

Diagnostic Radio-Vitamin B₁₂-Absorption and Retention
Studies with Test-Radioactivities which are within the
Range of the Natural Radioactivity Content of the Human
Body using the Landstuhl 2π -Whole Body Detector

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A. Introduction

The estimation of the absorption and the retention of tracer doses of ⁵⁸Co- or ⁶⁰Co-labeled vitamin B₁₂ in human beings is presently of considerable interest in the diagnosis and differential diagnosis of different haematological, neurological and gastrointestinal diseases. The application of the different radio-vitamin B₁₂-absorption-tests as routine methods in clinical diagnosis is described in detail elsewhere (HEINRICH, 1960b). Radioactive vitamin B₁₂ was also used during the last 9 years for several hundred more fundamental studies on the intestinal absorption, "in vivo"-retention, excretion and other phases of the vitamin B₁₂-metabolism in animals and human beings.

Mostly the clinical and biochemical investigations were performed with the help of "in vitro" counting arrangements measuring the γ-emissions of cobalt-labeled vitamin B₁₂ in more or less large samples of urine, faeces, blood or organs and tissues. The disadvantages of these "in vitro"-techniques for example in the analysis of the intestinal absorption and total body retention of radio-vitamin B₁₂ for diagnostic purposes are: unreliable cooperation of patients and nurses in the collection of excreta (faeces and urine), time consuming, unconvient and unpleasant procedures in the preparation of the test samples from the collected excreta. But the most limiting factor in the broad clinical application of these tests

is the amount of radioactivity required for a reliable performance of the "in vitro" tests. The radiation hazard introduced into the patients body especially with several repeated oral radio-vitamin B₁₂-absorption-tests is not negligible, since between 0,25² and 5 μC of ⁵⁸Co- or ⁶⁰Co-labeled vitamin B₁₂ are still today routinely used in the faecal-, urinary- and blood-tests.

Through the introduction of a combined annular beaker-welltype-scintillation detector (HEINRICH u. Mitarb., 1958; PFAU u. HEINRICH, 1959) it was at least possible to operate the radio-vitamin B₁₂-absorption-faecal- and -urinary-excretion-tests with low test radioactivities like 50 nC of ⁶⁰Co-B₁₂. But all the other disadvantages of the "in vitro"-procedures for the estimation of intestinal vitamin B₁₂-absorption are still remaining.

Therefore we became interested in the development of a test which (1) does not any longer require the cooperation of patients and nurses in the collection of excreta (2) does not require inconvenient and unpleasant procedures in the counting sample preparation from the collected excreta (3) is so sensitive that test radioactivities in the range of the natural radio-activity content of the human body are sufficient and (4) permits quantitative and rapid conclusions on the degree of the intestinal absorption and whole body retention of radio-vitamin B₁₂.

A liquid scintillation whole body detector was finally found to be extremely useful for the development of a radio-vitamin B₁₂-absorption-whole body-retention-test (= Radio-B₁₂-WBRT), which fulfills all the essential requirements given above.

B. Methods

In close cooperation with Dipl.Phys. A. PFAU (Max Planck Institute for Animal Nutrition, Mariensee near Hannover), Dr. E. ANDERSON and Dr. F.N. HAYES (Biomedical Research Group, Los Alamos Scientific Laboratory/New Mexico) and Dr. Ch. ONSTEAD (US Army Medical Research Unit No. 1, US-Hospital for Europe, Landstuhl) it was possible for us to use the Landstuhl 27-Whole Body Detector for the development of the Radio-B₁₂-WBRT. Physical and technical data for the Landstuhl-27-Whole Body Detector - which was originally developed and

operated for the 2nd. Geneva Conference on the Peaceful Uses of Atomic Energy - are given in detail in two publications of ANDERSON et. al. (1958).

Using point sources of $^{60}\text{Co-B}_{12}$ in front of the concave scintillator tank over-all efficiencies of 48 % can be obtained if the discriminator settings include the potassium-40 and cesium-137 channels. In our studies we used the potassium 40-channel for the measurement of ^{60}Co and the ^{137}Cs -channel was useful for ^{58}Co -measurements. However a special discriminator setting (the ^{58}Co -channel) was practical for more sensitive ^{58}Co -counting and therefore used in double-labelling experiments as a third channel.

