WHOLE-BODY MONITORING

AND

IN VIVO ACTIVATION ANALYSIS

IN

NUCLEAR MEDICINE

THESIS

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SUMMARY

The thesis describes the development and application of two new techniques in nuclear medicine. The first involves a fundamentally different approach to the attainment of high sensitivity using a whole-body monitor. It represents a significant advance on existing methods. The second technique, in vivo activation analysis of iodine in the thyroid gland, apparently has not been reported previously. It may prove an important clinical tool for diagnosis and research since a knowledge of the total iodine content of the thyroid will provide a better understanding of the aetiology of its associated diseases. No other technique can evidently provide this data.

A new design of whole-body monitor has been developed utilising a shadow shield weighing 7-8 tons compared with conventional shields of 30-50 tons. Construction of the prototype monitor and an assessment of its performance lead to the conclusion that sensitivity at least comparable with that of the conventional monitor should be attainable. The significant reduction in shield weight facilitates the incorporation of this design of monitor in a mobile laboratory. Clinical studies of iron metabolism and of vitamin B_{12} metabolism have been carried out using the prototype monitor.

The award of a research grant by the Scottish Hospital Endowments Research Trust enabled the construction of a high sensitivity mobile whole-body monitor (MERLIN). Its

performance is shown to be better than most conventional monitors and at least comparable with the remainder. Apart from the advantage of mobility, the monitor can be used as an installed monitor capable of incorporation in almost any existing laboratory. The sensitivity can be easily varied to meet individual requirements while the cost of an installed high sensitivity monitor, with a 100-channel pulse height analyser, can be less than £6,500. Commercial conventional monitors cost about £20,000 - £30,000 excluding transport and erection costs and the cost of a separate building if this is necessitated. The mobile monitor is now being used for medical research in collaboration with hospitals in Scotland.

A new technique has been developed to measure in vivo the total iodine content of the thyroid gland using activation analysis. The principle of the method is to irradiate the patient's thyroid in vivo using a collimated beam of neutrons from the U.T.R. 100 reactor. The iodine-128 induced by the neutron irradiation is then measured using a suitably shielded scintillation counter and pulse height analyser. Following preliminary experiments, including in vitro measurements on excised glands, the techniques were adapted for clinical use. A high sensitivity shadow-shielded thyroid monitor was designed and constructed for clinical trials.

The results of the clinical trials have led to improvements in the technique in the light of this experience. These modifications are being incorporated and further in vitro measurements made before the technique is used as a diagnostic and research tool.

PREFACE

This thesis contains an account of research conducted by the author at the Scottish Research Reactor Centre, East Kilbride and at the University of Glasgow. The development and the present situation and requirements of whole-body monitoring and of the need to measure the total iodine content of the thyroid gland to achieve a better understanding of the aetiology of associated diseases are considered. Solutions for these separate problems are proposed. (Chapter 1). Experimental investigation of the proposed solutions and their clinical application is the subject of the thesis.

The conception, design and responsibility for the construction and assessment of the performance of the prototype whole-body monitor (Chapter 2) and of the mobile monitor (Chapter 3) are entirely those of the present author. The clinical studies of aspects of iron metabolism (Chapters 4 and 5) and of vitamin B_{12} metabolism (Chapters 6 and 7) were undertaken in collaboration with Dr. G. Will, Royal Infirmary, Glasgow, and with Dr.J.F. Adams, Southern General Hospital, Glasgow, respectively. The analysis of the results and their interpretation, as presented here, are those of the present author.

The possibility of measuring the total iodine content of the thyroid gland by in vivo activation analysis was realised by the author, Dr. W.D. Alexander and Sir Edward J. Wayne, Western Infirmary, Glasgow. Preliminary experiments and development of the technique (Chapter 8), including the design and construction

of the shadow-shield thyroid monitor (Chapter 9), were the author's responsibility. Clinical trials (Chapter 10) were conducted in collaboration with Dr. W.D. Alexander. The analysis of the results and their present interpretation are those of the author.

PUBLICATIONS, etc.,

Chapter 2:

Boddy, K., 1965, Paper VIII. S, Conf. on Low Level Radioactivity Measurements: Limitations and New Techniques, 5-6, July, London.

Boddy, K., 1965, Report S.R.R.C. 11/65.

Boddy, K., 1966, Health Physics, 12, 1148.

Boddy, K., 1966, Report S.R.R.C. 13/66.

Boddy, K., 1967, Phys. Med. Biol., 12, 1, 43.

Chapter 3:

Boddy, K., 1966, Invited paper presented orally to the Society for Radiological Protection, Edinburgh.

Boddy, K., 1967, Paper submitted for publication, "A High Sensitivity Shadow Shield Whole Body Monitor, with Scanning-Bed and Tilting-Chair Geometries, Incorporated in a Mobile Laboratory".

Boddy, K., 1967, "Variations in the counting-rate due to isotopic redistribution in the body, using a whole-body monitor with scanning-bed geometry". In preparation.

Chapter 4:

Will, G. and Boddy, K., Scottish Med. J. (In Press).

Chapter 5:

Will, G. and Boddy, K., Scottish Med. J. (In Press).

Chapter 6:

Boddy, K. and Adams, J.F., "The Retention and Rate of Loss of Radio-vitamin B_{12} following Intravenous Administration and its Implications". In preparation.

Chapter 7:

Boddy, K. and Adams, J.F., "Some Considerations Concerning the Assumption of Tracer Equilibrium in the Excretion of Vitamin B_{12}". In preparation.

Chapter 8:

Boddy, K., 1966, Proc. of Seventh Int. Symp. on Radioactive Isotopes in Clinical Medicine and Research, Bad Gastein (In press).

Chapter 9:

Boddy, K., 1967, "A Thyroid Monitor of High Sensitivity using a Shadow Shield". Submitted for publication.

Chapter 10:

Boddy, K. and Alexander, W.D., 1967 Paper SM 91/13, accepted for I.A.E.A. Symp. on Nuclear Activation Techniques in the Life Sciences, Amsterdam, 8 - 12 May, 1967.

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The Hospital Endowments Research Trust kindly provided the capital grant and supporting costs for the construction and operation of the Mobile whole-body monitor.

The advice and practical assistance of Mr. J.A. Izatt, Deputy Director of the Reactor Centre, and members of the staff of the National Engineering Laboratory, East Kilbride, on engineering aspects of this work are greatly appreciated.

The work described here was greatly facilitated by the excellent technical assistance of Messrs. D. Dunn, P. Mellon, W. Slater and Misses P. King and B. Holmes while many others also assisted in innumerable ways to all of whom the author is extremely grateful. The co-operation of the Reactor operators, Messrs. T.H. Andrew and R.W. Wilson is also appreciated.

I should also like to acknowledge the assistance afforded by Mrs. I.M. Mills, Miss S. Cochrane and Miss L. Strangward.

My thanks are also due to Miss E.W. Telfer and the Tracing Office Staff, and of the Photographic and Reprographic Sections of the National Engineering Laboratory, East Kilbride, for their excellent assistance.

CONTENTS

CHAPTER I: Introduction:

Two techniques which have been introduced into nuclear medicine only in recent years are whole-body monitoring and in vivo activation analysis. The initial stimulus for the development of whole-body monitors was radiological protection measurements of internal contamination. The historical development of the monitors and the improvements in sensitivity are summarised in Table 1.1 (after Spiers, 1962). Probably the first international symposium at which a collection of papers dealing with the clinical application of whole-body monitors was presented was held as recently as 1961 (I.A.E.A. Symposium on Whole-Body Counting, Vienna, 1961). The first reports on in vivo activation analysis were even more recent (Anderson et al., 1964) by the present author (7th International Symposium on Radioactive Isotopes in Clinical Medicine and Research, Bad Gastein, January, 1966).

1.1 Whole-body monitoring:

The applications of whole-body monitors in nuclear medicine can be roughly classified into two groups, routine clinical measurements, for example of absorption of labelled iron or vitamin B_{12} in the diagnosis and treatment of iron deficiency anaemia or of pernicious anaemia, and research investigations which may require the measurement of body potassium-40 to provide an estimate of total body potassium or lean body mass or of the long-term turnover of slower metabolic compartments of the body. Routine clinical measurements usually require a comparatively simple and inexpensive monitor, (Veall, 1962, Hine et al., 1962, Warner and Oliver, 1966).

TABLE 1.1.

Early Development of Whole-Body Monitors.

Reference	TECHNIQUE	Subject Counting Time	Detection limit (or S.E.)	
			ug Ra equiv.	°/o total body K
Small Ionisation chambers:				
Schlundt et al (1929)	I.C. at 1 atm. + string electrometer		~5	
Schlundt et al (1933)	do.		~0.2	
Hess and McNiff (1947)	I.C. of 13 litres at 1 atm.		~0.03	
Geiger-Müller tube:				
Evans (1937)	1 metre arc.		0.1	
Large High Pressure Ionisation Chambers:				
Sievert (1951)	Circular array of 10 long chambers-411	2h	0.005(SE)	~50 (SE)
Burch and Spiers (1953)	do. + backing off chambers.	2h	0.003(SE)	~30 (SE)
Sievert (1956)	As before - underground	3-4h	0.001(SE)	~10 (SE)
Scintillators:				
a) Organic				
Anderson (1956)	4π liquid scintillator	15 min	~0.0001(SE)	1 (SE)
Bird and Burch (1958)	Three unit plastic scintillator	15 min	~0.0001(SE)	1.5 (SE)
b) Inorganic:				
Marinelli (1956)	4 in x 1.5 in NaI - chair geometry	15 min	~0.0003(SE)	3.5 (SE)

(SE) = standard error

ug Ra equiv. = ug Ra with all daughter products at equilibrium.

since the quantity of isotope administered is generally determined by less sensitive measurements carried out simultaneously such as those of serum, plasma or urine specific activities. These monitors are very valuable since the losses, inconvenience and inaccuracies of urine and faecal monitoring may be obviated as well as the consequent hospitalisation of the patient and its associated expense. Conventional high sensitivity monitors, on the other hand, are usually expensive and elaborate. Rooms of lead, steel or excavated from chalk subsoil have been utilised to reduce the background counting-rate. Commercial high sensitivity monitors cost about £20,000 - £30,000 excluding transport and erection of the steel room. These rooms are constructed from pre-1945 naval steel and since their weight is from about 26-50 tons, a special building may be necessitated to house the monitor. Despite these drawbacks, the temptation exists to consult a catalogue without careful consideration of the exact requirements of, or of the justification for, such a monitor. Spiers (1962) asked "What is the cheapest form of a total body potassium monitor for clinical work - can it be obtained for the price of a high-duty diagnostic X-ray set, say US $ 15,000?" and commented (Spiers, 1965) "The development (of whole-body monitors) has been rapid and today there are many more whole-body counters than there are thorough and comparable analyses of their performance. The choice of available apparatus is large and the cost variable but considerable." Similar considerations were the stimulus for the present studies which describe the development of a new design of whole-body monitor, which can be adapted to meet a prescribed sensitivity and the higher sensitivity of which is at least as good as that of most steel room monitors. The cost can be less than £6,500 which is comparable with the figure suggested by Spiers. Clinical studies described show that

ultimate sensitivity is not an essential pre-requisite for the prosecution of useful clinical research.

The present work began because no hospital in Scotland (in 1963) possessed, or had easy access to, a whole-body monitor of high sensitivity. The high capital cost of an installed conventional unit and the difficulties of transferring patients to a centralised facility argued against its establishment. It was considered that with a new design of monitor, high sensitivity might be attainable in a comparatively lightweight shield thus enabling the monitor to be incorporated in a mobile laboratory. As many clinical applications can be dealt with adequately by simple whole-body monitors, it was felt that if a high sensitivity monitor was available for the fewer investigations requiring such sensitivity, a mobile whole-body monitor might fulfill this need. While meeting the requirements of several hospitals as a mobile unit, the monitor design would ideally be suitable also as an installed monitor of high sensitivity and low cost.

1.2 Selection of design for investigation.

The choice of design to be investigated was limited in view of the ultimate aim of providing a mobile monitor. It was clear from the outset that significant reductions in shield weight could be achieved by concentrating shielding around the detector(s). By its nature, the steel or lead room must be sufficiently large to accommodate the patient so that although the total weight of shielding material is large, it can only reduce the background counting-rate of the detectors to that which would be obtained if each detector was surrounded by close fitting steel or lead of the same thickness as the room walls etc.

It was also apparent that to shield a single detector of large volume is simpler and more economical in weight than to shield a multiple-crystal system of the same total crystal volume. There are, however, other advantages in the use of a single crystal rather

than multiple crystals. For example, Miller (1962) points to greater ease and speed of operation since only one crystal needs to be calibrated, while counting-rates are equal or higher in the photopeak and considerably lower at lower energies than those observed with multiple-crystal arrays of the same total crystal volume, as shown in Fig. 1.1 The multiple-crystal array requires relatively complex mixing and gating electronic circuits either to add the various crystal outputs into one composite spectrum or to store the output of each crystal into different sections of the memory of the analyser. The possibility exists also of a shift in energy calibration of one of the multiple crystals leading to spectrum distortion. Probably the main advantage of the multiple-crystal geometry is that something can be learned of the distribution of the isotope in the body if the individual outputs of the crystals are sorted and recorded separately using either single channel analysers or separate sections of the analyser memory. If the single crystal is used to scan the patient, say, by passing the patient beneath the detector, this advantage no longer applies only to the multiple-detector system.

1.3 In vivo activation analysis:

Measurement of the total body content in vivo of a given element such as sodium or chlorine is usually not possible using existing techniques. An obvious exception, as mentioned earlier, is the estimation of total body potassium by measuring the potassium-40 content in a whole-body monitor. Isotope dilution studies provide an estimate of only the exchangeable fraction of the element and depend on the extent to which, and how rapidly, equilibrium between body compartments is established. In some cases the total body content of an element and the exchangeable fraction are similar as shown, for example, by comparison with analyses of cadavers.

Neutron activation analysis has found wide application in vitro in medicine and biology. Exposure of many elements to neutron irradiation causes their transformation to radioactive isotopes.

Using appropriate techniques, the radioisotope(s) can be identified and the quantity of the corresponding target element(s) estimated. Chemical separation is a common first step after irradiation to eliminate radioactivity from irrelevant and unwanted radioisotopes produced incidentally. However, separation is often neither feasible nor complete. The principal interfering isotopes following irradiation of biological material, whether serum, urine or tissue, are usually sodium-24 and chlorine-38 which are difficult to eliminate while lengthy separation procedures cannot be used when the isotope of interest (e.g. ^{28}Mg, ^{128}I, ^{49}Ca etc.) has a comparatively short half-life. Two properties characteristic of the isotope, its rate of decay and the type and energy of the radiation it emits, may make analysis possible even in these cases. Sequential measurement of the disintegration rate or radiation spectrometry, such as gamma-ray spectrometry, can be used to estimate separately but simultaneously the quantities of various elements present in the same sample.

Several accidents resulting from unexpected criticality in nuclear reactors or reactor assemblies have resulted in over-exposure of humans to neutrons. Radioactivity, particularly sodium-24, was consequently induced in elements of which the body is composed. These exposures, being accidental, involved neutron (and gamma) doses in the lethal or LD_{50} ranges. However, using a high sensitivity whole-body monitor to measure the induced activities and a controlled exposure to neutrons, the measurement of whole-body sodium and other elements can be achieved with doses of less than, or similar to, those of accepted procedures such as an abdominal radiograph (about 3 rem, I.C.R.P., 1960).

Whole-body neutron activation analysis in man in vivo using a neutron generator has been recently reported (Anderson J. et al. (1964)) in the investigation of the normal body content of sodium, chlorine and calcium involving total-body doses of about 1 rem. The major experimental difficulty was to produce a uniform neutron

flux throughout the body which represents a large hydrogenous sample. A further problem which has not been over-emphasised in this work is that of changes in the neutron spectrum due to moderation and capture of neutrons. This is of importance as the neutron capture cross-section of an element varies with neutron energy . Both of these factors may prevent each nucleus having an equal probability of transformation, which, strictly, is an essential criterion.

