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KINETIC MODEL BUILDING USING ADVANCE NUCLEAR MEDICINE TECHNIQUES - THE KINETICS OF CHROMIUM(III) IN THE HUMAN BODY

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Chromium is a recently discovered essential trace element which, in rats, is required as a component of a dietary factor necessary for optimal glucose utilization[1]. A dietary deficiency of chromium(III) produces a loss of control of glucose metabolism, and a severe deficiency in rats produces symptoms similar to diabetes melitus in human[2]. Recently there has been increasing interest in chromium in human nutrition, and several authors believe it is a nutritional requirement[3,4,5,6,7,8,9].

However the question whether low chromium status can be determined in humans from in vitro analysis, has never been demonstrated with satisfaction. Investigation of chromium concentration in blood plasma, hair, etc. have illustrated 2 major problems, namely the accuracy of the analytical measurements and the correct interpretation of analytical data. Most recent investigations of chromium concentration in human tissues have shown that previous values have to be revised downward, probably resulting in revisions of previous experimental findings. The uncertain results combined with the difficulties in the interpretation of analytical data, make it difficult, at least at the present time, to establish a valid index of chromium nutritional status in humans through in vitro analysis.

The purpose of this study is to investigate whether a valid index of chromium (III) nutritional status can be determined with satisfaction through in vivo kinetic analysis. Three normal subjects and three patients suffering from hemochromatosis were periodically scanned with the Donner Laboratory computerized whole body scanners, starting seconds after radiochromium(III) was administered intravenously, up to a period of 84 days. The activity in the liver, adipose and muscle tissues, spleen and bone was quantitated and corrected, by subtraction of the blood circulation activity in that organ; the major concentration was found in the liver and

spleen. From the series of scan images, a kinetic model for the radiochromium(III) metabolic pathway was constructed. Computer analysis showed a significant difference between the two classes of subjects in organs as well as whole body radiochromium (III) transfer. Interpretation of these results showed that in patients with excessive iron stores, a smaller amount of chromium bound to plasma protein was found and a corresponding decrease in transfer of chromium into stores in the liver and other tissues was also found.

This technique is able to determine standardised metabolic parameters for chromium(III) in normal subjects, and should be applicable in assessing nutritional requirements in the human diet, and its importance in disease processes such as diabetes.

Although advanced nuclear medicine techniques were used in the building of the kinetic model, the metabolic parameters were determined by using the whole body radiochromium(III) retention (or the excretion of radiochromium(III) into the urine) and the plasma clearance data as input to a minicomputer. The major advantage of this method is that analysis could be performed in any laboratory that is equipped with a reasonable radiation measuring device and a minicomputer.

This successful approach in kinetic model building is applicable to other γ emitting radiotracers as well. Depending on the physical characteristics of the radioisotope the experimental method could be modified to obtain optimum results.

Materials and Methods

$^{51}Cr\ Cl_3 \cdot 6H_2O$(T-1/2=27.8 days, γ energy of 0.320 MeV, Amersham-Searle) was used as a sterile pyrogen-free saline solution at pH 3-4 at a specific activity of 100-200 mCi/mg. The dose was injected directly into an antecubital vein. Subjects were asked to follow their regular routine activities prior to and during the course of the experiment. Subject and patient descriptions are listed in table 1.

Blood samples were drawn periodically from patients starting seconds after 100 µCi of $^{51}Cr\ Cl_3 \cdot 6H_2O$ was injected up to a period of 60 days. Intervals between

drawing ranged from 3 minutes to 14 days. The blood samples were centrifuged for approximately 30 minutes at 3000 rpm with a clinical centrifuge to separate red cells and plasma. During the first 24 hours post injection approximately 10 blood samples of 20 cc each were drawn. Following centrifugation, the plasma collected during the first 24 hours was ultracentrifuged for approximately 24 hours at 114,000g and 17°C. Under these conditions plasma protein sedimented to the bottom, leaving a relatively protein-free supernatant. This procedure separated the plasma protein-bound radiochromium(III) and radiochromium(III) which was free or bound to lower molecular weight molecules (smaller than m.w.90000). The plasma radiochromium(III) in the protein fraction and in the supernatant was counted, using counts in the ^{51}Cr photopeak, for periods ranging from 10 to 30 minutes with a 24 cm diameter and 10 cm thick NaI(Tl) crystal and a Packard 400 channel analyzer.