The overall-efficiencies for the three channels and the used isotopes (^{58}Co and ^{60}Co) as point sources are given in table No. 1.

Table 1: Percentage sensivity ($E_{\%} = \frac{\text{cpm} \cdot 100}{\text{dpm}}$) for ^{58}Co and ^{60}Co in the three counting-channels.

(radioactive sample as point sources in the center of the detector)

Test-	^{137}Cs -channel	^{58}Co -channel	^{40}K -channel
Radioactivity	(0,65 - 1,55)	(0,75 - 2,30)	(2,25-4,05)
$^{60}\text{Co-B}_{12}$ (10,14·10 ⁻⁹ C)	12	-	33
$^{58}\text{Co-B}_{12}$ -Coenzym (24,66·10 ⁻⁹ C)	35	52	4

C. Results and Discussion

After oral uptake and the "in vivo" distribution of the radio- B_{12} in the human body the overall-efficiency depends mainly on the geometric relation between the individual (size, diameter, fat content a.o.m.) and the detector. Immediately after oral uptake the radio- B_{12} is localized in the stomach and the upper duodenum of human

beings. The overall-efficiency of the 2π -detector then is between 8 and 13 % (Table 2). Usually after one day the "in vivo" distribution of the absorbed (liver and muscle incorporated) and unabsorbed vitamin B_{12} is approaching the optimal detector sensitivity and the highest values for the overall efficiency (12-15 %; table 2) are obtained. After this time the variations of the geometry depending overall efficiencies in the 2π -detector can be considered by the use of correction factors. They are less significant if 4π -Whole Body Detectors are used.

After 2 days the decrease of the overall-efficiency is mainly caused by the faecal excretion of the small amount of unabsorbed radio-vitamin B_{12} (fig. 1). After completed faecal excretion of unabsorbed radio-vitamin B_{12} the further reduction of the overall-efficiency can be used for the calculation of the biological half life or the turnover time of the mainly in the liver and muscle incorporated radio-vitamin B_{12} . In table 2 the overall-efficiencies are given as the percentage sensitivity for three volunteers during different phases of the intestinal ^{60}Co - B_{12} -absorption.

For the same three volunteers the net counts in the ^{40}K -channel are given in figure 1 as cps in relation to the elapsed time and phase of intestinal radio-vitamin B_{12} -absorption. From this figure 1 and the preceding tabulars it is possible to understand the details in the performance of the radio- B_{12} -WBRT:

1. In the first measurement before the oral application of the ^{60}Co - B_{12} -tracer dose the original or basal radioactivity in the patient (approximately 10^{-8}C natural ^{40}K in the muscle and about 10^{-8}C ^{137}Cs from nuclear weap on fall out) is estimated in the ^{40}K - and ^{137}Cs -channels, since it has to be considered in the calculation of the results. During this measurement also other radioactive contaminations from fall out, diagnostic radioisotope application or other sources will be recognized. The first measurement like all others are done in triplicate over 100 seconds each.
2. Then between 0,10 and 1,0 μg radioactive vitamin B_{12} labeled with about 10 nC (10^{-8}C) ^{58}Co or ^{60}Co are first counted for control purposes as a point source in the 2π -Whole Body Detector and are then administered