Interpretation of the results presented some difficulty because of the many different chemical elements of which the body is composed. Each of these elements may produce one or more radioactive isotopes as a result of neutron irradiation. The relative amounts of the isotopes produced depends upon the quantity of the stable element in the body, cross-section of the element, etc. so that the resultant gamma spectra may contain significant contributions from isotopes which are not pertinent to the investigation in hand. An example of this interference was the 0.51 MeV peak in the spectra obtained for the two human subjects reported. This peak was attributed to the annihilation radiation due to positron emission by nitrogen-13 produced by the ^{14}N (n, 2n) ^{13}N reaction. A computer programme carrying out spectrum-stripping with least squares fit analysis simplified the interpretation in this study.

1.4 In vivo activation analysis of iodine in the thyroid gland:

Direct measurement in vivo of the intra-thyroidal iodine stores has not, apparently, been made previously. Total thyroidal iodine, up to the present, has been measurable only after excision of the gland. Indirect methods in vivo, such as that described by Nodine (1957) measure the intrathyroidal exchangeable iodine and have marked limitations. Nodine's method involves the administration of a tracer dose of iodine-131 followed nine days later by an injection of thyroid stimulating hormone (TSH). The resulting increases in the plasma-bound iodine (PBI) and PBI^{131} after twenty-four hours are

measured. The increase in the PBI and PBI^{131} corresponds to the newly released thyroid hormone which is assumed to have the same specific activity as the intrathyroidal exchangeable iodine (IEI). If the thyroidal radioactivity is measured immediately before the injection of TSH, IEI can be estimated since,

$$\frac{\text{thyroid } I^{131} \text{ activity}}{\text{IEI}} = \frac{\text{rise in } PBI^{131}}{\text{rise in PBI}} \quad \text{and, hence,}$$

$$\text{IEI} = \frac{\text{rise in PBI} \times \text{thyroid } I^{131} \text{ activity}}{\text{rise in } PBI^{131}}.$$

The difficulties in this technique include:-

1. The method fails when injection of TSH produces no effect as in thyrotoxicosis, endocrine exophthalmos etc.
2. Only the "exchangeable" iodine is measured.
3. Any iodine which has not equilibrated with the tracer dose in nine days is not measured. This fraction may vary between individuals.
4. The uptake by the gland of the tracer dose is influenced by the level of the intrathyroidal stores as well as the metabolic rate of the gland. For example, the test does not differentiate between high uptake due to "depleted" stores, in which case the tracer does not, presumably, equilibrate with "exchangeable" iodine, and that due to a high rate of metabolism. The converse situation is open to corresponding misinterpretations.

Data on the intra-thyroidal iodine stores may throw some light on the aetiology of non-toxic goitre. Ermans (1961) found that in goitrous patients from the Congo, the total iodine content of the thyroid gland was normal. Values within the normal range have been found also by Wayne et al (1964). However, Wilson (1963) reports finding in patients with non-toxic goitre, that the iodine content of the gland may greatly exceed that found in normal thyroids. This latter observation, if confirmed, would support the concept of an intra-thyroidal metabolic fault as opposed to dietary iodine deficiency.

A knowledge of the intra-thyroidal iodine stores is also of considerable practical importance since in its absence all radioiodine tests giving an estimate of the release of thyroid hormone from the thyroid gland (e.g. PBI-131) must remain on an empirical basis. Estimation of the intra-thyroidal stores is clearly not necessary in every case, but would be of particular value in those cases (about 5°/o) where the radioiodine test was inconsistent with the clinical findings. Patients with a small intra-thyroidal pool could be distinguished from those with true over-secretion of thyroid hormone, both of which give a similar pattern of radioiodine release (Koutras et al., 1961).

In vivo activation analysis of iodine in the thyroid gland would estimate the total iodine content and not that of exchangeable iodine. As the gland is close to the surface of the body, problems of non-uniformity of a single irradiation should be less than in irradiation of the total body. This is an important factor since irradiation from both sides of the body was necessary to produce an approximately uniform flux throughout the whole body (Smith, and Osborne 1965 Private communication) and such a procedure might be less appropriate for the thyroid. In particular, the flux of 14 MeV neutrons from a neutron generator, as used by Anderson et al., is presently less than 10^7 n/cm^2 sec. even at a distance of only 10 cm from the target. The thermal neutron flux may be at least an order of magnitude less and a simple calculation suggests that a flux at least in the region of 10^7 n/cm^2 sec is required. Such fluxes are obtainable from nuclear reactors with the reservation that the uncollided fission neutron energy spectrum shows that the maximum number of neutrons have energies of about 1 MeV. The problem of non-uniform irradiation may, therefore, be more acute than with neutrons of higher initial energies.

The method of irradiation, which implies the use of a collimated beam of neutrons limited to the area of the gland, is probably achieved more easily using a reactor beam tube or stinger since the biological shield of the reactor should already be very

effective in confining emergent neutron and gamma radiation to these regions.

With these factors in mind, the feasibility of utilising the UTR-100KW reactor at the Reactor Centre for in vivo activation analysis of iodine the thyroid gland was examined. Preliminary experiments were conducted and a trial series of clinical measurements were carried out. The results of these have been also reported elsewhere (Boddy, 1966). Improvements have been made in the techniques in the light of this experience and further clinical trials are imminent prior to the wider application of the technique.

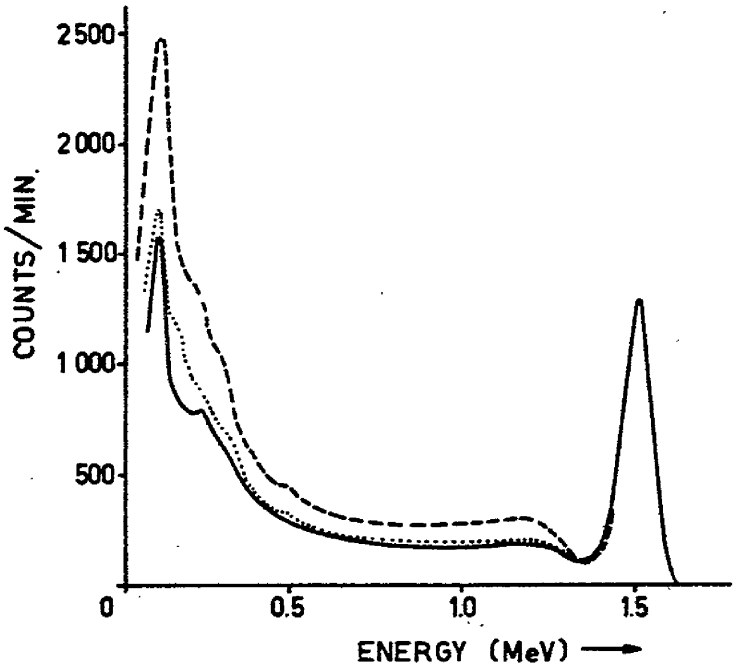


Fig. 1.1.

Gamma-ray spectra obtained with three crystals over a subject in the tilting chair. The three K^{42} spectra were normalized to the same area in the photopeak to demonstrate the difference in counting-rates at low energies

4- in × 4-in crystal - - - - - - -
9- in × 4-in crystal . . . . . .
11.5-in × 4-in crystal ————

CHAPTER II: The Prototype Shadow Shield Whole Body Monitor.

The ultimate aims in developing the prototype monitor were to provide a design capable of high sensitivity at low cost and which could be incorporated in a mobile laboratory. As a static monitor, it should be able to provide various degrees of sensitivity according to individual requirements.

The criteria adopted were:

a) A comparatively lightweight shield with a limit of about 7 tons for a commercial vehicle chassis.
b) High sensitivity viz. low background counting-rate and high counting-rate per unit activity or per gram of potassium.
c) Small variation of counting-rate due to the redistribution of isotopes in the body.
d) Reasonable cost.

Several possible designs were considered, the most promising of which seemed to be the use of a suitably shielded single detector beneath which the patient was passed. With this configuration, the shield weight could be greatly reduced and redistribution effects might be minimised.

2.1 Equipment:

No direct financial assistance was available for this work, so that materials and equipment originally acquired for other purposes were used with some improvisations.

The largest available sodium iodide detector assembly had a 3 inches diameter x 3 inches crystal. Lead was available largely as four-inches chevron bricks and was not of selected low background quality. Initially, a remote Laben 512-channel pulse height analyser was used until a 100-channel T.N.C. Gammascope became available.

2.2 Development of the shadow shield.

To obtain high sensitivity, the requirement was for a low background counting-rate. Miller (1958) and May and Marinelli (1962), during the construction of a steel room whole-body monitor, obtained the background reductions shown in Fig. 2.1. In the final shield, comprising 20.3 cms. of iron and 3 mms. of lead, the background counting-rate from 0.05 MeV to 1.5 MeV is reduced to between $\sim$ 1-4 °/o of the unshielded background counting-rate. These reductions depend to some extent on the initial conditions in which the unshielded background was determined as well as the potassium-40 and impurities contained in the crystal assembly. For these reasons, the background reductions obtained by these authors could not be taken as an absolute guide for our different circumstances but, for a similar performance, the reduction in background required of the shadow shield could be assumed to be about 2 °/o of the unshielded background.

The stages in the development of the prototype and the average background reductions attained are shown diagrammatically in Fig. 2.2. The final stage is shown in Fig 2.3. The results are summarised in Table 2.1 for the four energy ranges considered. These ranges were chosen since they covered approximately the principal photopeak energies of most of the isotopes of medical interest.

The unshielded and final shield background spectra are shown in Fig 2.4.

The overall background reductions were very close to the target suggested from the data of Miller and May and Marinelli. The largest reduction is for the 1.1 - 1.5 MeV range which includes the photopeak (1.46 MeV) of the naturally occurring potassium-40 isotope. This may be attributable to potassium-40 in the building materials of the floor, walls etc. producing a high unshielded counting-rate whilst the lower energy ranges may appear to be less well shielded because of scattered gamma rays reaching the detector.

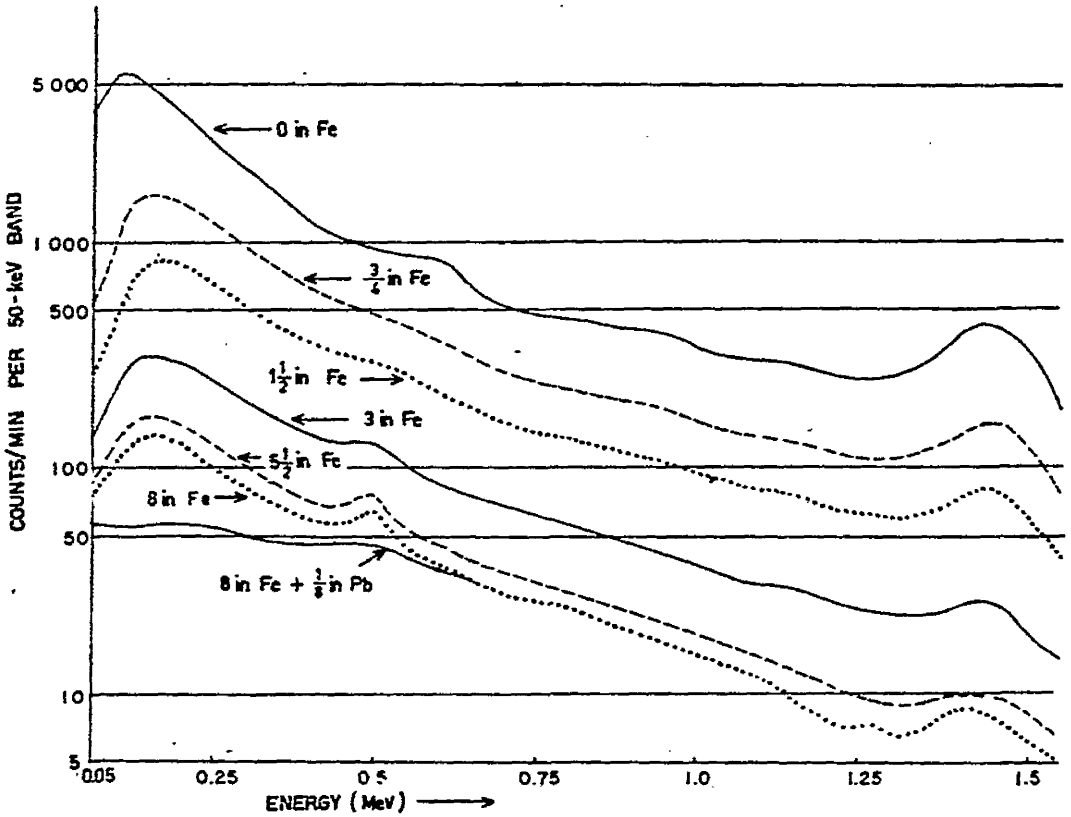
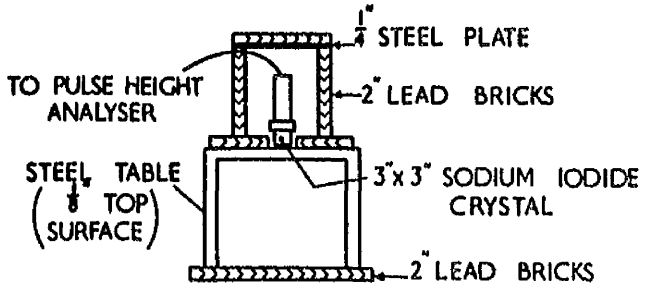


Fig. 2.1.

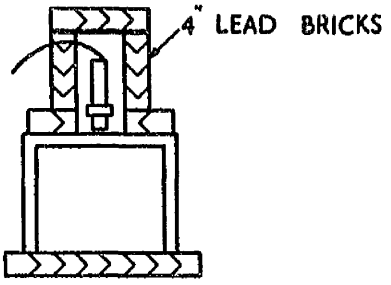
Reduction in gamma-ray background of a 8-in×4-in (20-cm×10-cm) NaI (Tl) crystal shielded by various thicknesses of iron and lead. Internal dimensions of shield 2.4 by 2.2 by 1.9 m