Localization of radiochromium(III) in the human body was performed with the Mark II computerized rectilinear whole-body scanner[10,11]. Subjects were periodically scanned starting seconds after 100 μCi of $^{51}CrCl_3 \cdot 6H_2O$ was administered intravenously up to a period of 84 days. Scan duration varied from 3 to 44 minutes, both anterior and posterior. Intervals between scanning ranged from 3 minutes to 14 days. The total counts originating from activity present in any organ of interest were obtained by integrating the area of the scan-image of the organ of interest. The assumption was made that counts in the area over the organ of interest include counts from radioactivity of the cells within the organ and counts from radioactivity in the blood circulating in the organ of interest. Correction for the activity from circulating blood is made by subtracting the circulating blood counts in that region from the total counts (fig. 1). As an initial condition the assumption was made that at time t=o, the total counts were contributed by the circulating blood alone, and that none had accumulated in the cells of any organ of interest. Other corrections include background and radioactive decay.

The total radiochromium(III) remaining in the body as a function of time

(up to a period of 6 months) was determined with a whole-body counter[12,13].

The kinetic model was built from the series of scan-images, combined with whole body and plasma clearance data acquired during the experiment.

A PDP-12 minicomputer and the FOCAL program MMC5CII were used to compute the transfer rates[23]. In this program the computation is divided into several time intervals. Except for the first interval, at each interval two or more compartments "collapsed" to form a system of a maximum of 3 compartments. Thereby we reduced a model with 5 or more compartments to a one consisting of a maximum of only 3 compartments. Given a set of rough estimates of the value of the parameters and the initial conditions as mentioned earlier, the solution of the differential equations were then solved. The whole body and plasma radiochromium(III) clearance data were then fitted directly to the model. The calculated parameters were "adjusted" and the calculation repeated until the best fit of experimental versus calculated data was found[14,15,16,17,18,19,20].

Experimental Results

It was found that during the first minutes post injection the ditribution of radiochromium(III) in blocd plasma in two patients with hemochromatosis was on the average 80% in the plasma protein and 20% in the supernatant (m.w. <90000). In three normal subjects it was found that on the average 4% of radiochromium(III) was in the supernatant. After this initial period the percentage of radiochromium(III) in the supernatant levelled off to an average of 9% in two hemochromatotics and an average of 3% in the three normals. This number remained constant for at least 24 hours, beyond which the activity was so low that it could no longer be determined accurately in our system. The third patient, diagnosed as in the early stages of hemochromatosis, showed levels within the range of normal subjects. The radiochromium (III) in the supernatant is believed bound to low molecular weight molecules. We refer to this as "radiochromium(III) unbound to plasma protein" or just "unbound radiochromium(III)".

From scan images, radiochromium(III) was found localized primarily in the liver, spleen, body soft tissues and bone (fig. 2). Concentration of radiochromium (III) in the liver and spleen was found to be the highest among all of the body organs. Qualitative examination of data points of radiochromium(III) retention in the liver, spleen and thigh, of all six subjects, showed three major accummulation and clearance components in each organ. These components can be grouped in ranges of half-lives of 0.5 to 12 hours, 1 to 14 days and 3 to 12 months. For simplicity we called them respectively the fast, medium and slow components. Radiochromium(III) was also found accumulated in the bone; excessive accumulation in the joints was detected in one patient suffering from arthritis. Qualitative determination of accumulation and clearance components in the bone could not be performed successfully, due to the high activity of radiochromium(III) in the blood and overlying tissues. Accumulation of radiochromium(III) in other organs, such as the kidneys, lungs, central nervous system and the heart could not be detected with the present experimental techniques. This is primarily due to the high activity of the circulating blood compared to the probably relatively low concentration in the above mentioned organs.

In general the tissues extracted radiochromium(III) very rapidly. More than 50% of the blood plasma radiochromium(III) was absorbed by different body organs within hours after intravenous administration (fig. 1). Clearance from different body organs as well as whole body was found to be more rapid in patients with hemochromatosis. Radiochromium(III) 3 months after administration was found concentrated primarily in the liver (fig. 3); it was estimated that half of the total was in this organ, with the remainder distributed in other body tissue.

Metabolic Pathway and Model Building

On the basis of data obtained from various experiments mentioned earlier, a schematic diagram showing the proposed chromium(III) pathway in the human body was developed (fig. 4). Transport of chromium(III) is by the plasma protein, transferrin[21,22].