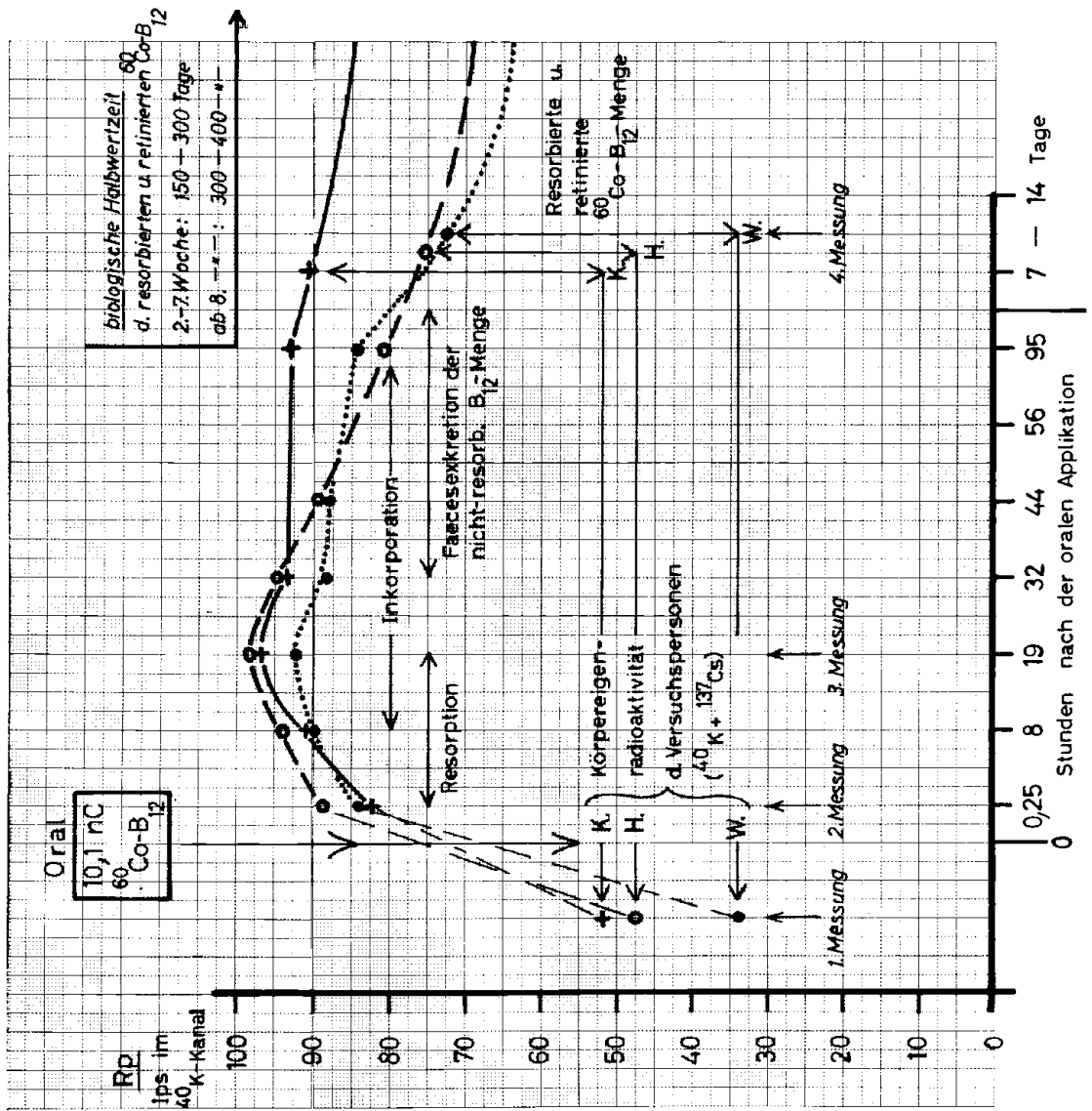


Fig. 1. Radio-vitamin B_{12} -absorption data for 3 subjects.

Table 2: Percentage sensitivity ($E_{\%} = \frac{\text{cpm} \cdot 100}{\text{dpm}}$) for $^{60}\text{Co-B}_{12}$

"in vitro" as well as "in vivo" before, during and after intestinal absorption of the $^{60}\text{Co-B}_{12}$ (in the ^{40}K -channel)
(calculated on the theoretical basis of 100 % retention)