FIG 2.2
STAGES IN THE DEVELOPMENT OF THE PROTOTYPE SHADOW SHIELD WHOLE BODY COUNTER



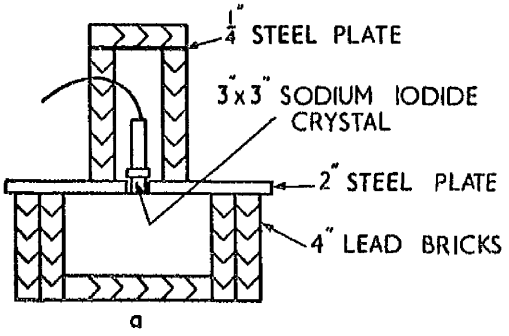
STAGE 1

% OF UNSHIELDED BACKGROUND : 13·7%

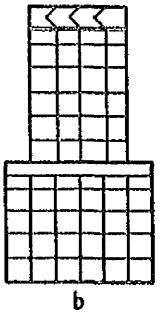


STAGE 2

% OF UNSHIELDED BACKGROUND : 7·2%



a



b

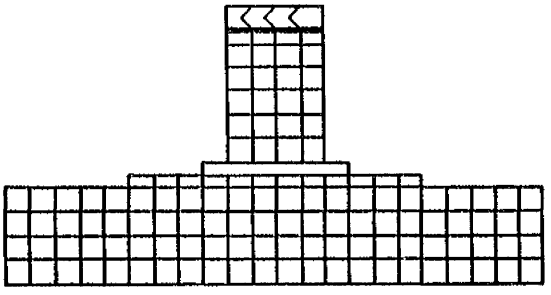
STAGE 3

% OF UNSHIELDED BACKGROUND : 4·8%

% OF PREVIOUS BACKGROUND : 67·4%

FULL BASE % OF UNSHIELDED BACKGROUND : 2·5%

% OF PREVIOUS BACKGROUND : 51 4%



STAGE 4

% OF UNSHIELDED BACKGROUND : 2·3%

% OF PREVIOUS BACKGROUND : 92·9%

FINAL

% OF UNSHIELDED BACKGROUND : 2·2%

% OF PREVIOUS BACKGROUND : 96·1%

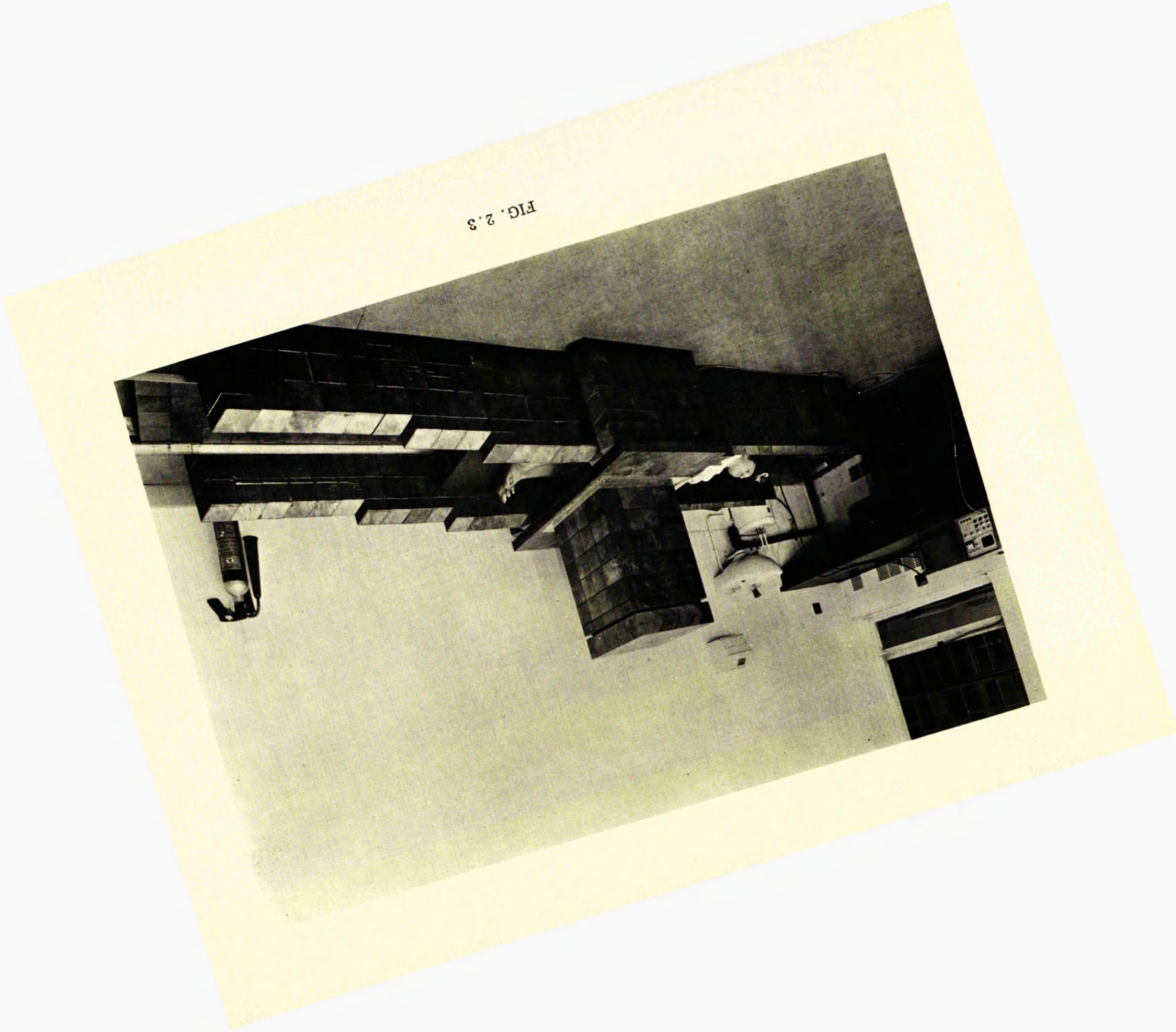


FIG. 2.3

TABLE 2.1

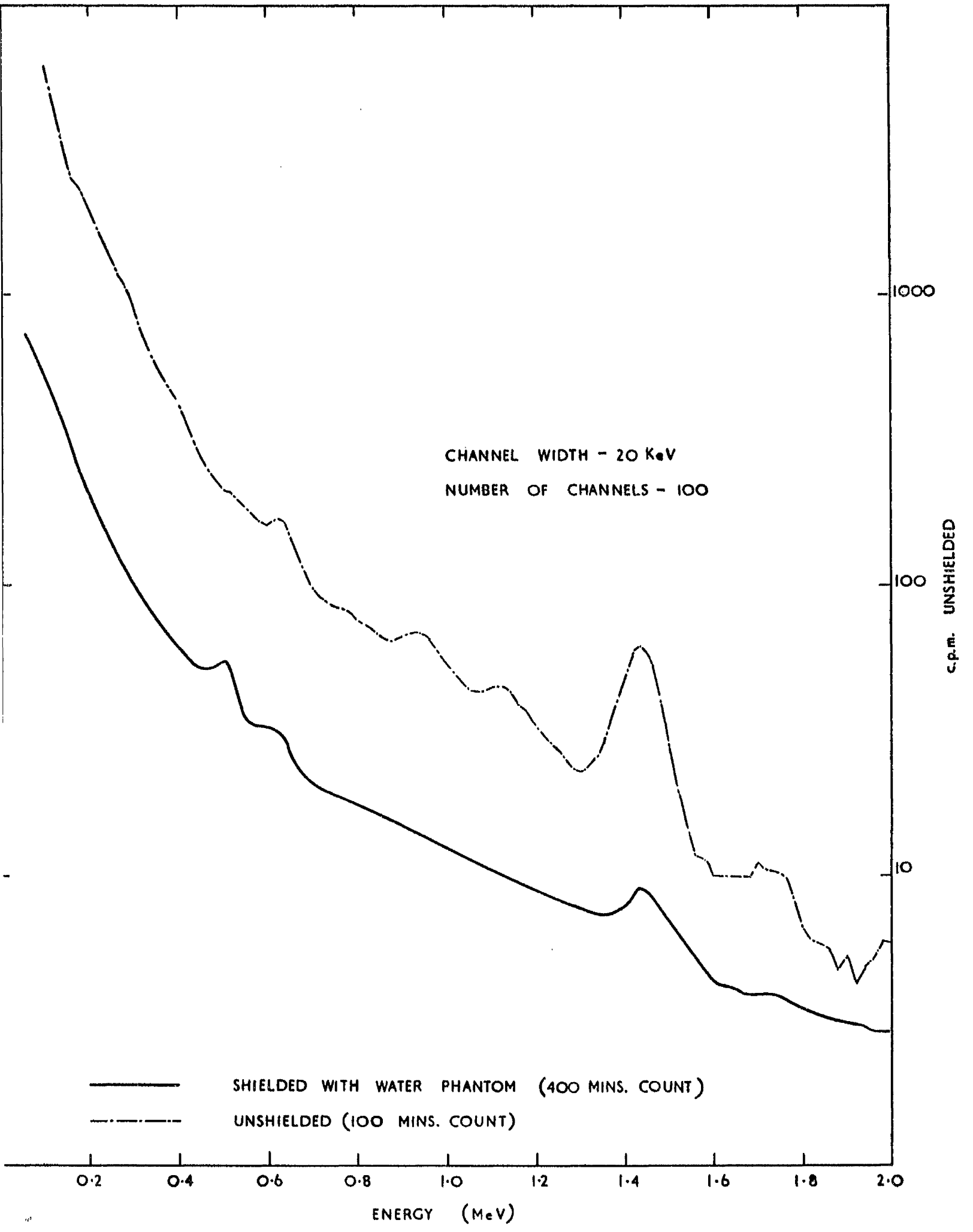
Effect of Stages in Development of Prototype on Background Counting-Rate.

Energy Range (MeV)	Unshielded			Stage 1			Stage 2			Stage 3 ≠			Stage 3 ≠ + Full base			Stage 4 ≠			Final Stage ≠		
	cpm	%/o U	%/o P	cpm	%/o U	%/o P	cpm	%/o U	%/o P	cpm	%/o U	%/o P	cpm	%/o U	%/o P	cpm	%/o U	%/o P	cpm	%/o U	
1.1 - 1.5	866	-	-	130	15.1	-	67.3	7.8	51.8	32.5	3.75	48.2	15.9	1.83	48.9	12.7	1.47	80.3	12.4	1.43	9
0.52 - 0.9	1998	-	-	282	14.1	-	145	7.3	51.5	95.7	4.79	66.0	44.7	2.23	46.7	44.0	2.20	98.4	43.9	2.19	9
0.23 - 0.52	3487	-	-	411	11.8	-	229	6.6	55.8	179	5.13	78.3	108	3.11	60.6	103	2.94	94.6	90.1	2.58	8
0.4 - 0.58	1788	-	-	246	13.8	-	125	7.0	50.7	96.4	5.39	77.1	47.5	2.66	49.3	46.6	2.61	98.1	46.4	2.60	9
Mean					13.7			7.2	52.5		4.8	67.4		2.46	51.4		2.31	92.9		2.20	9

%/o U = percentage of unshielded background counting-rate.

%/o P = percentage of background counting-rate in previous stage.

≠ = with water phantom.


CHANNEL WIDTH - 20 KeV
NUMBER OF CHANNELS - 100
1000
100
10
c.p.m. UNSHIELDED
SHIELDED WITH WATER PHANTOM (400 MINS. COUNT)
UNSHIELDED (100 MINS. COUNT)
0·2
0·4
0·6
0·8
1·0
1·2
1·4
1·6
1·8
2·0
ENERGY (MeV)

2.3 Description of the prototype:

The shield is 12 ft. 8 ins. in length, 3 ft. 4 ins. maximum width and 3 ft. 2 inches maximum height. The detector in the central turret views the patient through a hole of $5\frac{1}{2}$ inches diameter cut through the steel supporting plate. A bed, comprising a metal stretcher covered with polythene foam and rexine and with wheels attached beneath, was motorised by means of a rotating screw 9 feet in length driven by a two-speed 1/8th h.p. motor. The scan speeds are 2 ins per minute and 1 inch per minute. From the crystal face to patient mid-line is 9 inches.

In operation, the bed is manually de-coupled and set at the extreme limit of travel. The patient lying supine, and subsequently prone, rests the top of the head against a fixed head-rest defining the position with reasonable reproducibility. Counting is started automatically as a wheel passes over a micro-switch fixed in the rails on which the bed runs and is stopped by an adjustable micro-switch set according to the patient's height. The patient's head is beneath the centre of the crystal when counting begins and the feet when counting ends.

2.4 Performance of the prototype:

The performance of the prototype and its sensitivity, defined as the quantity of the isotope giving three times the standard deviation of the background in the same counting time (Trott, 1965), are summarised in Table 2.2.

2.5 Redistribution effects:

In addition to sensitivity, the results of patient monitoring may be influenced by redistribution of the isotope in the patient's body. The extent of this influence has been examined using point sources and water phantoms and also patients. A source of sodium-22 was placed consecutively at points four inches apart along the longitudinal axis and at points three inches apart along the lateral axis

TABLE 2.2

Summary of the Performance of the Prototype Monitor.

Isotope	Energy Range (MeV)	Counting-rate$_x$ (cpm/uc) with patient^x or$_+$ "active" phantom$^+$	Background (cpm) with water phantom	Sensitivity (uc) for 30 min. scan.
- 59^x	1.0 - 1.38	550	18.4	4.1×10^{-3}
	0.4 - 1.38	1670	103	3.4×10^{-3}
- 58^x	0.74 - 0.89	490	13.7	4.0×10^{-3}
	0.3 - 1.0	1800	112	3.2×10^{-3}
- 57^x	0.035- 0.188	3430	330	2.9×10^{-3}
- 40^x	1.36 - 1.56	0.03$^{\mp}$	8.0	-
- 22^+	1.18 - 1.38	552	9.7	4.3×10^{-3}
- 131^+	0.3 - 0.42	1515	64.4	2.9×10^{-3}

$^{\mp}$ cpm/gm K

of the monitor at the height of the patient mid-line. Sources of caesium-137 and cobolt-60 were also placed at various depths in a water phantom directly below the crystal.

a) Longitudinal variation:

The results obtained in examining the longitudinal variation are summarised in Table 2.3

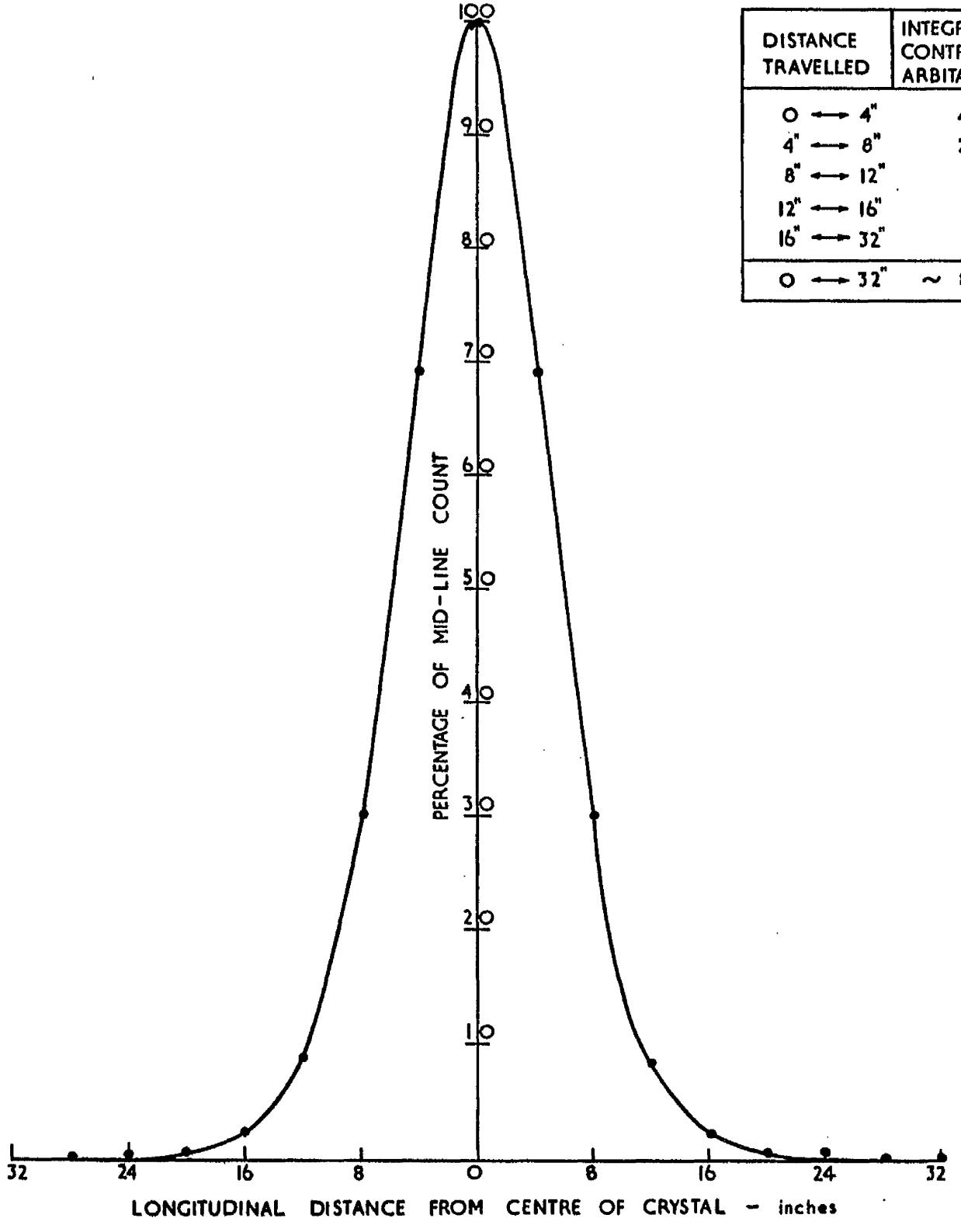
Mean values of both photopeak percentages are plotted against source position in Fig 2.5 and symmetry is assumed. Graphical integration gives the contribution over given distances of travel and these results are also shown on the same figure. It is apparent that counting along the longitudinal axis at this height is virtually confined within about 16 inches on each side of the detector mid-line.