Chromium(III) is believed to be stored primarily in the liver and spleen. Utilization of chromium(III) is suspected to be primarily by adipose and muscle tissues. Excretion of dialyzable chromium(III) is through the kidneys into the urine.

Further examination of the proposed pathways leads to a centralized multicompartment physiological model for chromium(III) kinetics as shown in figure 5. The compartment model considers blood plasma chromium(III) as the central compartment. This compartment consists of two subcompartments, the plasma protein bound (BB) and the plasma protein unbound (BF) chromium(III). Exchange of chromium(III) exists between the two sub-pools with the major transfer directed towards the plasma bound. The liver and spleen chromium(III) compartments are assumed to consist of a compartment that utilizes chromium(III) and a compartment that stores chromium(III). The muscle and adipose tissue chromium(III) compartment is assumed to consist primarily of a compartment that utilizes chromium(III). The compartment that utilizes chromium(III) has a faster transfer rate compared to the storage compartment. A bone chromium(III) compartment was added to the model since scan images indicated accumulation of radiochromium(III) in the bones. To complete the model a hypothetical compartment consisting of organs that accummulate chromium(III) but cannot be detected with the present imaging techniques was added.

Although the physiological model consists of at least 6 main compartments, analysis of the relative radiochromium(III) clearance rates from the liver, spleen and thigh as well as the whole body showed only 3 major clearance components. This can be explained by assuming that some organs metabolized chromium (III) with approximately the same time constant[14]. Furthermore, as explained earlier, the physiological model is far from complete, in the sense that clearance component or compartment sizes of the bones and some other organs such as the heart, lungs, etc. were not available. For these two reasons a model was developed

which grouped all physiological compartments metabolizing chromium(III) with the same time constant in one functional compartment. This model is called a functional model to distinguish it from the physiological model discussed earlier. The functional model is characterized by the fast, medium and slow compartments. As a first approximation we assumed that all functional compartments were linearly related to the central compartment; also the transfer-rates were assumed to be time-independent (fig. 6).

Computational Results

Analysis using the "collapsed" compartment method FOCAL program MMC5CII[23], indicated that the average standard deviation of the differences between calculated and experimental data in logarithmic units was approximately 20%. Thirteen data points each of the whole body retention and plasma clearance were provided for the input. The program computed 10 parameters (fig. 7). The calculated parameters are listed in table 2. The chromium(III) balance in different functional compartments as a function of time for 1 normal subject is listed in table 3. The balance error for all the 6 subjects was found not to exceed 0.03%.

Discussion

Inspection and comparison of the scan-images, the experimental data, the calculated metabolic parameters and the relative functional compartment sizes leads to the following observations:

a. The metabolic pathway and the whole body distribution of chromium(III) in six human subjects were found to follow the same pattern. Differences in chromium(III) metabolic parameters between the two groups of 3 normals and 3 hemochromatotics were noted (table 2). These results suggest that standard metabolic parameters for chromium(III) metabolism that depend on certain physiological conditions (health, diseases, etc.) do exist. Our findings support the statement made by previous experimenters, whose studies were mostly based on

in vitro experiments, that chromium(III) is an essential trace-element.

b. This functional model explains in detail chromium(III) metabolism in several combined organs. The fast compartment, the compartment that utilizes chromium(III) with half-lives in the range of 0.5 to 12 hours, was found to consist primarily of the adipose and muscle tissues. The medium compartment, the compartment that metabolizes chromium(III) with half-lives in the range of 1 to 14 days was found to consist of the adipose and muscle tissues, the spleen, the liver and bone with the amount of chromium(III) probably equally distributed among them. Storage of chromium(III) was found primarily in the liver and spleen (the slow compartment).

c. The calculated average turnover rate, k(1), of unbound chromium(III) in the blood plasma in the 2 hemochromatotics was on the average 5 times higher compared to the average in 3 normals (table 2). The average percentage of protein unbound chromium(III) was also found to be 2 times higher in the 2 hemochromatotics. The higher percentage and turn over rate of the unbound chromium(III) in hemochromatosis can be explained by the fact that the plasma protein transferrin in the 2 hemochromatotics was more saturated with iron (>70%) compared to the 3 normals (<50%), so that more binding-sites for chromium(III) are available in normals compared to patients with hemochromatosis[21,22].