		^{40}K -channel (2,25 - 4,05)		
Test-radioactivity "in vitro" ($10,14 \cdot 10^{-9}\text{C } ^{60}\text{Co-B}_{12}$) as a point source in the detector-centre		33,2		
Test-radioactivity "in vivo"		volunteers		
Time after	phase of B_{12} -ab-	♂	♂	♀
oral appli-	sorption or	164 lbs	174 lbs	132 lbs
cation	excretion	(H)	(K)	(W)
5-15 min.	in the stomach be-	11,1	8,2	13,4
	fore absorption			
8 hours	during absorption	12,3	10,5	15,0
19 "	absorption finished	13,5	12,1	15,5
32 "	" "	13,8	12,0	14,4
44 "	beginning faecal	11,3	11,2	14,8
	excretion of unab-			
	sorbed B_{12}			
	Absorption	65 %	91 %	87 %
56 "	faecal excretion of	8,8	10,7	13,4
	B_{12}			
95 "	faecal excretion	8,9	11,1	13,5
	finished			

orally to the patient. Again only for control purposes it is advisable now to measure the patient who now contains all the test radioactivity - still unabsorbed - in the stomach and the upper duodenum. If the container of the test-radioactivity was washed 5-8 times with water practically no radio-B₁₂ (detectable in the 2 - whole body counter) remains.¹² The washings are administered to the patients immediately after the original content of the container.

3. One day after the oral uptake of the radio-B₁₂-test-solution the patients are measured again (3¹² times for 100 seconds) since now the highest values for the overall efficiency - caused by an optimal distribution of the absorbed and the small amounts of unabsorbed radio-B₁₂ within the human body - will be obtained and are representing the 100 % reference point. All total counts in the different channels have to be corrected for the ⁴⁰K- and ¹³⁷Cs-content of the individuals. Also differences in the sample-detector geometry which effect the overall-efficiency (e.g. different sizes and diameters of the patients) can be more or less easily corrected to a standard value.
4. After 7 days the (in the normal individual small) amounts of unabsorbed radioactive vitamin B₁₂ are nearly completely excreted with the faeces.¹² Therefore all remaining vitamin B₁₂ radioactivity now represents the absorbed radio-B₁₂ which is incorporated and retained in the main B₁₂-storage organs and tissues (e.g. liver, scelet muscle). For the calculation from the counts in the ⁴⁰K- or ¹³⁷Cs-channels the ⁴⁰K- and ¹³⁷Cs-content of the patients is subtracted and than for example the ⁶⁰Co-B₁₂-counts in the ⁴⁰K-channel or the ⁵⁸Co-B₁₂-counts in the ¹³⁷Cs-channel compared with the corresponding values for the 100 % reference point (1 day after oral B₁₂-uptake). The intestinal absorption and consequent¹² retention of the absorbed radio-B₁₂ in the whole body can be calculated in % of the oral Test radioactivity.

As shown on table 3 the results which were obtained with ⁶⁰Co-labeled Cyanocobamid and ⁵⁸Co-labeled B₁₂-Coenzym using the 2π-Whole Body Detector are in excellent agreement with the results of the radio-vitamin B₁₂-absorption-faecal-excretion-test. With both tests it is¹² evident that the labeled vitamin B₁₂ is much better absorbed than its Coenzym. This has been¹² confirmed in the meantime also

for other organisms (rats and guinea pigs) and with "in vitro" counting-methods (HEINRICH u. Mitarb., 1960).

Table 3: Intestinal Absorption of ^{60}Co -Vitamin B_{12} and ^{58}Co -Vitamin B_{12} -Coenzym in Norman Human Beings as measured with the 2π -Whole Body Detector and the Faecal Excretion-Test

Radio-Vitamin B_{12} - Absorptions-Test	0,50 nMol ^{60}Co -Vitamin B_{12}	0,50 nMol ^{58}Co -Vitamin B_{12} -Coenzym
Total body-retention-test (0,50 nMol ^{60}Co - B_{12} = 10 nC)	59 - 90 % (3)	51 - 54 % (3)
Faecal-excretion-test (0,50 nMol ^{60}Co - B_{12} = 100 nC)	55 - 88 % (110)	32 - 55 % (11)