An estimate can be made of the variation in the whole-body count and the differential count due to different sections of the body as a function of the position of starting and stopping counting. It is assumed that the activity is uniformly distributed at points four inches apart along the body (of dimensions after Bush (1946)) commencing four inches from the top of the head to four inches from the feet as shown in Fig. 2.6. The integrated contributions of each section before and after passing the crystal mid-line can then be calculated using the data of Fig. 2.5. If 16 inches from the mid-line is chosen as the starting-stopping distance, the total body count can be expected to be constant for any longitudinal redistribution. A loss of sensitivity, inevitably results. It can be seen that commencing and ending at 8 inches, 4 inches and directly below the mid-line leads to variations of only $\sim 0.4^{o}/o$, $\sim 1.3^{o}/o$ and $\sim 4^{o}/o$ respectively. Consequently, for the prototype, the mid-line was chosen as the starting and ending point giving maximum sensitivity. The variation along the length of the body is then a maximum of $\sim -20^{o}/o$ and, in practice, is unlikely to exceed $\sim -7^{o}/o$.

TABLE 2.3

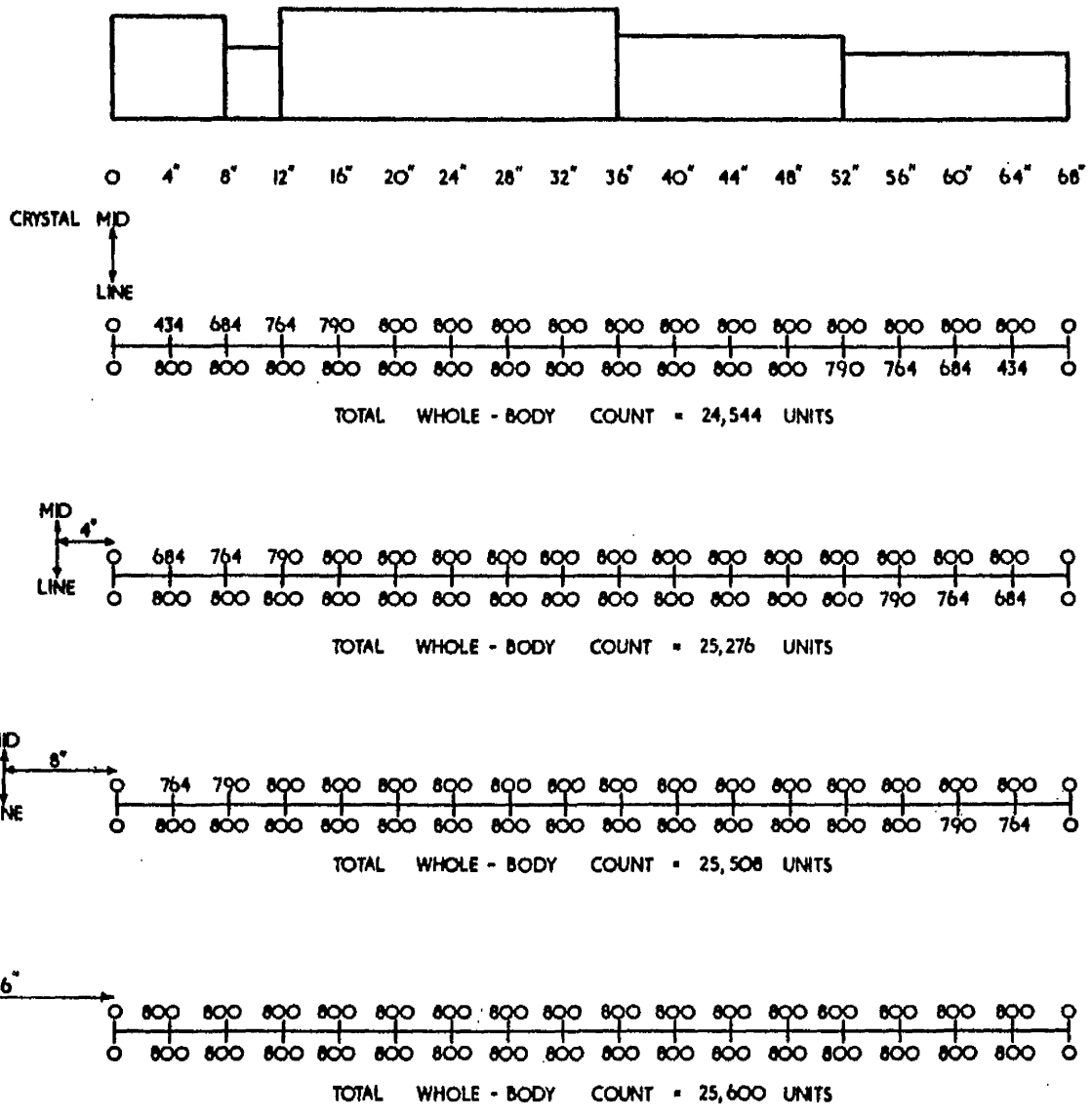
Source Position.	0.51 MeV photopeak.		1.28 MeV photopeak.	
	cts. in 4 mins.	°/o of maximum	cts. in 4 mins.	°/o of maximum
eath Xtal centre	401697	100	91851	100
4 inches	281579	70.1	62456	68.0
8 inches	119652	29.8	27738	30.2
.2 inches	33446	8.3	8187	8.9
.6 inches	8205	2.0	2056	2.2
0 inches	2773	0.7	631	0.7
4 inches	1426	0.4	244	0.3
8 inches	958	0.2	118	0.1
2 inches	730	0.2	102	0.1
6 inches	591	0.1	77	-

2.5 VARIATION OF COUNTING-RATE (AS PERCENTAGE OF MID-LINE COUNT-RATE) WITH LONGITUDINAL DISTANCE



DISTANCE TRAVELLED	INTEGRATED CONTRIBUTION ARBITARY UNITS
0 ⟷ 4"	434
4" ⟷ 8"	250
8" ⟷ 12"	80
12" ⟷ 16"	25
16" ⟷ 32"	10
0 ⟷ 32"	~ 800

FIG 2.6 INTEGRATED COUNTING - RATES OF PHANTON SCAN - DISTRIBUTED POINT SOURCES



b) Lateral variation:

The results obtained in examining the lateral variation are presented in Table 2.4.

TABLE 2.4

Source Position	0.51 MeV photopeak cts. in 4 mins.	1.28 MeV photopeak cts. in 4 mins.
Below xtal centre	99597	22378
+ 3 ins.	94061	22086
+ 6 ins.	78838	18999

If symmetry is again assumed, it can be calculated that σ (lateral) = $\pm$ 9.7°/o. Part of this variation may be attributable to the small diameter of the crystal.

c) Vertical or depth variation:

Sources of cobalt-60 and caesium-137 were placed successively one inch above the bed to 7 inches above the bed in a water phantom eight inches deep. The results obtained are summarised in Table 2.5.

The variation which might be observed in counting a patient in the supine and prone positions and summing the results may be simulated by summing reciprocal results of Table 2.5. The effect of this procedure is shown in Table 2.6. Standard deviations of $\pm$ 19°/o and $\pm$ 15°/o are obtained.

d) Redistribution effects in patients:

In studies of iron metabolism (Will, G and Boddy, K., 1966) (and see Chapter 4), five patients were measured at various times up to six hours following oral administration of iron-59. The results are repeated in Table 2.7 along with percentage absorption at 20 days calculated for each initial result.

TABLE 2.5

Source Position	Co^{60} photopeak cts. in 4 mins.	Co^{137} photopeak cts. in 4 mins.
Under 7" water	6108	9453
Under 6" water	7191	11451
Under 5" water	9678	14752
Under 4" water	12241	19585
Under 3" water	17612	26158
Under 2" water	22149	34075
Under 1" water	31683	45055

TABLE 2.6

Positions summed	Co^{60} photopeak summed cts.	Co^{137} photopeak summed cts.
Under 7" and 1" water	37791	54508
Under 6" and 2" water	29340	45526
Under 5" and 3" water	27290	40910
Under 4" water x 2.	24482	39170
σ =	19.3°/o	14.68°/o

TABLE 2.7

Variation in Whole Body Counting Rate in the Post Ingestion Period and its effect on Percentage Iron Absorption Results.

Case	WHOLE BODY COUNTS				PERCENTAGE IRON ABSORPTION				MEAN ABSORPTION
	Immediate c.p.m.	2 hrs. c.p.m.	4 hrs. c.p.m.	6 hrs. c.p.m.	Immediate o/o	2 hrs. o/o	4 hrs. o/o	6 hrs cpm.	
1.	9721	8635	9699	9625	4.2	4.7	4.2	4.2	4.3 ± 0.4
2.	29933	X	34726	26810	14.6	X	12.6	16.3	14.5 ± 1.9
3.	34054	X	32700	X	15.1	X	15.7	X	15.4 ± 0.3
4.	11744	11696	10117	10010	11.9	11.9	13.8	13.9	12.9 ± 1.0
5.	6156	5327	5999	5825	18.1	20.9	19.1	19.2	19.3 ± 1.5

The maximum variation observed did not exceed $\pm$ 10 per cent. This variation produces differences in the final absorption figures which are trivial compared with the normal absorption range of 5.8-19.3 per cent.

The redistribution effects in the prototype are slightly greater than those described by Warner and Oliver (1966) for a different design of shadow shield monitor. These authors describe overall variations of $\pm$ 15°/o for various distributions compared with a point source of the same activity in a phantom and for cobalt-58 in patients a maximum variation of 3°/o. However, the distance from the crystal face to patient mid-line is greater (18 inches) in the latter monitor than in the prototype (9 inches), while the prototype is about six times better in sensitivity for the same crystal volume and counting-time, when using the wide energy band technique described by these authors.

2.6 Sensitivity as a function of shield and of crystal volume.

It can be shown (e.g. Watt and Ramsden, 1964) that the coefficient of variation C is a minimum with an optimum division of total available counting-time T between subject and background and

$$C = \frac{\frac{B^{\frac{1}{2}}}{D} + \left(\frac{B}{D^2} + \frac{1}{D}\right)^{\frac{1}{2}}}{T^{\frac{1}{2}}}$$

where B is the background counting-rate D is the subject counting-rate and $C = \frac{O}{D}$

Thus, approximately, the percentage standard error (100XC) and the sensitivity, as defined in section 2.4, are proportional to $\frac{B^{\frac{1}{2}}}{D}$. If D is constant, as will be the case for a fixed crystal/patient geometry and crystal volume, then the standard error and sensitivity are directly proportional to the square root of the background counting-rate. For example, the Stagel shield (13.7 per cent of unshielded background counting-rate) will be $\sqrt{13.7/2.2} = 2.5$ times less sensitive or have a standard error 2.5 times greater than the final prototype (2.2 per cent of unshielded background). This simpler design may, therefore,

have adequate sensitivity for many clinical applications.

Further, both background and subject counting-rates are roughly proportional to the crystal volume (Miller, 1962) so that the standard error and sensitivity are proportional to $\frac{B^{\frac{1}{2}}}{D}$ and $\frac{V^{\frac{1}{2}}}{V} = \frac{1}{V^{\frac{1}{2}}}$ i. e. they are roughly inversely proportional to the square-root of the crystal volume. Thus, if a total counting time of 100 mins. is optimally divided between patient and background measurements, the standard error in measuring 140 gm. of body potassium in the prototype is about 15 per cent, (from the data of Table 2.2), which is of course too great for clinical studies. Using an $11\frac{1}{2}$ inches diameter x 4 inches detector instead of the 3 inches diameter x 3 inches currently used will reduce the standard error to about 3 per cent which is comparable with that of steel room monitors (Boddy, 1965) and similar to that obtained in a mobile monitor at Hanford, U.S.A. described recently by Palmer and Roesch (1965).

2.7 Conclusions:

The prototype has sufficient sensitivity for many clinical investigations and is being used for this purpose. On average, about 14 patients from hospitals in Glasgow and Greenock are examined each week and some of these studies are described later.

It has been shown that, with a detector $11\frac{1}{2}$ inches x 4 inches, sensitivity comparable with steel-room monitors can be expected. By suitable choice of shield design (as in Fig. 2.2) and of crystal volume, sensitivity can be varied according to individual requirements and the depth of the pocket.

CHAPTER III: The Mobile Whole-Body Monitor (MERLIN)[*]

On the basis of the performance of the prototype, (Boddy, 1965 and Chapter 2), an application (Boddy, 1964) was made to the Scottish Hospital Endowments Research Trust for financial support in constructing a mobile whole-body monitor of high sensitivity. A capital grant of £19,745 was awarded by the Trust in May, 1965.

3.1 Special requirements:

Three special requirements for the mobile whole-body monitor required consideration, to reduce the weight of shielding and to increase sensitivity. The third requirement was to measure body potassium in patients who could not lie flat, such as those suffering from osteoporosis or heart complaints.

a) Reduction of shield weight:

The prototype shield weighs approximately 8 tons, while a reduction to 7 tons was desirable for incorporation in a mobile laboratory on a standard vehicle chassis.