d. From steady state analysis of the blood (the fast and the medium compartments table 2), it was found that patients with hemochromatosis have a relatively larger fast and medium chromium(III) compartments. Whether this might be related to the enlarged liver in hemochromatosis which thus has the ability to absorb more chromium(III), is still not understood.

e. The much smaller release rate k(9) compared to the absorbtion rate k(8) (table 2) in the slow functional compartment in both normals and hemochromatosis suggest the existence of chromium(III) storage in the slow functional compartment.

f. This model assumed that some chromium(III) in the body is excreted by a route other than the kidney. The physiological significance of such excretion is believed related to the involvement of chromium(III) in cell organelles, so loss of dead cells from the body result in loss of chromium(III). This route of loss, k(10), has approximately the same value in all 6 subjects (table 2), compared to the rate of loss through the kidney k(1) which has much larger values in subjects with hemochromatosis. This result suggests that chromium(III) is metabolized by some cell organelles of both groups with the same metabolic parameter or the same time characteristics. It is important to note that k(10) was not included in the original kinetic model MAMC5C. By adding k(10) in the modified kinetic model MMC5CII, it was found that the average standard deviation of the differences between calculated and experimental data in logarithmic units was reduced from 25% to 20%.

At the present time the chromium(III) kinetic model, presented in this work, is the only model which is based on results obtained from in vivo experiments of six metabolically unperturbed human subjects. This model is able to provide some insights into disease characteristics in patients with hemochromatosis relative to normal subjects. Direct results of this study are more understanding related to metabolic differences in hemochromatosis, chromium(III) transport in the body, and the existence of protein unbound chromium(III) and chromium(III) storage in the liver. This study supports statements made by previous experimenters, that chromium(III) is an essential trace-element. Since there is reported evidence that chromium(III) is important for glucose metabolism in humans, this model should be useful in assessing the metabolism of chromium(III) and its nutritional requirement in human subjects, and its importance in disease processes such as diabetes.

This successful approach in kinetic model building is based on actual

distribution of the radiotracer radiochromium(III) as seen from the series of scan images. As far as we know, it is the first kinetic model of chromium(III) which has been built on the basis of in vivo metabolism of a metabolically unperturbed system.

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CLINICAL LABORATORY TEST DATA

SUBJ. SEX-AGE	DIAG.	S.I.	% SAT.	SGOT [mU/ml]	GLUCOSE TOLERANCE/INSULIN TESTS [mg/100ml] / [uU/ml] FAST	30 min.	60 min.	120 min.	180 min.	GTT**
N#1 M-38	Norm.	95	34	38	94/16.5	156/73.2	123/113	95/62.4	65/18.5	Norm.
N#2 M-27	Norm.	96	32	20	91/10.8	120/55.3	112/81.1	120/56.1	85/22.5	Norm.
N#3 M-41	Norm.	118	31	23	80/22.2	167/160.7	172/161.3	151/142.7	122/20.9	Pre-Diab.
H#1 F-31	Hemo-chr.	236	75	22	90/18.9	107/163.5	72/88.7	90/152	93/81.4	Norm.
H#2 F-52	Hemo-chr.	208	79	176	94/8.9	218/62.1	193/57.9	191/86.5	149/43.6	Adult Diab.
H#3 M-38	Early Hemo-chr.	173	60	20	71/6.7	139/69.4	129/97.7	65/19.3	56/78	Norm.

* S.I.: Serum Iron [µg/100ml]

** This comment is based on FAJAN and CONN criteria. Syllabus Twenty-eighth Annual Postgraduate Assembly of the Endocrine Society, held in Seattle, Wash., Oct. 1976, pg. 25.

Table 1

CALCULATED RATE-CONSTANTS USING THE FOCAL PROGRAM "MMC5CII"

SUB-JECT*	k(1)**	k(2)**	k(3)**	k(4)**	k(5)**	k(6)**	k(7)**	k(8)**	k(9)**	k(10)**	S.D.***
N#1	5.295	247.3	16.000	77.55	124.5	0.871	0.269	0.1894	0.0021	0.1402	0.2230
N#2	5.206	172.0	8.118	44.28	145.0	0.900	0.356	0.1400	0.0030	0.0845	0.2078
N#3	4.000	238.1	12.180	126.50	303.6	0.716	0.305	0.1707	0.0016	0.0881	0.1841
H#1	28.500	292.0	11.000	123.30	53.3	0.807	0.127	0.3050	0.0034	0.0630	0.1734
H#2	18.840	84.88	4.243	41.60	42.4	2.097	0.368	0.2123	0.0051	0.0651	0.2956
H#3	6.772	243.2	8.810	133.4	399.9	0.774	0.287	0.1497	0.0023	0.0731	0.2257