The retention of the incorporated ^{60}Co - B_{12} was measured in three volunteers over a period of 12 months. From this study we know that the biological half life of vitamin B_{12} in the human body is not a constant value. From the 2nd. to the 7th. week after incorporation the biological half life is increasing from 150 to 300 days (Fig. 2). After the 8th. week the biological half life is continuing to increase till it finally approaches a value of 400 days (turnover time = 800 days). These values agree with the results of liver surface scintillation countings and excretion studies (see for references HEINRICH, 1960a). They correspond to a final vitamin B_{12} turnover rate of 0,125 % of the B_{12} -body pool/day. Since the total body content of a normal human being is at least 5 mg (see for references HEINRICH, 1960a), the turnover rate is at least 6,25 μg vitamin B_{12} /day. But the results concerning the estimation of the turnover rate of vitamin B_{12} are only of preliminary value, since we presently do not know how many different metabolic pools of the vitamin B_{12} are existing in the cell or the total body. All calculations are done on the possibly wrong assumption that there is only a single vitamin B_{12} -metabolic pool. The biological half life (400 days) or the turnover time

(800 days), which was measured in the 2π -whole body detector can easily represent just the average of several turnover times of several different vitamin B₁₂-pools, which individually can have not identical turnover rates.

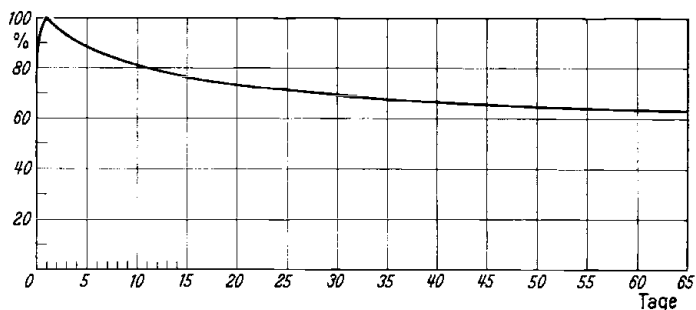


Figure 2: Whole Body Retention of ^{60}Co -Vitamin B₁₂ after oral application of 0,50 nMol (= 10,14 nC) ^{60}Co -B₁₂ to normal persons as measured over 65 days with a 2π -Whole Body Detector.

(The average of the values from three volunteers is given in percent of the 24 hour-(100 %)-reference point, see text).

Much more delicate techniques are required for the solution of such a complex problem. Presently we do not know anything about the intermediar metabolism of the B₁₂-structure. But there is the possibility that the estimation of the turnover time of absorbed or injected radio-vitamin B₁₂ can be of importance in the clinical diagnosis of diseases which are connected with alterations in the turnover time of the B₁₂-vitamin.

Approximately 10 months after the body incorporation of the absorbed ^{60}Co -vitamin B₁₂ it was possible through the kindness of Dr. Marvin A. van DILLA, to measure one of the volunteers with a large (9" x 6") NaI-Crystal-Spectrometer at the Los Alamos Scientific Laboratories. The γ -spectrum obtained in a 30 min. counting period is given in fig. 3 and shows the peaks of the natural ^{40}K content, the ^{137}Cs -fall out contamination (about 14 nC ^{137}Cs) and the 1,17 MeV-peak of the incorporated ^{60}Co -B₁₂.