The prototype shielding studies showed that the final stages of the shield contributed comparatively little in reducing the background counting-rate. This may be explained by the small geometrical probability of a gamma-ray originating in this vicinity reaching the detector. Further, if the gamma-ray travelled in a straight line to the detector its oblique path length through a base or wall of constant thickness would, for geometrical reasons, be much greater than that of a gamma-ray passing perpendicularly through the base or wall i.e. from directly below the detector. It may be inferred, therefore, that the limits of the base and walls are "over-shielded" compared with the area directly around the crystal. Elementary calculations were carried out to ascertain

[*] Monitoring Equipment for Radioactivity at Low-levels IN vivo.

the distances and heights of shield at which the centre of the crystal could not "see" the surrounding walls or floor or through which a gamma-ray must travel at least six inches. The calculations are presented in Appendix 1 and the calculated design is shown in Fig. 3.1.

b. Choice of crystal size:

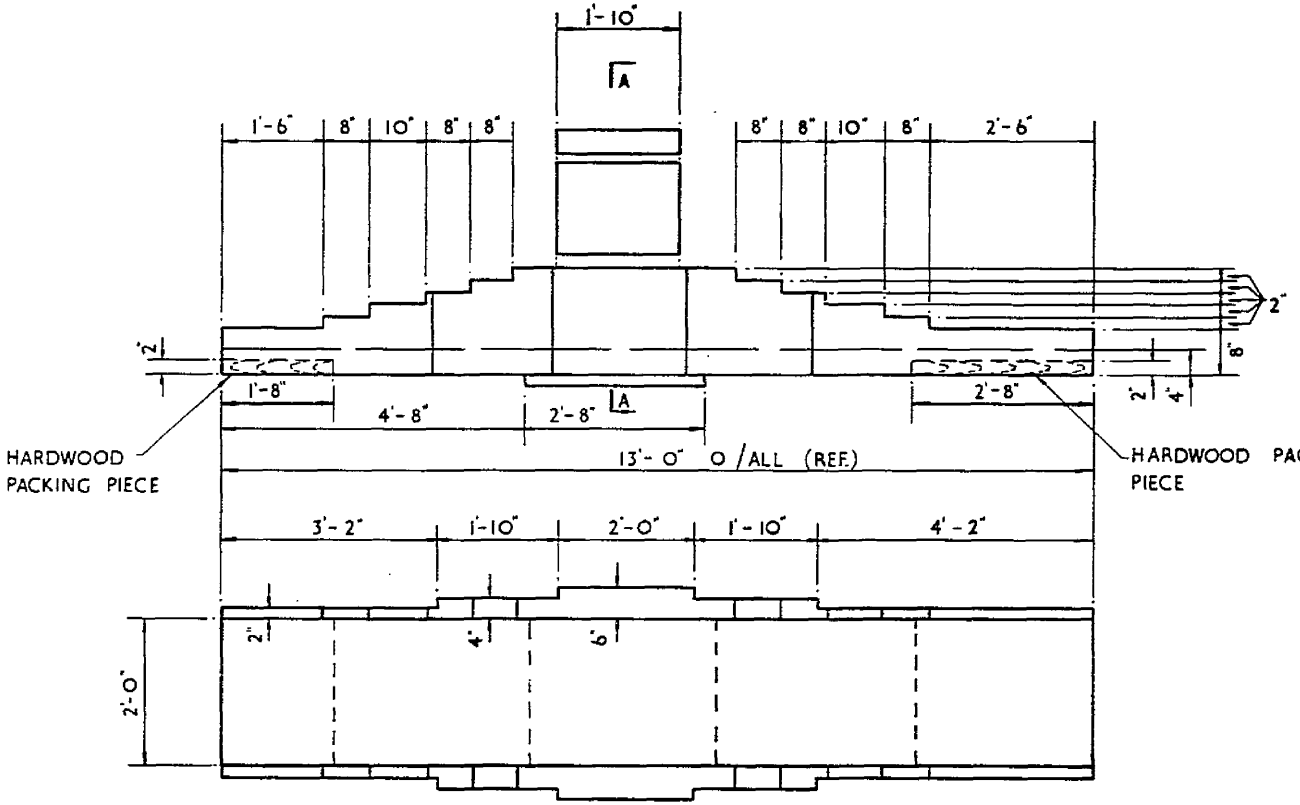
From the discussion of 2.6 it may be anticipated that a crystal volume about twenty-five times greater than that of the 3 inches diameter x 3 inches detector of the prototype is required to provide sensitivity comparable with steel-room monitors. The choice of detection system seemed to be between a single detector $11\frac{1}{2}$ inches diameter x 4 inches, the largest detector available at that time at reasonable cost, or four crystals 6 inches diameter x 4 inches. The advantages of a single crystal (scanning) system over the multiple-detector system and the comparative simplicity of shielding have already been discussed. A single detector of $11\frac{1}{2}$ inches diameter x 4 inches was consequently selected. May and Marinelli (1962) have described the advantages of multiple photomultipliers over a single large photomultiplier for a crystal of these dimensions and the former arrangement was chosen.

c. Monitoring of patients unable to lie flat:

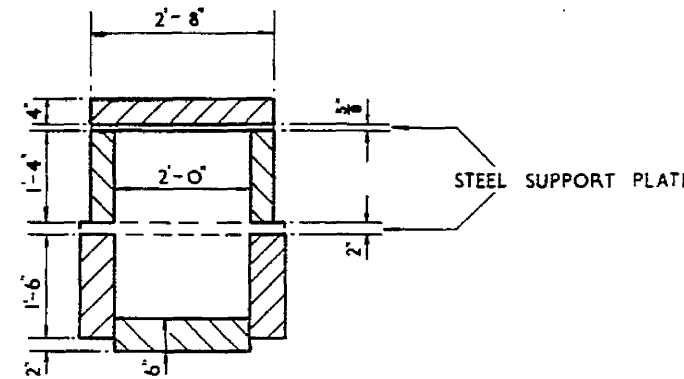
A criticism offered of the prototype was the difficulties which would be presented in monitoring patients who were unable to lie flat. In particular, one group of workers wished to measure body potassium in patients suffering from heart conditions. As potassium is distributed fairly uniformly throughout the body, redistribution or geometrical effects are of lesser importance and a tilting-chair geometry should be completely satisfactory (Miller, 1962). The shield could be modified appropriately by mounting the central turret on trunnions, allowing it to be rotated, and raising a section of the base behind the seated patient. Alternatively, when this geometry was required, the turret could be raised by jacks or a gantry to an appropriate height and supplementary lead

SHADOW SHIELD

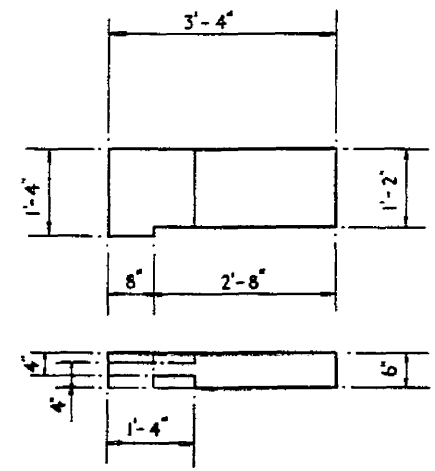
MATERIAL - PURE LEAD



PLAN (WITH TURRET REMOVED)



SECTION A-A



TURRET EXTENSION

1 OFF AS DRAWN
1 OFF OPP. HAND (AS PER CHAIN DOT LINE)

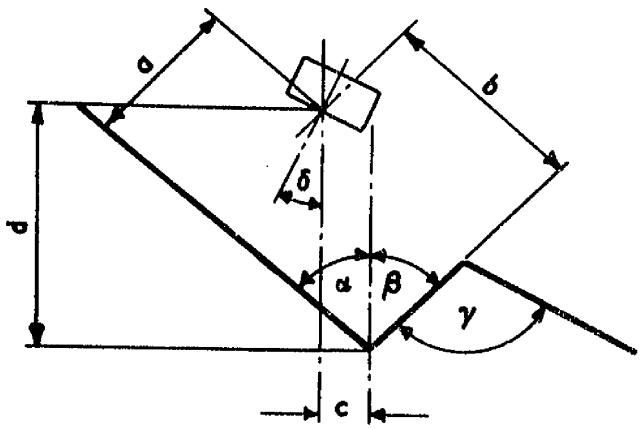
side walls added beneath the steel plate. Both arrangements require a wall across the monitor on the side opposite to the patient and the latter arrangement requires a wall which can be moved into position behind the patient. However, the engineering aspects of the latter arrangement are simpler to achieve and the weight limitation on the mobile laboratory means that in either case the supplementary lead must be transported separately. Mock-ups showed that the minimum satisfactory clearance from the monitor base to the base plate of the turret was approximately 28 inches. With a tilting chair of which the back and base are both at 45° to the vertical, the top of the patient's head and the eyes are then outwith the steel plate. The geometrical error involved in this procedure is likely to be small and is off-set in practice by the elimination of claustrophobic effects which is of particular importance for patients with heart conditions.

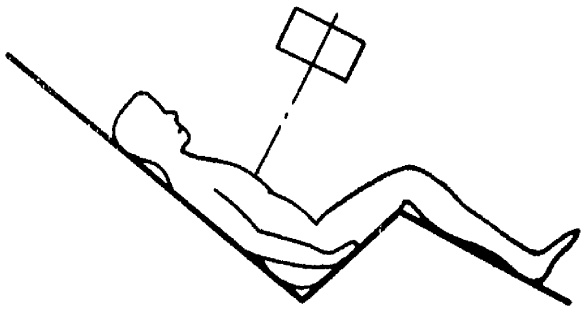
The depth of the steel plate supporting the turret is $2\frac{1}{4}$ inches so that the crystal protrudes by some 1 3/4 inches below the plate. The geometry is shown diagrammatically in Fig. 3.2 and in Fig 3.3 the actual arrangement. A similar geometry is used, for example, in the monitors at Los Alamos, Oak Ridge and Vanderbilt University.

Experience showed that to raise the turret while keeping it horizontal was extremely tedious, difficult and, with the detector in the turret, nerve-racking when three or four separate jacks were used. Hydraulic jacks coupled to a common cylinder were considered since a horizontal lift should be more easily attainable. Failure, for example, through leakage, could not be ruled out, however, and, during the lowering of the turret, simultaneous control of the jacks is less adequate. As a lift of 16 inches is required with an initial clearance from base to steel plate of only 14 inches, two or three stages of lift are required. The cost of the best system was quoted as between £250 - £500 as a preliminary estimate. A firm tender was not requested! A gantry with pulley, capable of lifting 3 tons and tested to $4\frac{1}{2}$ tons, was kindly designed and constructed by members of

Fig. 3.2.

MERLIN TILTING - CHAIR GEOMETRY





a = b = 40·4 cm
c = ZERO
d = 57·2 cm

α = β = 45°
γ = 45°
δ = ZERO

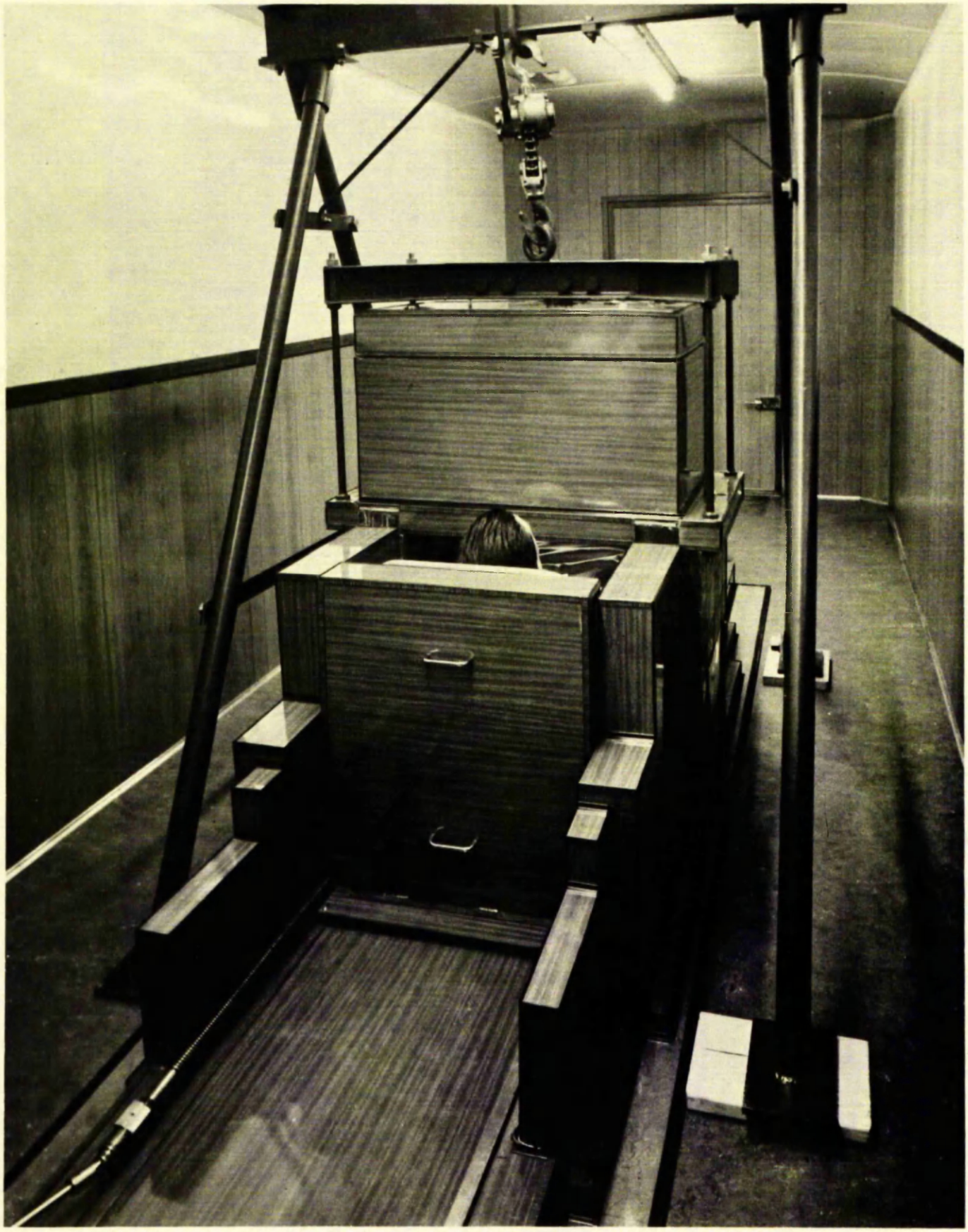


Fig. 3.3. MERLIN Chair Geometry
with Lifting Gantry

the National Engineering Laboratory, East Kilbride. The gantry in use is shown in Fig. 3.3 from which it may be seen that the structure can be completely assembled and disassembled in the mobile laboratory. The lift is inevitably slow and is well controlled by the lifting assembly. To maintain the plate and turret horizontal presents no problem and small adjustments of the suspended turret are simply achieved whereas with jacks such adjustments were virtually impossible.

It was anticipated that a need might arise to make lateral scans or to count over individual organs. A tapered slot cut across one half of the steel plate supporting the turret could accommodate a smaller supplementary detector with a collimator, if necessary. The slot would normally be filled with a lead block made specifically for this purpose. This facility was not difficult to arrange and it seemed worthwhile to incorporate.

3.2 Selection of materials and equipment.

Of necessity, the prototype monitor was constructed from available materials. For MERLIN, on the other hand, some selection of materials and equipment could be made bearing in mind the limitations of finance and time.

a) The detector:

Two tenders were received for the supply of the 11½ inches diameter x 4 inches sodium iodide detector. Surprisingly, the lower tender (£2,600) from Quartz et Silice, Paris, was less than half of the higher tender (£5,800). The specification and performance guarantees were identical. At this time, however, it appeared that the Quartz et Silice detectors were less widely-known than those of their competitors. It, therefore, seemed prudent, before accepting this tender, to survey the experience of other workers. Information was sought on the ability to produce crystals of this size and their performance in terms of

low inherent background (1 p.p.m. of potassium) and resolution of 11 o/o or better guaranteed for the Cs-137 photopeak.)

Nuclear-Chicago Corporation (Shevick, 1965) examined a Quartz et Silice detector $11\frac{1}{2}$ inches diameter x $\frac{1}{2}$ inch and found this extremely well made. Other crystals used for conventional gamma ray analysis were also examined and Shevick intimated "they appear excellent with regard to resolution and background, certainly as good as those made by Harshaw". The University of Helsinki (Kantele, 1965) employs an anticoincidence annulus in two "pineapple slices" each 12 inches long x 8 inches diameter with a 3 inches tunnel. The resolution of this unit is apparently better than 13 o/o while the best reported in the literature was quoted as 14.2o/o. It was also shown by Hill (1965) that, at least, for smaller detectors, the resolution of Quartz et Silice detectors compares very favourably with that of any of their competitors.

An examination of the background counting-rate of a Quartz and Silice 4 inches diameter x 4 inches detector and a Harshaw 3 inches diameter x 5 inches detector was made at Argonne National Laboratory (May, 1965). In the energy range 0.3 - 1.5 MeV, the Quartz and Silice background was 19 o/o greater but the crystal volume was 42 o/o greater. A detailed examination was not made but it would seem that the background performances are at least comparable and May commented "the basic crystal was certainly as clean as anything I've ever seen".

The most detailed comparison has been made by Grinberg and Gallic at the Centre d'Etudes Nucleaires de Saclay of the French Atomic Energy Commission. Table 3.1 summaries the results (Gallic, 1965), and gamma ray spectra obtained are shown in Fig. 3.4 Table 3.1.