* For more information concering the subjects, see Appendix B
** in [day^{-1}]
*** Standard deviation of the differences of calculated and experimental data in logarithmic unit

Table 2

CALCULATED ^{51}Cr(III) DISTRIBUTION IN FAST, MEDIUM, AND SLOW COMPARTMENT (% OF TOTAL BODY)--SUBJECT: N#2

T (Days)	F-^{51}Cr Calc.	T-^{51}Cr Calc.	T-^{51}Cr Exp.	Fast Calc.	Medium Calc.	Slow Calc.	Excr. Calc.	Excr. Exp.	SD	%BL
0.022	5.0984	75.696	77.60	19.77	1.153	0.180	3.203	2.64	0.2078	0.00
0.045	3.2066	72.109	71.40	21.13	2.582	0.405	3.777	3.60	0.2078	0.00
0.091	3.0297	68.851	65.30	20.22	5.304	0.838	4.782	4.70	0.2078	0.00
0.166	2.8119	64.008	55.00	18.77	9.388	1.503	6.324	8.00	0.2078	0.01
0.356	2.3511	53.518	45.00	15.69	18.02	2.991	9.768	15.4	0.2078	0.01
0.938	1.4547	33.114	30.00	9.710	33.55	6.264	17.36	27.0	0.2078	0.01
1.960	0.8215	18.700	21.60	5.484	41.10	9.595	25.12	34.3	0.2078	0.01
7.000	0.3758	8.5530	10.90	2.508	28.23	17.30	43.41	44.9	0.2078	0.01
15.000	0.1775	4.0394	5.200	1.185	13.26	23.24	58.27	53.4	0.2078	0.01
28.000	0.0563	1.2808	1.700	0.376	4.089	26.40	67.84	62.0	0.2078	0.01
42.000	0.0205	0.4656	0.390	0.137	1.384	26.77	71.24	65.8	0.2078	0.01
84.00	0.0077	0.1743	0.300	0.051	0.429	24.91	74.43	72.1	0.2078	0.01
112.000	0.0071	0.1604	0.200	0.047	0.391	23.53	75.87	75.4	0.2078	0.01

F-^{51}Cr: % of free ^{51}Cr in blood plasma; T-^{51}Cr: total ^{51}Cr in blood plasma (% of total in the body); EXCR: excretion of ^{51}Cr from the body (% of total in the body); SD: Standard Deviation of the differences of calculated and experimental data; %BL: % balance error.

Table 3

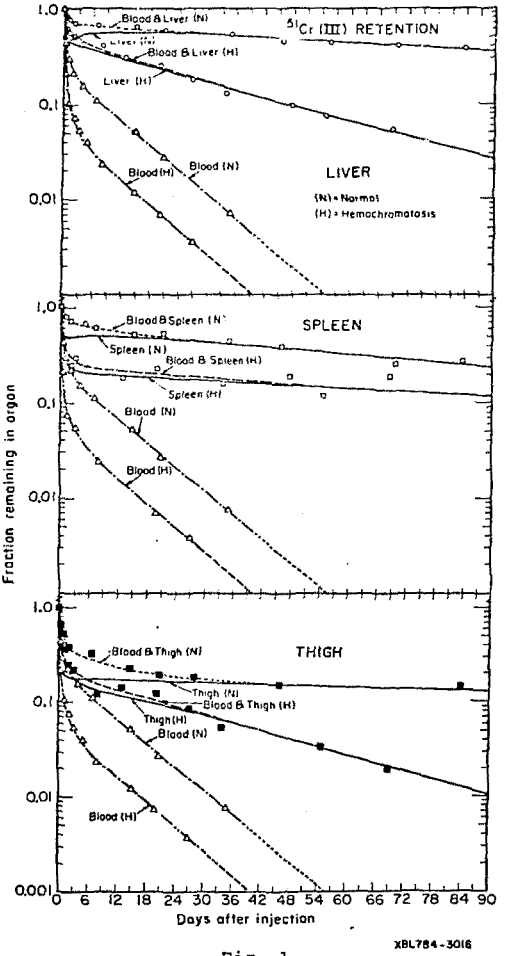
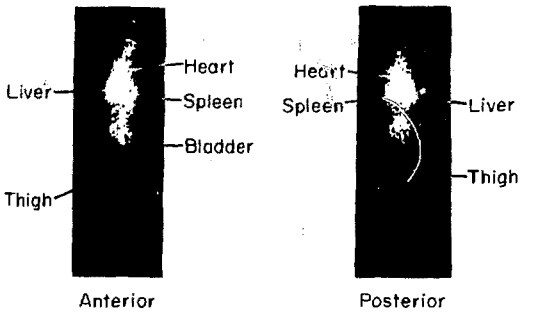
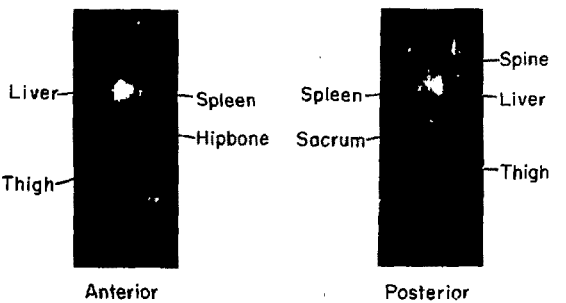