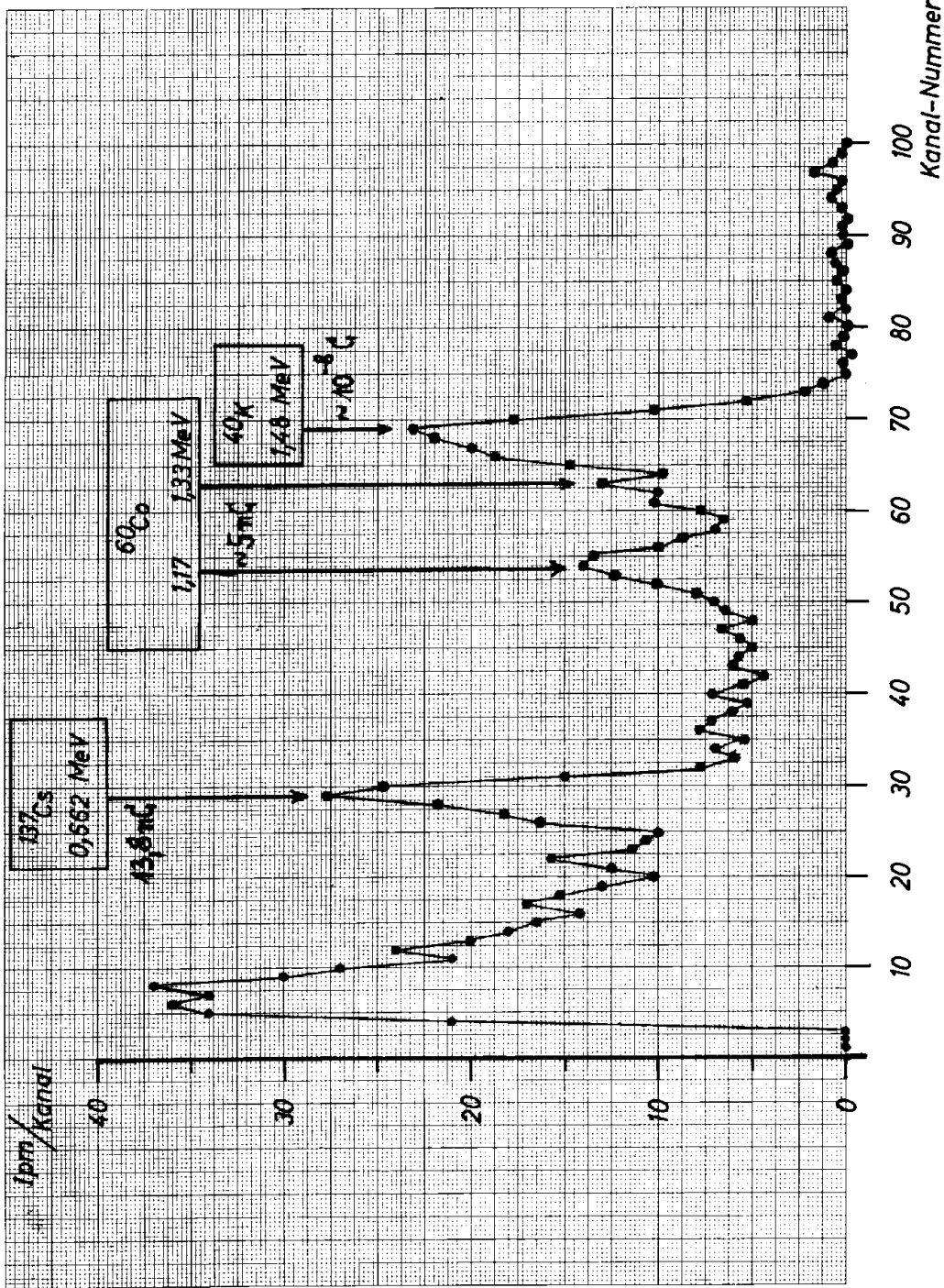


Fig. 3. Gamma-spektrum einer Versuchsperson (H.) 10 Monate nach oraler Verabfolgung von: 10 nC ⁶⁰Co-Vit-B12; gemessen m. 20 x 15 cm NaJ(Tl)-Scintillations-Spektrometer-Detektor der Los Alamos Scientific Laboratory.

The 1,33 MeV ^{60}Co -peak is overlapping with the left side of the ^{40}K -peak.

The ^{60}Co - B_{12} -retention (as well as the ^{137}Cs and ^{40}K -content) in this volunteer was estimated with three different whole body detectors: the 2π -Liquid Scintillation Detector at Landstuhl (Genco), the 4π -Liquid Scintillation Detector at Los Alamos (Humco I) and the 9"x6" NaI-Detector at Los Alamos. The values obtained with the three detectors are in reasonably good agreement.