The measurements were made in the Low Activity Laboratory of the Laboratoire de Mesure des Radioelements in a cave of 4 inches of

TABLE 3.1

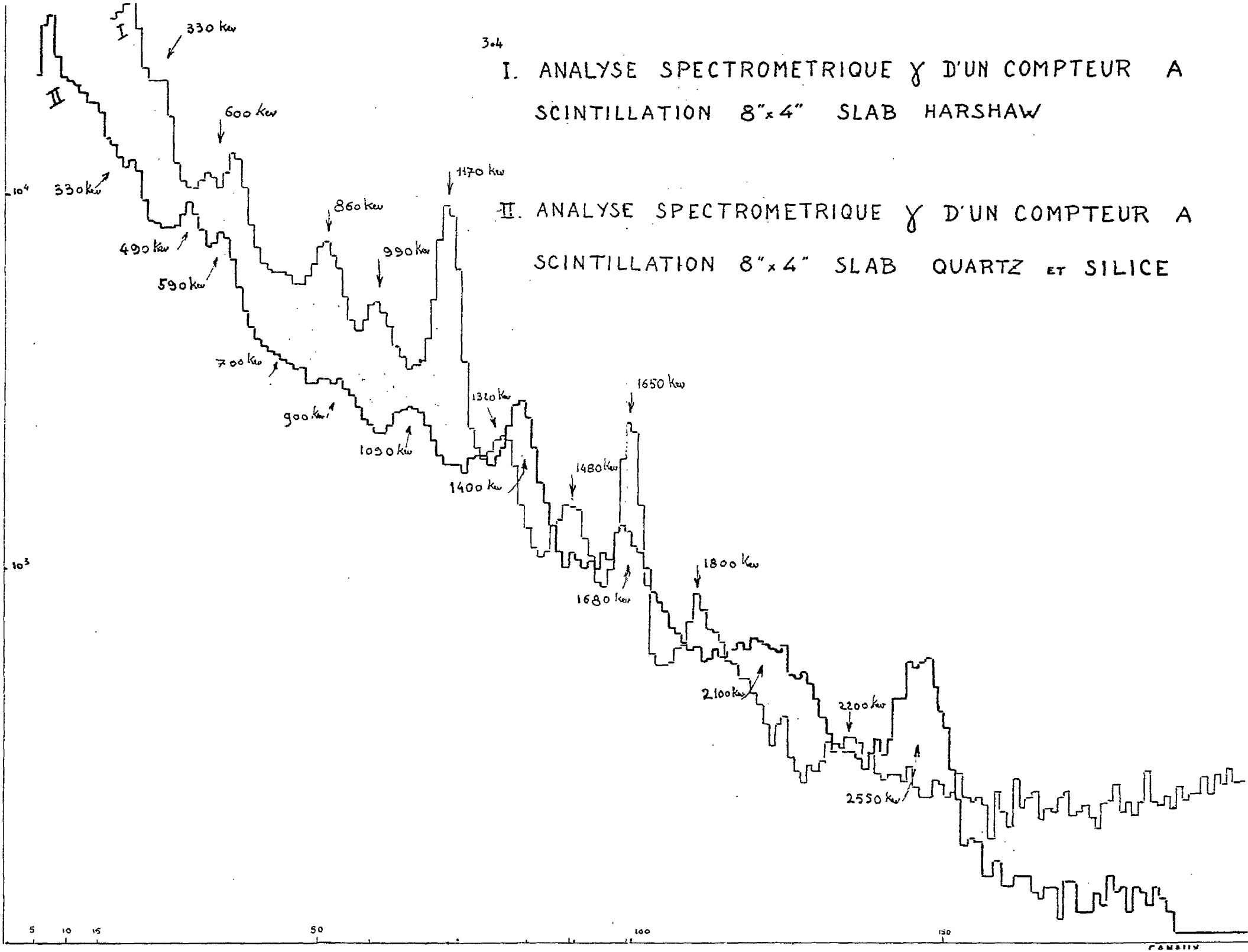
DETECTOR	Cs - 137 Resolution o/o	Background 0.1 - 3.2 MeV cpm
Harshaw - 8" x 4" with unactivated slab	8.6	685
Q. and S. 8" x 4" with unactivated slab	8.6	456
Q. and S. 8" x 4" without unactivated slab.	8.5	670

TABLE 3.2

SOURCE	Counting Time (Mins)	ENERGY RANGE (MeV)					
		0.11 - 0.41		0.41 - 0.70		0.57 - 0.70	
		Counts	cpm.	Counts.	cpm.	Counts.	cpm
Virgin Lead	1363.8	201448	147.7	76693	56.24	27066	19.85
Aged Lead	1768.1	265507	150.2	103528	58.55	36275	20.52
Background	656.7	140973	215.2	403035	65.53	14833	22.59

I. ANALYSE SPECTROMETRIQUE γ D'UN COMPTEUR A SCINTILLATION 8"x4" SLAB HARSHAW

II. ANALYSE SPECTROMETRIQUE γ D'UN COMPTEUR A SCINTILLATION 8"x4" SLAB QUARTZ ET SILICE



lead. Three significant conclusions can be drawn. The resolution of the large Quartz and Silice detectors is as good as those of Harshaw and the inherent background seems rather better. Close examination of the spectra of Fig. 3.4 suggests that the contaminants of the crystals are different, the thorium-232 chain in the former and the uranium-238 chain in the latter.

The Quartz and Silice tender was accepted. The crystal assembly is shown in Fig. 3.5. Its resolution for caesium-137 is 10°/o.

b) Lead:

The lowest tender for the lead shield and also the most flexible arrangement was received from Associated Lead (£1,730). Lead without antimony was specified as it has been suggested (Rundo, 1965) that some contamination was attributable to its conclusion. Samples of virgin lead and aged lead, which would be used for the shield, were obtained and monitored in the prototype monitor. An investigation of the radioactive contamination of lead (Weller et al., 1965) showed that the principal contaminant was 21.4 - year lead - 210. The energy bands chosen were consequently, 110-410 KeV covering the bremnstrahlung continuum peaking at about 170 KeV and 410 - 700 KeV covering the most prominent structure of the radium daughter spectrum. Fall-out caesium-137 was a possible further contaminant and a range of 0.57 - 0.70 MeV was also examined. Fig. 3.6, shows the spectra obtained and the results are summarised in Table 3.2

The specimen slabs were of the same area and thickness and both reduced the background counting-rate in each energy range. However, the virgin lead was marginally better throughout. The spectra showed no differences in structure compared with the background spectrum. Both samples appeared free of contaminants and the final choice of virgin lead was influenced by knowledge of its source.

The virgin lead (TADANAC - the reverse of CANADA. T) originated

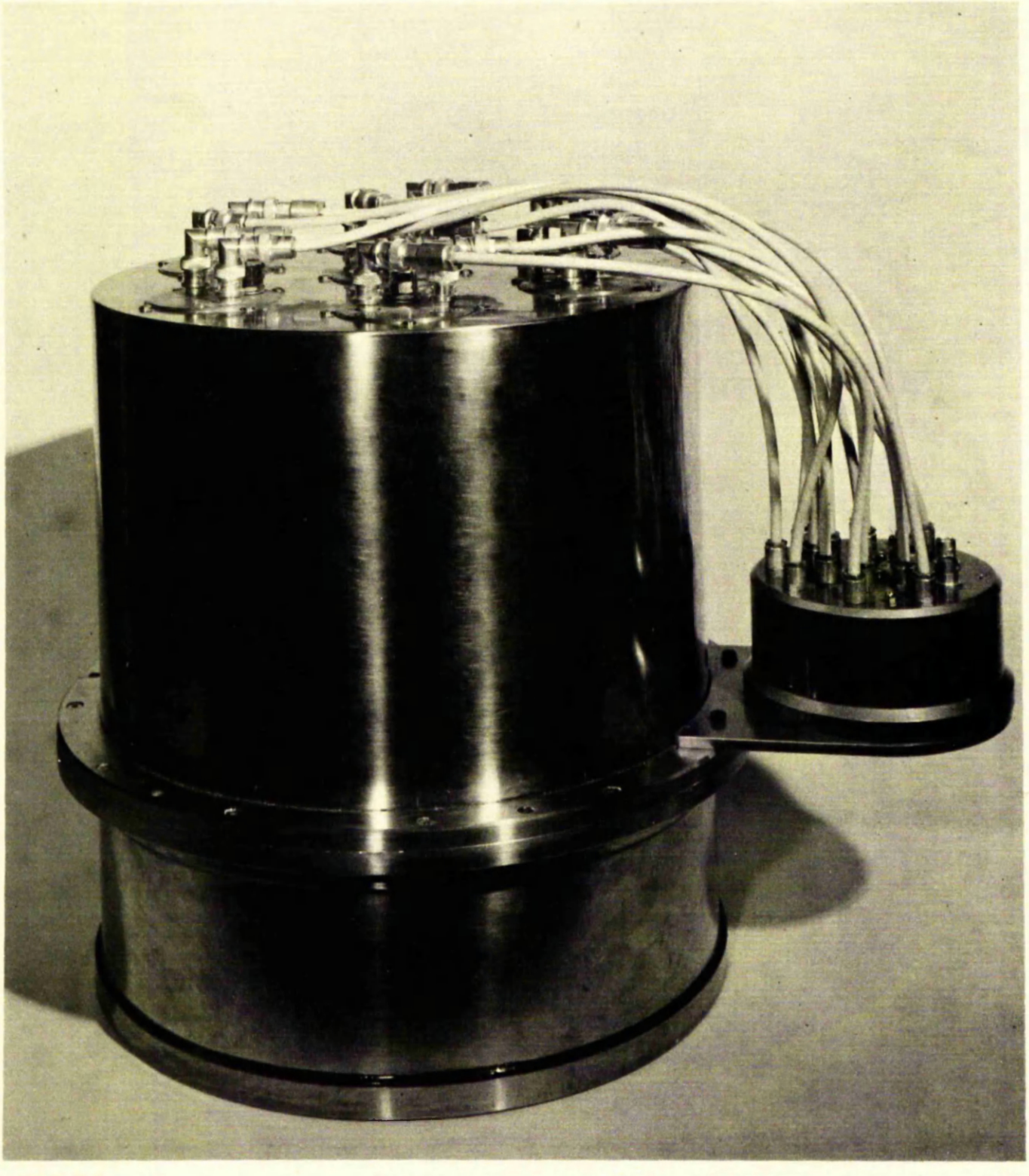
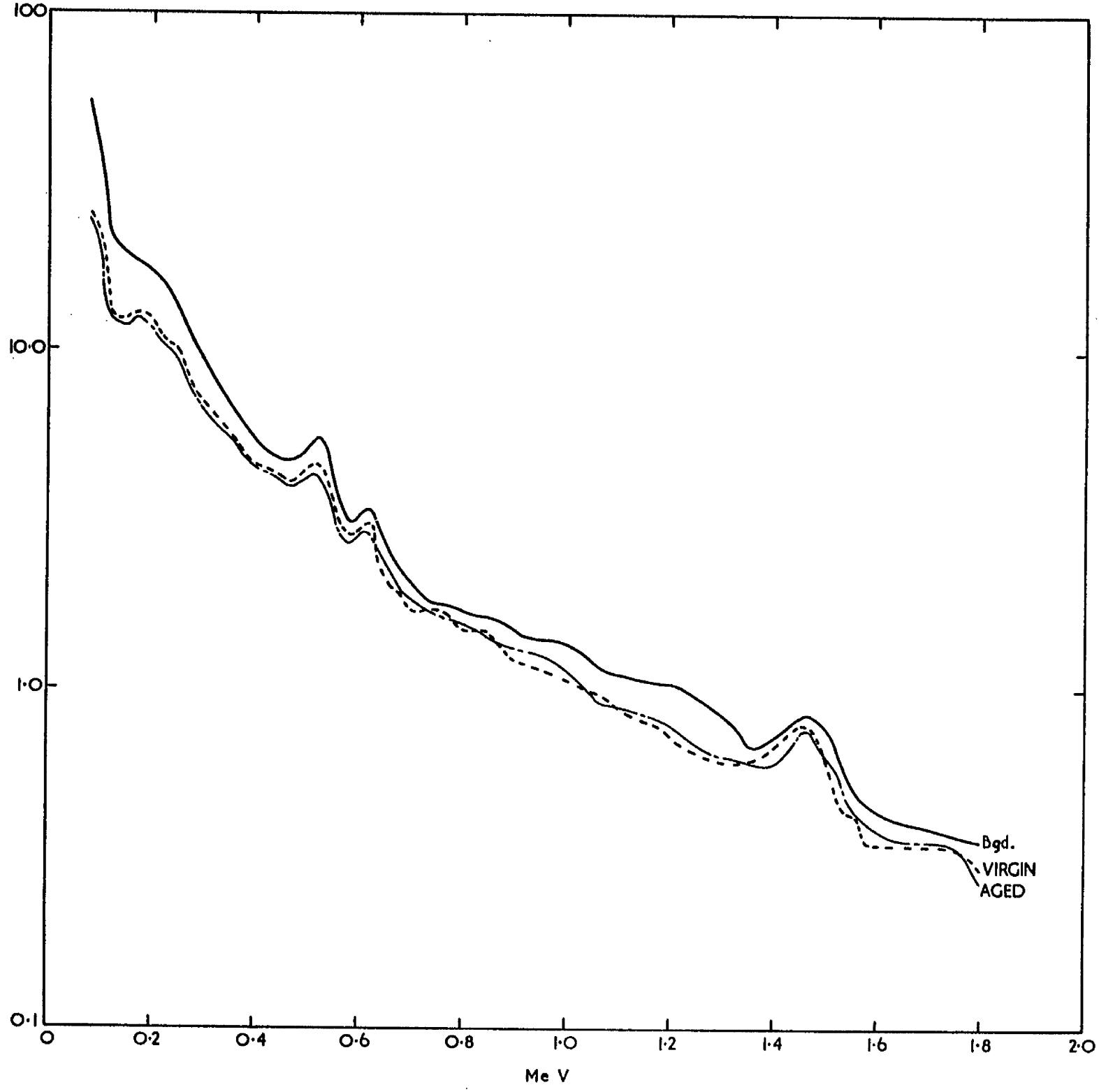


Fig. 3.5. Sodium Iodide Detector Assembly - $11\frac{1}{2}$ inches diameter x 4 inches

3·6 SPECTRA OF LEAD SAMPLES



from Trail in Canada. The geological distribution of uranium-bearing ores was described by Van Wambeke, (1965), and it could be seen that the nearest deposits (mainly near Lake Elliot) were an appreciable distance from Trail. Uranium ores are of primary importance since lead-210 is a member of the uranium-238 series while the thorium and actinium series contain no long-lived isotopes of lead.

c) Steel:

It has been reported (for example Spiers (1962)) that modern steels may contain contamination in the nature of cobalt-60, occasionally used as a tracer for wear in furnace linings, and caesium-137 as a long-lined fission product. Vennart (1965), on the other hand, suggests that in Britain the use of cobalt-60 was limited to only a few foundries as was also the practice of incorporating large amounts of scrap, which might be contaminated. A limited amount of steel was required for MERLIN as a base plate, distributing the load evenly on the vehicle chassis, as a supporting plate for the turret and also for the lid of the turret. In view of the high cost of pre-1945 naval steel and the difficulties of obtaining the required differing thicknesses, local steel[※] was monitored.

Three energy ranges were chosen, 0.60 - 0.72 MeV, 1.1 - 1.4 MeV, and 1.36, - 1.56 MeV, corresponding to the photopeaks of caesium-137, cobalt-60 and potassium-40 respectively. Monitoring was carried out using the prototype and the results, presented in Table 3.3, show no significant effects upon the background counting-rate and no significant contamination.

d) Formica, etc.

To create the impression of lightness of weight and to facilitate cleaning of the monitor, formica was chosen to cover

※ Samples kindly provided by Colvilles Ltd., Glasgow.

TABLE 3.3

RESULTS OF MONITORING PLATES OF LOCAL STEEL

	Gross Plate (cpm)			Background (cpm)			Net Plate (cpm)		
eel	0.60	1.10	1.36	0.60	1.10	1.36	0.60	1.10	1.36
ate	-0.72	-1.40	-1.56	-0.72	-1.40	-1.56	-0.72	-1.40	-1.56
No.	MeV	MeV	MeV	MeV	MeV	MeV	MeV	MeV	MeV
1.	17.8	14.2	8.5	17.6	14.3	8.9	0.2	-	-
2.	15.7	12.6	7.1	15.8	13.7	7.3	-	-	-
3.	17.4	13.7	8.0	16.9	13.7	8.8	0.5	-	-
4.	18.8	13.7	7.8	18.5	13.9	7.3	0.3	-	0.5
5.	16.1	12.7	7.4	15.8	12.7	7.4	0.3	-	-
6.	16.0	13.3	7.3	16.2	11.9	7.7	-	1.4	-
7.	17.8	12.7	7.2	17.2	13.1	7.2	0.6	-	-
8.	16.8	13.3	7.2	17.2	14.1	7.0	-	-	0.2

the shield. Samples were pre-monitored with the results shown in Table 3.4. Potassium-40 and caesium-137 seemed the most probable of possible contaminants but the differences in counting-rate are not statistically significant and no extraordinary peaks were observed in the spectrum.