^{51}Cr (III) RETENTION
LIVER
(N) = Normal
(H) = Hemochromatosis
Blood & Liver (N)
Liver (N)
Blood & Liver (H)
Liver (H)
Blood (H)
Blood (N)
SPLEEN
Blood & Spleen (N)
Spleen (N)
Blood & Spleen (H)
Spleen (H)
Blood (N)
Blood (H)
THIGH
Blood & Thigh (N)
Thigh (N)
Blood & Thigh (H)
Thigh (H)
Blood (N)
Blood (H)
Fraction remaining in organ
1.0
0.1
0.01
0.001
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Days after injection
XBL784-3016

Fig. 1

^{51}Cr (III) DISTRIBUTION IN DIFFERENT ORGANS



Normal Subject
2 Days post-injection



Normal Subject
28 Days post-injection

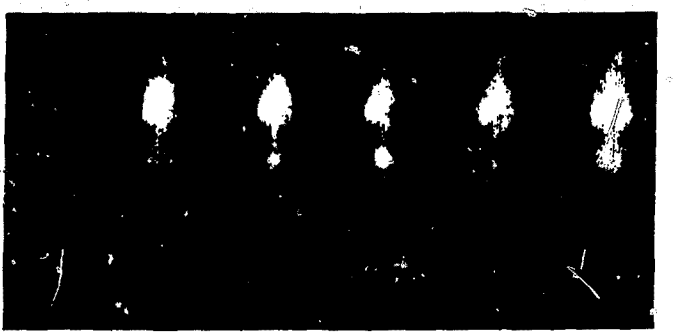
Fig. 2 XBB 785-6825

Cr^{51} Distribution (Anterior)