In the diagnostic application of radioisotopes in nuclear medicine the sometimes considerable radiation burden by amounts of test-radioactivities, which are very often far away from being real tracer doses (e.g. 1-100 μC of different radioisotopes are used in many routine applications of radioisotopes in clinical diagnosis) is normally neglected. With already a single test in some cases 100 % or more of the maximum permissible incorporation radioactivity for the total body or critical organ are incorporated and the radiation burden with several repeated tests comes up to the limit or even more than the maximum permissible total body radiation burden (100 m rem/week).

Therefore it is highly desirable to use super-sensitive radiation detection equipments especially in nuclear medical diagnosis, allowing the application of test radioactivities which are so low that they do not offer any longer any radiation hazard for the patient. The utmost of course would be the use of test radioactivities which are within the range of the natural radioactivity content of the human body ($10^{-8}\text{C } ^{40}\text{K}$, $8 \cdot 10^{-8}\text{C } ^{14}\text{C}$ and $10^{-10}\text{C } ^{226}\text{Ra}$) and the unavoidable contamination of the human being with radioactive fall out products from nuclear weapons ($10^{-8}\text{C } ^{90}\text{Sr}$ and ^{137}Cs).

"In vitro" counting equipments offer already a certain approach to the problem, since the sensitive annular beaker arrangement of a NaI-Scintillation detector makes possible the application of only $5 \cdot 10^{-8}\text{C}$ of ^{60}Co - or ^{58}Co -labeled vitamin B_{12} in the urinary- and faecal excretion test (PFAU u. HEINRICH, 1959). By the application of 4π -liquid or plastic scintillation detectors with effective detector volumes of 1-10 liters it can be expected that even $1-2 \cdot 10^{-8}\text{C}$ of labeled vitamin B_{12} would be sufficient for a reliable test. Presently however the use of a 2- or 4π -Whole Body

Detector represents the most sensitive technique in the measurement of incorporated and retained γ -emitting radioisotopes and is by a factor of at least 5-100 more sensitive than the different conventional "in vitro" counting procedures in nuclear medical diagnosis.

In table 4 the several biological, medical and biophysical data for the five radio-vitamin B₁₂-absorption tests, their advantages and disadvantages are summarized. From this comparison it can be easily concluded that the radio-vitamin B₁₂-absorption-Total Body Retention Test is by far the most reliable, convenient and sensitive test for the estimation of intestinal absorption, total body retention and many other phases of vitamin B₁₂-absorption.

For the first time in the diagnostic application of radioisotopes in nuclear medicine it is now possible to work with test-radioactivities which are within the range of the natural radioactivity-content of the human body and therefore do not represent any longer any radiation hazard.

With the radio-vitamin B₁₂-absorption-Total body retention-Test the biological radiation burden from the incorporated and retained test radioactivity of 7 μC ⁶⁰Co-B₁₂ (equal to 0,07 % of the maximum permissible ⁶⁰Co-incorporation radioactivity of 10 μC) was calculated to be only 50 μ rem/week (table 4).

The natural radiation burden for the human being from exogeneous sources (cosmic rays and environmental irradiation) and endogeneous sources (⁴⁰K, ¹⁴C, ²²⁶Ra, ⁹⁰Sr and ¹³⁷Cs) is presently about 5,5 m rem/week (for details see table 5). Therefore the biological radiation burden introduced with a single radio-vitamin B₁₂-absorption-whole body retention-test into the human body (0,05 m rem/week) does not represent more than 1 % of the natural radiation burden from exogeneous and endogeneous sources which influence life already for more than several million years without demonstrated harmful effects. No more restrictions in the diagnostic application of γ -emitting radio-nuclids during pregnancy, childhood and other radiation-sensitive situations are any longer necessary, if a sensitive organic scintillation-whole body counter is available as a detector.

