's						
9	F	33	31 ± 3	31 ± 3	0.39 ± 0.04	0.39 ± 0.04
Hyperparathyroidism						
10	F	62	49 ± 3		0.34 ± 0.03	0.40 ± 0.03
11	F	65	31 ± 3	34 ± 8	0.46 ± 0.04	
12	F	48	23 ± 1		0.40 ± 0.01	
Acromegaly						
13	F	30	28 ± 2		0.47 ± 0.03	
14	F	64	31 ± 4		0.48 ± 0.06	
15	F	49	22 ± 1		0.48 ± 0.01	
16	F	60	28 ± 3	32 ± 3	0.52 ± 0.05	0.50 ± 0.02
17	F	33	29 ± 4		0.60 ± 0.07	
18	F	48	49 ± 4		0.49 ± 0.04	
19	M	49	34 ± 2		0.45 ± 0.03	
Normals						
20′	M	26	33 ± 1		0.30 ± 0.02	
20″		27	31 ± 3		0.28 ± 0.04	
21	M	32	45 ± 4	36 ± 3	0.27 ± 0.04	0.28 ± 0.01
22	M	51	34 ± 2		0.33 ± 0.03	
23	F	45	39 ± 3		0.25 ± 0.03	
24	F	49	31 ± 1		0.27 ± 0.01	

* See footnote to Table 1.

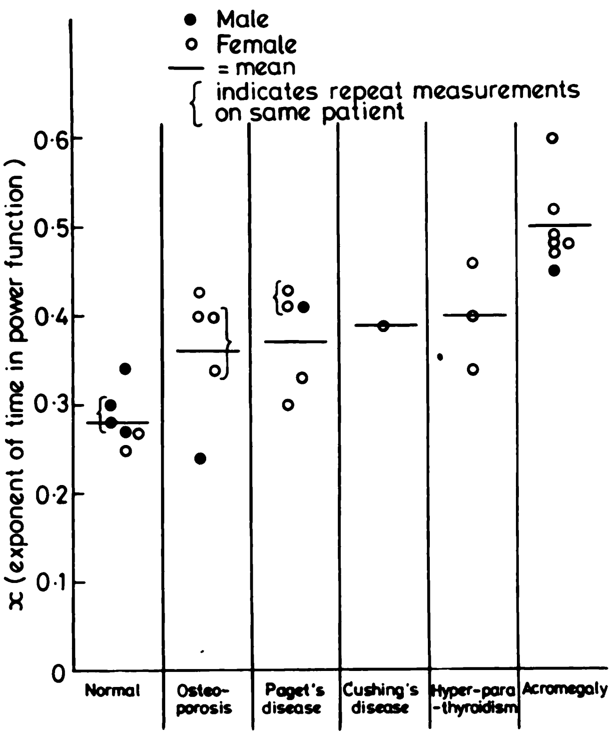

FIG. 2. Diagram showing values of x (Eq. 2), the index of sodium clearance, in each group of subjects.

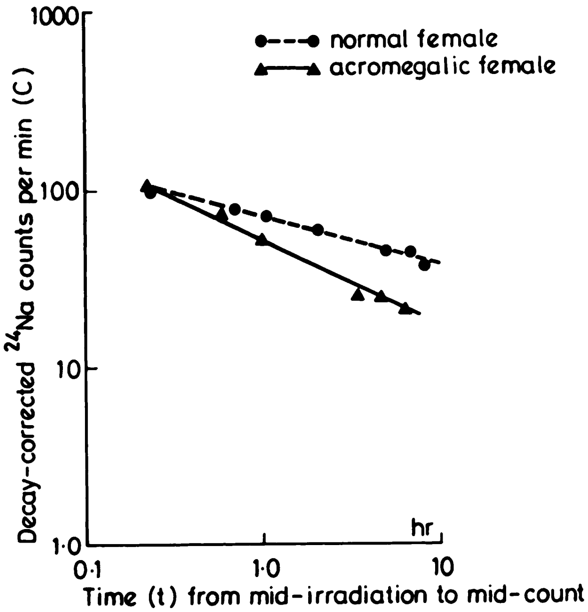

FIG. 3. Comparison between slopes for healthy individual (No. 24) and patient suffering from acromegaly (No. 15).

galic patient (No. 15) and a normal subject (No. 24) is shown in Fig. 3 to demonstrate the difference in slope. Of the Na-24 in the hand at t = 0.1 hr, 90% has been lost in the acromegalic at 10 hr, and 70% in the normal.

DISCUSSION

The results of our preliminary report (*1*) showed that there was a significant difference in the average value of the parameter x in Eq. 2—an index of the rate of sodium clearance—between a group of normal subjects and a group suffering from various bone diseases. There were no clear distinctions on the basis of the two-exponential model. These findings are re-emphasized by the results presented here. The inadequacies of the data arise from the relatively low count rates and the difficulty of counting at very frequent intervals. The attempt to obtain four parameters of clearance from the two-exponential model does not reveal significant differences between patients and healthy subjects, although the two compartments may have some physiological significance. For instance, it is likely that the smaller compartment represents the relatively fixed proportion in bone. On the other hand, analysis by means of the power-function model yields clearly different results. Without making comment about the relative goodness of fit of Eqs. 1 and 2, there are clear differences between certain groups in the single parameter of clearance, x, in Eq. 2. These distinctions are not apparent in the parameters λ_1 and λ_2 in Eq. 1. The values of x (Table 2) were also found to be relatively insensitive to the weighting factors used. For instance, the mean change was less than 2% when the inverse variances were replaced by equal weighting for each point over the 10-hr period. However, the reasonable fit to the power function may also be fortuitous and not necessarily due to more fundamental physiological processes. The small numbers of patients in some groups currently prevents differences in x (if they exist) from being observed, and the accuracy of the method is probably not high enough for definite detection of abnormality in an individual. However, the clearly faster rate of sodium turnover exhibited by patients suffering from acromegaly suggests that x may be a sensitive function of this particular disease. Examination of the ages of both normals and patients does not reveal any clear dependence of x on age, and it can also be seen that many of the patients who had been receiving treatment for a considerable period still had clearance rates well above the normal values. This was particularly evident in the acromegalic group, where raised clearance rates were apparent in all cases, despite the previous therapy aimed at curbing the pituitary hyperfunction. A further point to consider is that only the loss of sodium is being observed in this procedure. Since a considerable fraction of sodium is contained in bone, it is suggested that the parameter x might provide evidence of the rate of bone resorption.

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For further information contact:

Mitchell H. Stromer, M.B.A.
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