NORMAL MALE SUBJECT #2

Cr^{51} Cl_3 Intravenously

Mark II Whole Body Scanner

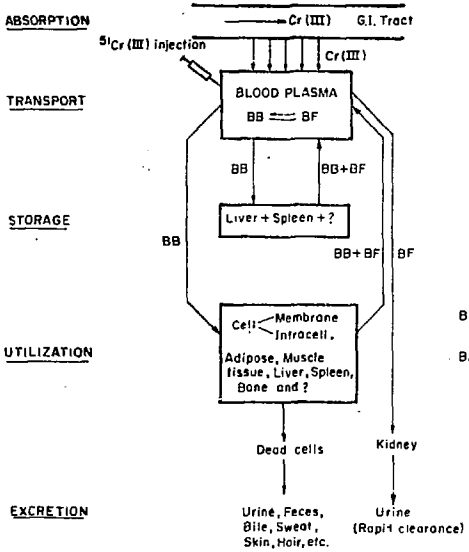


Am 241 Transm | 3 min | 1 h | 4 h | 1 d | 5 d

15 d | 28 d | 46 d | 56 d | 70 d | 84 d

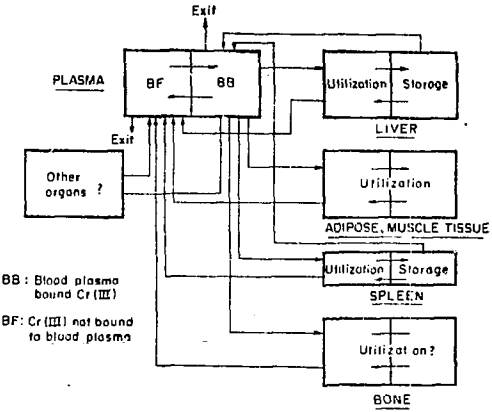
Fig. 3

XBB 768-7589



PROPOSED CHROMIUM (III) PATHWAY

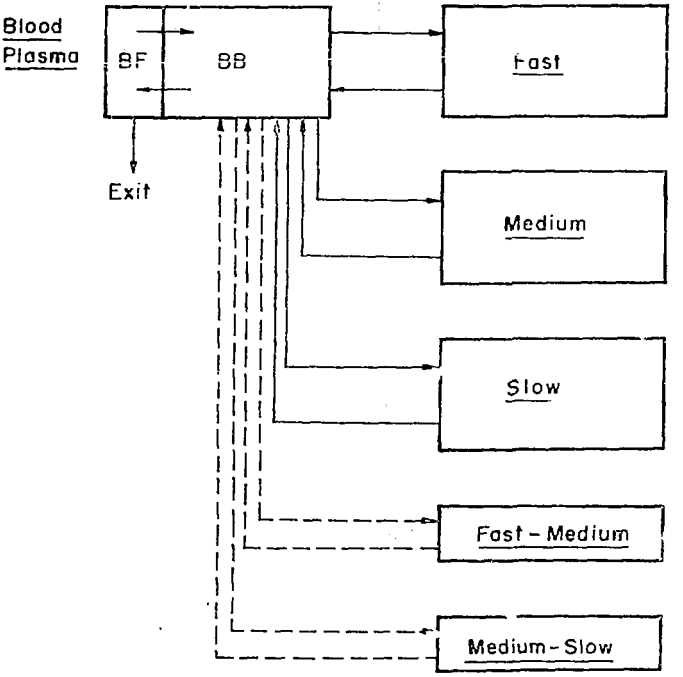
Fig. 4



PROPOSED CHROMIUM (III) PHYSIOLOGICAL COMPARTMENT MODEL

Fig. 5

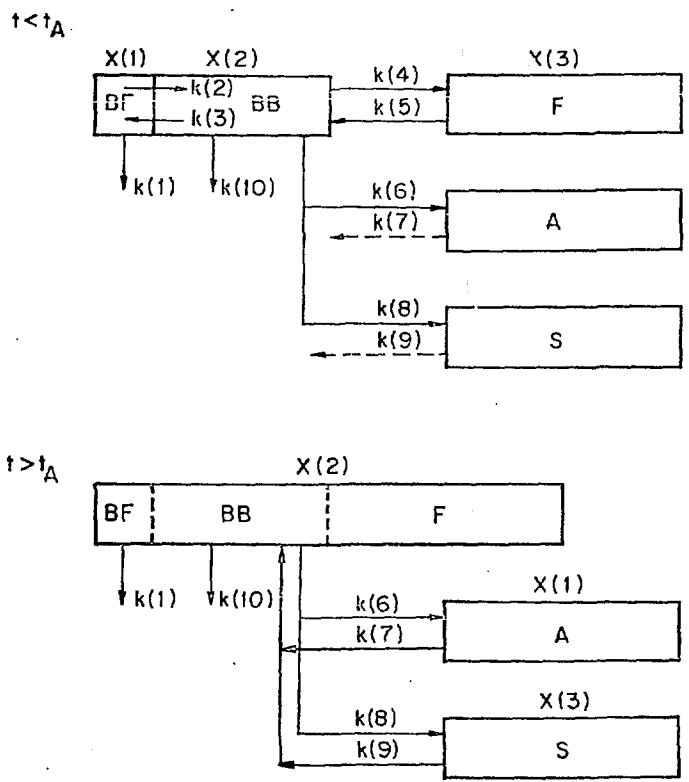
XBL 785-3206



FUNCTIONAL COMPARTMENT MODEL
FOR CHROMIUM(III)

XBL7612-10737

Fig. 6



MODEL MMC5C II

Fig. 7

XBL785-3205