Table 4: Survey on different biomedical and radiobiological data for the five Radio-Vitamin B₁₂-Absorption-Tests

(All biophysical data are calculated for ⁶⁰Co; the maximal permissible incorporation-radioactivity for ⁶⁰Co is 10 μC, which represents a total body radiation burden of 77 mrem/week (<100 mrem/week))

Radio-Vitamin B ₁₂ -Absorption-Test	<u>counting technique and sample</u>	<u>required time for assay (days)</u>	<u>quantitative check for absorption</u>	<u>possible errors (by patients, nurses, technicians)</u>	<u>influence on assay by diseases of</u>
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FET =	"in vitro"	5 - 8	yes	yes	-
Faecal-Excretion-Test	<u>faeces</u>			(lost faeces)	
UET =	"in vitro"	2 - 3	limited	yes	kidney
Urinary-Excretion-Test	<u>urine</u>			(lost urine)	
BCT =	"in vitro"	0,5	no	no	-
Blood-Concentration-Test	<u>blood</u>				
LIT =	"in vivo"	5 - 8	no	yes	liver
Liver Incorporation-Test	<u>liver</u>			(reproducibility of geometry)	
WBRT =	"in vivo"	5 - 8	yes	no	-
Whole-Body-Retention-Test	<u>total body</u>				

Table 4 (continued)

Radio- Vitamin B ₁₂ - Absorptions- Test	B ₁₂ -metabolism or clinical situation influenced by applied assay	60 Co-B ₁₂ -Test- Radioactivity retained (in nC)	"in vivo"- Retention in % of the maximal per- missible 60Co-Incorpo- ration-Radio- activity (= 10 μ C)	biological Radiation Burden by retained 60Co-B ₁₂ (m rem/week)	
FET	no	50	35	0,35	0,27
UET	yes	50	20	0,2	0,15
BCT	no	1000	700	7,0	5,39
LIT	no	200	140	1,4	1,08
WBRT	no	10	7	0,07	0,05

Table 5: Comparison of the total body radiation burden from the 10 nC ^{60}Co -Vitamin B_{12} -Test-Radioactivity with the natural exogenous and endogenous radiation burdens for human beings.

Radiation Source	Total body content (nC)	Biological radiation burden (mrem/week)
<u>Exogeneous sources</u>		
Cosmic radiation	-	~ 0,67
Environmental irradiation	-	~ 2
		~ 2,7
<u>Endogeneous sources (incorporated radioisotopes)</u>		
^{40}K (1980 dpm/gK)	10	~ 0,37
^{14}C (15 dpm/g C)	80	~ 0,019
^{226}Ra ($222 \cdot 10^{10}$ dpm/gRa)	0,1	~ 1
^{222}Rn - decay products		~ 1
		~ 2,4
<u>Contamination from nuclear weapon-fall out</u>		
^{90}Sr	1 - 10	~ 0,04 - 0,4
^{137}Cs	10	~ 0,02
<u>Retention from a</u>	7	~ 0,05
<u>10 nC ^{60}Co-B_{12}-</u>		
<u>Test-Radioactivity</u>		

Only a few physical or technical problems have still to be handled to enable a more general application of organic scintillation whole body detectors in nuclear medicine. The most important problems are the poor energy resolution of organic scintillators (due to the multiple Compton scattering) for double labelling procedures and the sometimes difficult reproducibility of the counting geometry if the test samples or individuals vary in size, diameter, fat content a.o.m.

Large NaI-crystals of course offer a reasonable good energy resolution (due to the predominant photoelectric effect), which is by a factor 2-3 better than that of an organic scintillator. They are however available only with relatively small efficient detector volume sizes and do - in fact - not represent whole body detectors. Their low specific volume sensitivity ($\frac{\text{cpm}}{\text{dpm/ml}}$) has to be compensated by long counting periods (about 30 minutes), which are inconvenient for the patients and cannot be tolerated from time and capacity reasons for routine work. Only for very few applications in double labelling experiments the poor energy resolution of the organic scintillator is not sufficient and requires the use of the NaI-crystal spectrometer. For practical all single radionuclide studies the energy resolution is not a limiting factor and the 2π - or 4π - organic scintillation detectors offer the considerable advantage of their high specific volume sensitivity resulting in the required short counting periods (3-times 100 seconds) for very low activities ($3 \cdot 10^{-10} \text{C}$ with a statistical precision of about $\pm 3\%$) of γ -emitting radionuclides in extended samples like human beings.

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