The materials of which the bed and chair were to be constructed were also monitored and shown to have no significant contamination.

e) Electronic equipment:

The most expensive items of the electronic equipment are clearly the multichannel analyser and peripheral units. The large number of analysers currently manufactured generally results in a marginal preference for one analyser compared with competitive models. Following demonstrations of several makes of analyser, however, the T.M.C. 404 analyser was selected for its compactness, simplicity of manipulation, and its versatility included resolution and integration the only analyser at that time with such a facility. The peripheral equipment chosen included a built-in H.T. supply, typewriter and tape output and tape reader. The H.T. and L.T. supply (Farnell) were chosen for their stability and low ripple specifications. A mains filter unit (recommended by J. Rundo) and a mains stabiliser unit were incorporated and a change-over unit was home-built (J. Rowan) to avoid switching-off the electronic equipment when changing from the generator to a mains supply and vice versa.

The electronic lay-out is shown schematically in Fig. 3.7.

f) The Mobile Laboratory:

The principal requirements for the mobile laboratory were as follows:

i) Ability to carry at least 7 - $7\frac{1}{2}$ tons weight.

ii) Integral chassis to prevent possibility of "jack-knifing" as could occur with an articulated vehicle on, for example, icy roads.

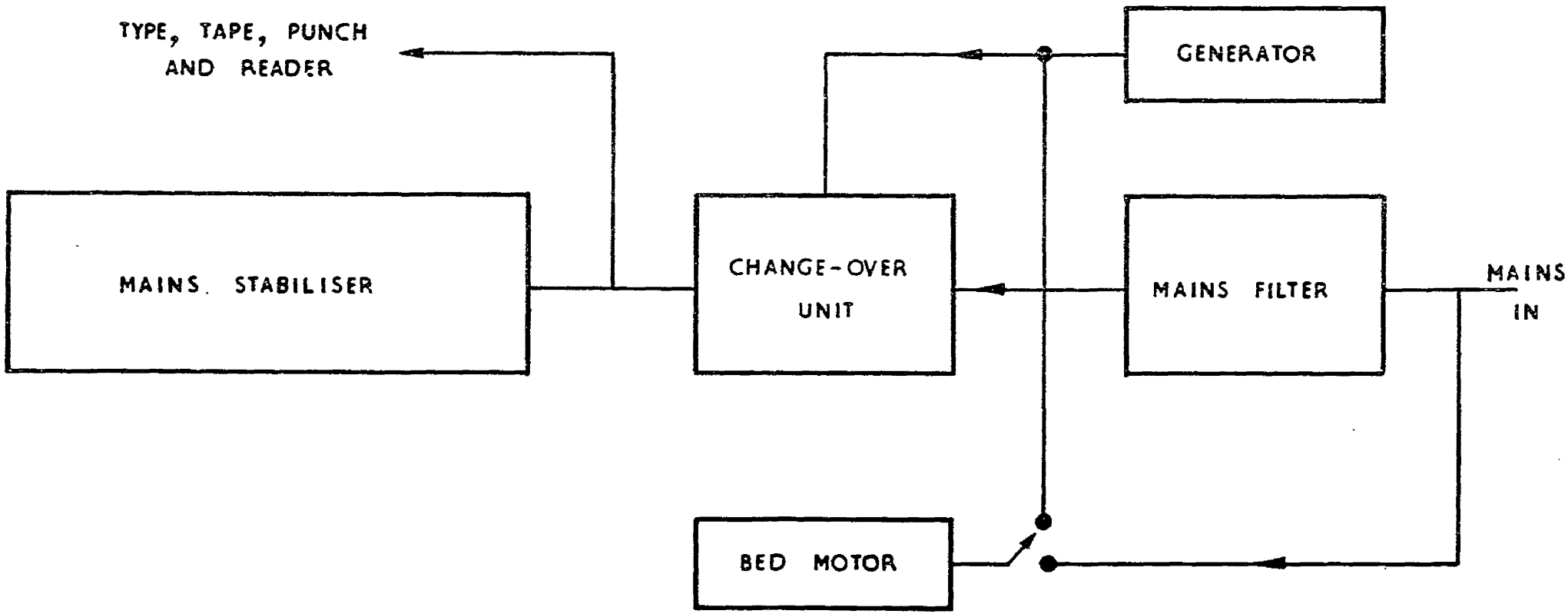
TABLE 3.4

Examination of Formica

Energy Range (MeV)	Formica + Bgd. cpm.	Bgd. cpm.	Net cpm.
0.6 - 0.72	14.8	14.6	0.2
1.36-1.56	7.30	7.23	0.07

Fig. 3.7.

DIAGRAMMATIC PRESENTATION OF ELECTRONIC EQUIPMENT



iii) Laboratory length of approximately 24½ feet with recessed instrument compartment behind the driver's cab.

iv) Generator to provide electricity, making the laboratory self-contained.

v) Heating and air conditioning unit, with thermostatic control, to provide temperature stability and improve gain stability of the electronic equipment as well as ensuring patient comfort.

The tender from S.M.T., Glasgow best met these requirements. The interior of the vehicle and the scanning-bed geometry are shown in Fig 3.8.

3.3 Shielding studies with 5" x 5" and 3" x 3" detectors:

To allow the shielding studies to proceed before delivery of the 11½ inches diameter x 4 inches detector, Quartz and Silice kindly loaned a 5 inches diameter x 5 inches detector. Additionally, the 3 inches diameter x 3 inches detector selected for counting over specific organs was delivered promptly. The 5" x 5" detector was used throughout because of its larger volume but measurements were also made with the 3" x 3" detector for comparison.

The shield was built up in the stages indicated in Fig 3.1. Background measurements were made at each stage with the detector at the height calculated in Appendix 1, (1.22 inches above lower face of the base plate, the "high" position, and with the crystal face level with the lower face of the base plate (the "low position"). The results are summarised in Table 3.5 and Table 3.6.

With the complete shield, the low position background is about 3 - 10 o/o greater than in the high position for the high energy range. The high position is about 20 o/o lower in the lower energy ranges. The 2 inch stages are more effective with the crystal in the low position, as might be expected, but the back ground reductions compared with the previous stages are small, confirming the findings

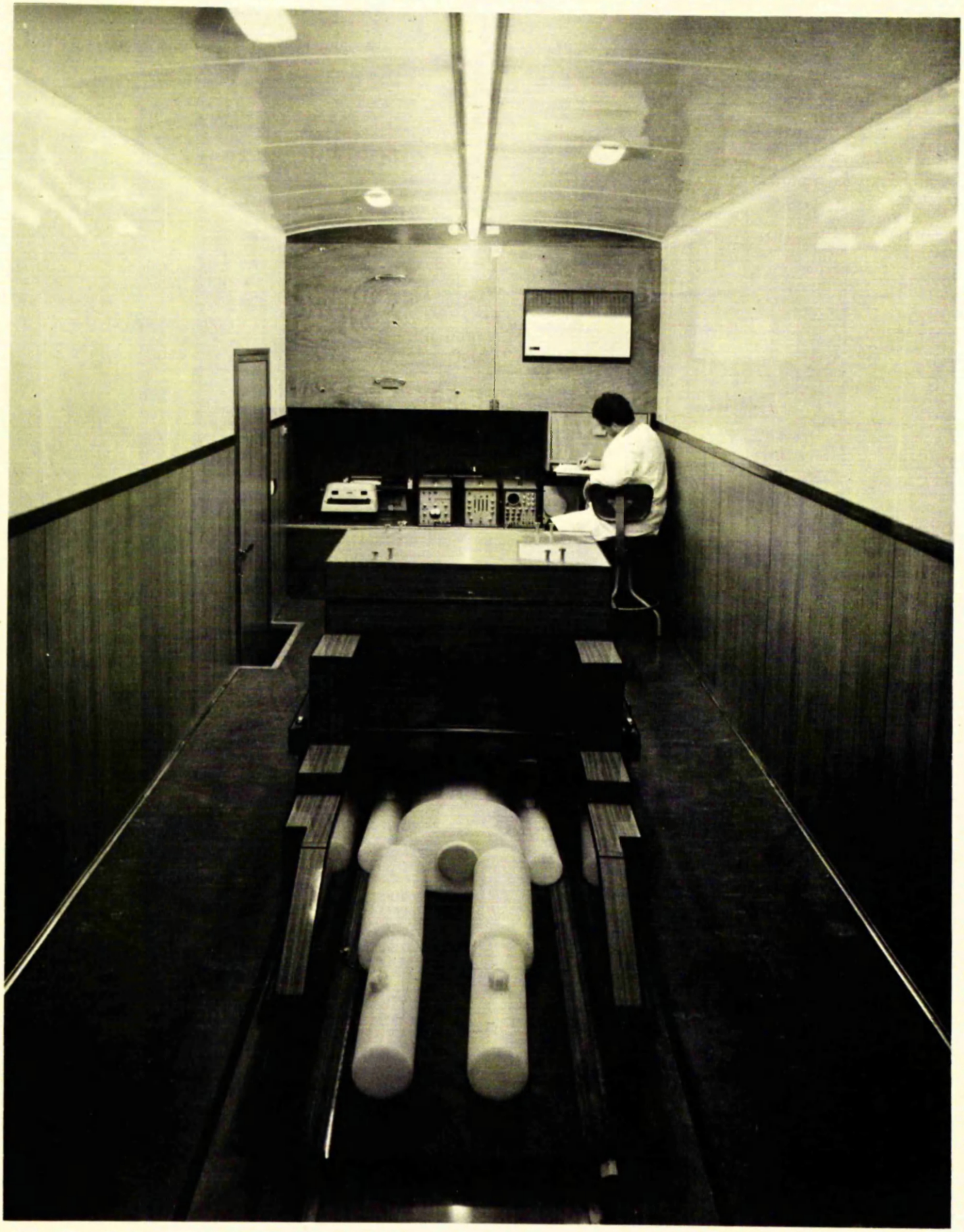


Fig. 3.8. MERLIN - Scanning-bed Geometry

TABLE 3.5

Effect of Shield Development on Background Counting-Rate with 5" x 5" crystal in High Position.

(cts = counts in 40 mins.)

(o/o U = percentage of unshielded background counting-rate)

(o/o P = percentage of background counting-rate in previous stage)

SHIELD CONDITION	ENERGY RANGE (MeV)											
	0.28 - 0.52			0.4 - 0.58			0.52 - 0.9			1.1 - 1.6		
	cts.	o/o U.	o/o P.	cts.	o/o U.	o/o P.	cts.	o/o U.	o/o P.	cts	o/o U.	o/o P.
1. Unshielded	598907	100	-	287876	100	-	324698	100	-	158384	100	-
2. Turret and turret side walls	46280	7.7	-	22654	7.9	-	25545	7.9	-	15354	9.7	-
3. Stage 2 + 6" base	19013	3.17	41	10028	3.48	44	11749	3.62	46	5873	3.71	38
4. Stage 3 + 4" wall	15796	2.64	83	7174	2.50	72	8496	2.61	72	4502	2.84	77
5. Stage 4 + 4" base	8216	1.37	52	5130	1.78	71	5497	1.69	65	2902	1.83	64
6. Complete calculated shield.	7928	1.32	96	5031	1.75	98	5407	1.66	98	2708	1.71	93

TABLE 3.6

Effect of Shield Development on Background Counting-Rate with 5" x 5" crystal in Low Position.

(cts = counts in 40 mins.)

(o/o U = percentage of unshielded background counting-rate)

(o/o P = percentage of background counting-rate in previous stage)

SHIELD CONDITION	ENERGY RANGE (MeV)											
	0.28 - 0.52			0.4 - 0.58			0.52 - 0.9			1.1 - 1.6		
	cts.	o/o U.	o/o P.	cts.	o/o U.	o/o P.	cts.	o/o U.	o/o P.	cts.	o/o U.	o/o P.
1. Unshielded	58907	100	-	287876	100	-	324698	100	-	158384	100	-
2. Turret and turret side walls.	66436	11.1	-	34714	12.1	-	41761	12.9	-	21942	1319	-
3. Stage 2 + 6" base.	32869	5.49	50	18331	6.38	53	20720	6.38	50	10489	6.62	48
4. Stage 3 +4" wall.	25824	4.31	79	10204	3.55	56	12166	3.74	59	6603	4.17	63
5. Stage 4 x 4" base.	14690	2.45	57	6230	2.16	61	7183	2.21	59	3430	2.16	52
6. Complete calculated shield.	10881	1.82	74	5508	1.92	88	6027	1.85	84	2766	1.75	81

with the prototype. The background counting-rate with the calculated shield was less than 2°/o of the unshielded background.

The shield was modified empirically, bearing in mind the requirements of the tilting-chair geometry, to determine if the background counting-rate could be further reduced. The results are shown in Table 3.7. Using the bricks which comprised the 2 inches thick walls and base, the walls supporting the turret were increased to 8 inches and the height of the remaining walls were increased by about 6 inches in a configuration more suitable for the tilting-chair geometry (shield condition 2). The overall background was reduced by about 10°/o compared with that of the calculated shield.

Cadmium has been used as the lining of lead rooms (I.A.E.A., 1964) largely to absorb lead X-rays of about 75 KeV. A shield of cadmium, 0.5 mms. thickness, was placed around the detector (shield condition 3) and produced no statistically significant difference in any of the energy ranges of Table 3.7. The energy range 0.05 - 0.15 MeV was also examined and no significant reduction could be established.

The effects of an inert water phantom are shown in shield condition 4. In the lowest energy range, the background was increased by about 7°/o and reduced by roughly the same amount in the higher energy ranges. These changes are of similar magnitude to those described by Rundo, (1962), Vennart, (1962) and Burch (1962), and smaller than those observed by Liden, (1962).

To investigate the effect of additional lead close to the crystal without increasing the shield weight, the bricks comprising the last layer of the 8 inches wall were removed. One layer, 4 inches high and 2 inches thickness, was then placed close to the detector inside the turret. As may be seen in shield condition 5, the backgrounds are then about 15°/o less than those of the calculated shield. Three layers high were then constructed, further reducing the background by about 7°/o on average.

Effects of Modifying Calculated Shield with the crystal in the high position.

(cts = Counts in 40 mins.)

(o/o C = percentage of calculated shield counting-rate)

(o/o P = percentage of background counting-rate in previous stage)

SHIELD CONDITION: Xtal high.	ENERGY RANGE (Mev)											
	0.28 - 0.52			0.4 - 0.58			0.52 - 0.9			1.1 - 1.6		
	cts.	o/o C.	o/o P.	cts.	o/o C.	o/o P.	cts.	o/o C.	o/o P.	cts.	o/o C.	o/o P.
1. Complete calculated shield.	7928	100	-	5031	100	-	5407	100	-	2708	100	-
2. 2in. walls and base re-distributed in making 6 in side wall to 8 in. and raising wall heights by 6 ins.	7195	91	-	4184	83	-	5144	95	-	2504	92	-
3. As 2 with cadmium shield around crystal.	7213	91	100	4220	83	100	5251	95	100	2563	92	100
4. As 3 with water phantom	7737	97	107	4168	83	100	5147	95	100	2444	90	95
5. Turret side wall returned to 6 in and 1 layer of 2 in. bricks placed inside turret close to crystal.	6621	84	86	4093	82	100	4661	86	91	2239	83	92
6. As 5 but 3 layers of 2in thick bricks inside turret close to crystal.	6370	80	96	3832	76	94	4075	75	87	1991	74	89

The shield configuration of condition 6 seemed to produce lower background counting-rates while being quite suitable for the tilting-chair geometry.

3.4 Shielding studies with the $11\frac{1}{2}$ inches x 4 inches detector.

The shielding studies with the 5 inches diameter by 5 inches detector were repeated with the $11\frac{1}{2}$ inches x 4 inches detector as far as the complete calculated shield. The modified shield was then constructed. There were two reasons for this procedure, firstly the difficulties of extrapolation from crystals of smaller volume and face area and, secondly, it is of possible interest to be able to estimate the sensitivities which can be achieved at the various stages of the shield construction. The results of the background measurements, with the crystal in the high and low positions, are presented in Tables 3.8 and 3.9 respectively.

Comparison of the present results with those obtained using the 5 inches diameter x 5 inches detector shows that the initial shielding stages are less effective with the larger detector. This may be explained by the larger surface area and face area of this detector, whose diameter is almost half the length of the 6 inches thick base directly beneath the detector. The complete calculated shield, however, appears to be equally effective and the background reductions are similar to those obtained by Miller, (1958), and May and Marinelli (1962), (see section 2.2) viz. 1 - 2°/o.

The modified shield was marginally better than the calculated shield but the improvement was less than with the 5 inches x 5 inches detector. In view of its additional advantages for the tilting-chair geometry, the modified shield design was adopted. It is shown in Fig. 3.8 and diagrammatically in Fig. 3.9

3.5 Comparison of background counting-rate with other monitors in Britain.

Effect of Shield Development on Background Counting-Rate with $1\frac{1}{2}$" x 4" Crystal in High Position.

(cts x 10^4 = counts in 40 mins).

(o/o U = percentage of unshielded background-rate).

(o/o P = percentage of background counting-rate in previous stage).

SHIELD CONDITION	ENERGY RANGE (MeV)																	
	0.05 - 0.15			0.28 - 0.52			0.4 - 0.58			0.52 - 0.9			1.1 - 1.6			0.1 - 2.0		
	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P
1. Unshielded	183	100	-	136	100	-	70.4	100	-	88.1	100	-	52.6	100	-	556	100	-
2. Turret and turret side walls.	20.5	11	-	17.6	13	-	9.3	13	-	12.4	14	-	8.1	15	-	74.7	13	-
3. Stage 2 and 4" base	8.3	4.5	40	7.6	5.6	43	4.2	6.0	45	5.2	5.6	42	3.3	6.3	41	31.4	5.6	42
4. Stage 3 and 6" base	7.7	4.2	93	6.7	4.9	88	3.8	5.4	90	4.8	5.4	92	3.0	5.7	91	27.9	5.0	89
5. Stage 4 and 4" walls	4.4	2.4	57	4.6	3.4	69	2.7	3.8	71	3.2	3.6	67	2.1	4.0	70	17.8	3.2	64
6. Stage 5 and 4" base	2.41	1.32	55	2.51	1.84	54	1.62	2.3	60	1.87	2.12	58	1.02	1.9	49	9.28	1.67	52
7. Stage 6 and 2" base	2.50	1.37	104	2.70	1.98	108	1.68	2.39	104	1.92	2.18	103	1.04	2.0	102	9.58	1.72	103
8. Stage 7 and 2" walls	2.43	33	97	2.73	2.00	101	1.68	2.39	100	1.97	2.23	103	1.11	2.11	107	9.89	1.78	103
9. Modified stage 6.	2.15	1.18	88	2.51	1.84	100	1.54	2.19	95	1.84	2.08	98	1.02	1.9	100	9.07	1.63	98

Effect of Shield Development on Background Counting-Rate with $11\frac{1}{2}$" x 4" Crystal in Low Position.

(cts x 10^4 = counts in 40 mins)

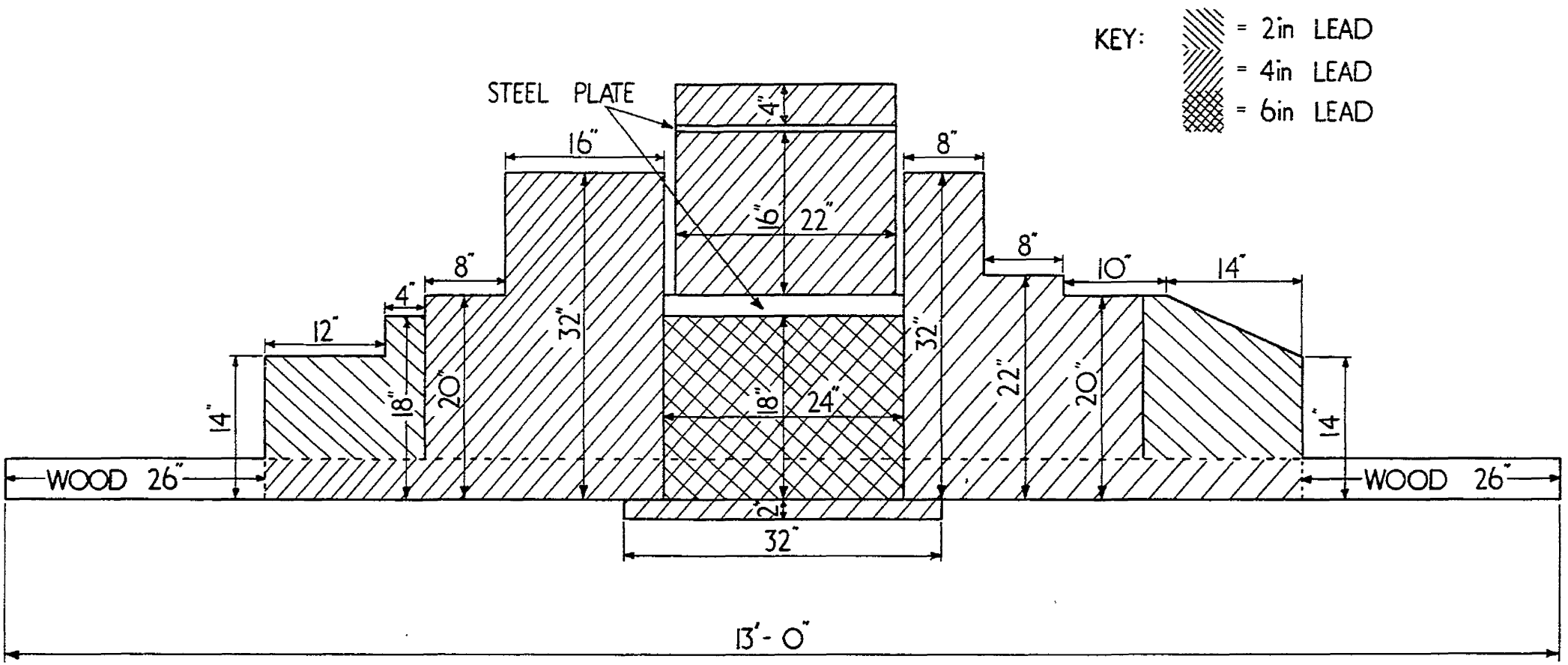
(o/o U = percentage of unshielded background counting-rate)

(o/o P = percentage of background counting-rate in previous stage)

SHIELD CONDITION	ENERGY RANGE (MeV)																	
	0.05 - 0.15			0.28 - 0.52			0.4 - 0.58			0.52 - 0.9			1.1 - 1.6			0.1 - 2.0		
	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P	cts$_4$ x10^4	o/o U	o/o P
1. Unshielded	183	100	-	136	100	-	70.4	100	-	88.1	100	-	52.6	100	-	556	100	-
2. Turret and turret side walls.	24.8	14	-	22.2	16	-	12.1	17	-	15.1	17	-	10.0	19	-	94.7	17	-
3. Stage 2 and 4" base	13.0	7.1	52	11.3	8.3	51	6.11	8.7	51	7.35	8.3	49	4.62	8.8	46	46.6	8.4	49
4. Stage 3 and 6" base	10.3	5.6	79	9.57	7.0	85	5.37	7.6	88	6.45	7.3	88	4.26	8.1	92	38.9	7.0	83
5. Stage 4 and 4" walls	5.60	3.1	54	6.00	4.4	63	3.51	5.0	65	4.18	4.7	65	2.71	5.1	64	23.3	4.2	60
6. Stage 5 and 4" base	3.07	1.68	55	3.14	2.31	52	2.00	2.84	57	2.26	2.56	54	1.18	2.24	44	11.6	2.08	50
7. Stage 6 and 2" base	3.07	1.68	100	3.35	2.46	107	2.05	2.91	103	2.29	2.60	101	1.14	2.16	97	11.7	2.10	101
8. Stage 7 and 2" walls	2.95	1.61	96	3.31	2.43	99	2.01	2.86	98	2.20	2.50	96	1.20	2.28	105	11.6	2.08	99
9. Modified Stage 6.	2.75			3.35			2.15			2.66			1.47			12.5		

Fig. 3.9.

FINAL SHIELD FOR MERLIN



To put the effectiveness of the shield of MERLIN into perspective, a comparison has been made of the background counting-rate per unit crystal volume (High position) with whole-body monitors in Britain using the data of the I.A.E.A. Directory of Whole-Body Radioactivity Monitors (1964) or of a comparison conducted by Glass (1965). Table 3.10 summarises the results for the higher energy range and Table 3.11 those for the lower energy range.

In the higher energy range, it can be seen that the Background Index for MERLIN is smaller, and therefore better, than those of the steel-room monitors of the U.K.A.E.A. and Addenbrooke's Hospital, Cambridge and those of the monitors at Sutton and the Radcliffe Infirmary, Oxford. It would appear to be similar to the Background Indices of the Harwell lead room and the steel-room monitor at the University of Birmingham. The Monitor at the General Infirmary, Leeds, is significantly better than MERLIN with respect to the background counting-rate. Direct comparison, however, is slightly misleading. The Leeds monitor is situated in a basement with a 30" slab of concrete and a four-storey concrete building above it equivalent to at least 5 ft. of concrete shielding. A difficulty in making such intercomparisons in terms of counting-rate/unit volume, is thus illustrated and this criticism applies equally to the cases favourable to MERLIN. It was for this reason that the MERLIN shield performance at each stage was described as the percentage reduction of background counting-rate, which has more significance regardless of the initial unshielded counting-rate.

Table 3.11 shows that, even in the lower energy range where scattered radiation may be significant in an open system such as MERLIN, its performance relative to the other monitors is generally not worsened. The ratio Monitor Background Index/MERLIN Background Index is actually greater for the lower energy region than the higher energy region for all monitors but the Leeds monitor and, possibly, the Harwell monitor in the range 0.27 - 0.45 MeV.

TABLE 3.10

Comparison of Background Indices (cpm/cc) in Higher Energy Region

Monitor location	Energy range MeV	Monitor Background Index (cpm/cc) x 10^{-2}	MERLIN Background Index (cpm/cc) x 10^{-2}
, Sutton C.L.	1.37 - 1.55	4.99	1.52
, Windscale S.	1.295 - 1.625	2.99	2.48
, Winfrith S.	1.28 - 1.78	3.71	3.21
, Dounreay S.	1.27 - 1.65	4.66	2.75
of Birmingham S.	1.27 - 1.61	2.60	2.58
E. Harwell L - multiple - single	1.0 - 1.4	3.35 3.79	3.33
rooke's Hosp. Cambridge S.	0.95 - 1.4	5.03	3.87
ffe Inf. Oxford L* Marsden Hosp. Sutton C*	0.4 - 1.5	28.0 76.5	17.0
l Inf. Leeds S.L.	0.1 - 2.0	13.9	38.0

Enclosure key:

C. Underground chalk

C* Chalk in bags

L. Lead room

L* Lead shadow-shield

S. Steel room.

TABLE 3.11

Comparison of Background Indices (cpm/cc) in Lower Energy Region.

nitor cation	Energy range MeV	Monitor Background Index (cpm/cc) x 10^{-2}	MERLIN Background Index (cpm/cc) x 10^{-2}
.S. Sutton [CL]	0.6 - 0.73	18.0	2.68
.E. Winfrith [S]	0.58 - 0.81	6.36	4.16
eral Inf., Leeds [SL]		3.13	
.E. Windscale [S]	0.52 - 0.80	7.88	5.77
v. of Birmingham [S]	0.44 - 0.58	5.28	4.91
.R.E. Harwell [L] multiple	0.32 - 0.4	3.48	3.22
single [C≠]		2.94	
al Marsden Hosp, Sutton [C≠]		15.7	
enbrooke's Hosp, Cambridge [SL]	0.27 - 0.45	12.9	7.25
eral Inf. Leeds.		2.0	
cliffe Inf. [L] Oxford	0.17 - 0.44	32.9	12.9
al Marsden Hosp. Sutton [C≠]		59.9	

Enclosure Key:

C Underground chalk

C≠ Chalk in bags

L Lead room

L≠ Lead shadow-shield

S Steel Room

MERLIN's favourable performance compared with, for example, the steel-room monitors may be surprising at the first impression, particularly in view of the much smaller shield weight. It must be realised, however, that the 30 - 50 tons of 6 inches thick steel room represents no better shield than if this thickness of steel was limited to and completely surrounded the detector(s) only. The 4 - 6 inches of lead used in MERLIN is, therefore, equivalent to a complete room of these thicknesses except that the system is "open" and may be susceptible to scattered radiation.

However, the detector(s) inside the steel or lead room are also susceptible to scattered radiation since a gamma ray having entered the room may have equal difficulty in leaving it!

This may be illustrated by the reduction in residual background in the steel/lead room at Leeds when a close-fitting lead shield was placed around the detectors (Wilson, 1964). The scattering area and volume of heavy elements is less with the shadow shield and only the crystal face area is "exposed" while a close shield on the crystal walls might be considered unnecessary inside a steel room. The effects of atmospheric radon, thoron and their daughter products and the variation in their concentration may similarly be reduced because of the proximal shielding, the smaller exposed area of the detector and the smaller volume of air between the detector and shield.

3.6 Redistribution effects in scanning bed geometry:

The variation of counting-rate with distribution of the isotope in the body was again investigated using point sources and water phantoms and also patients (see section 2.5).

a) Longitudinal variation:

The results for the 0.51 MeV and 1.28 MeV photopeaks of a sodium-22 source, placed centrally and consecutively at points six inches apart along the longitudinal axis, are summarised in Table 3.12 for the crystal in the high position.

The results for the crystal in the low position are presented

TABLE 3.12

Table 3.12 for the crystal in the high position.

JRCE SITION	0.51 MeV photopeak		1.28 MeV photopeak	
	cts in 4 mins	o/o of maximum	cts in 4 mins	o/o of maximum
ıth xtal centre	632800	100	202300	100
.nches	505000	80	166000	82
inches	230000	36	81500	40
inches	72800	11	27000	13
inches	24000	3.8	8200	4.1
inches	8800	1.4	1700	1.4
inches	3800	0.6	900	0.5

in Table 3.13.

Tables 3.12 and 3.13 show that the longitudinal variation is very similar for both crystal positions and photopeak energies. Mean values are plotted against source position in Fig. 3.10. Symmetry is assumed. The results of graphical integration over given distances of travel are presented on the same figure. Assuming again the source distribution of section 2.5, the integrated contribution of each section before and after passing the crystal mid-line has been calculated for various positions of starting and stopping counting. The results are shown in Fig. 3.11.

Fig. 3.10 shows that the counting-rate falls to 10°/o of the maximum value at about 20 inches from the crystal mid-line and is virtually confined to 32 inches on either side of the crystal mid-line. The counting region is about twice the size of that found with the 3 inches x 3 inches detector in the prototype monitor. Sensitivity will be improved consequently while redistribution effects are marginally worsened. Fig. 3.11 shows that commencing and ending the scan 12, 8 and 4 inches at each side of the crystal centre line and directly beneath the crystal centre would produce variations of 0.8°/o, 1.9°/o, 4.2°/o and 8.4°/o respectively.

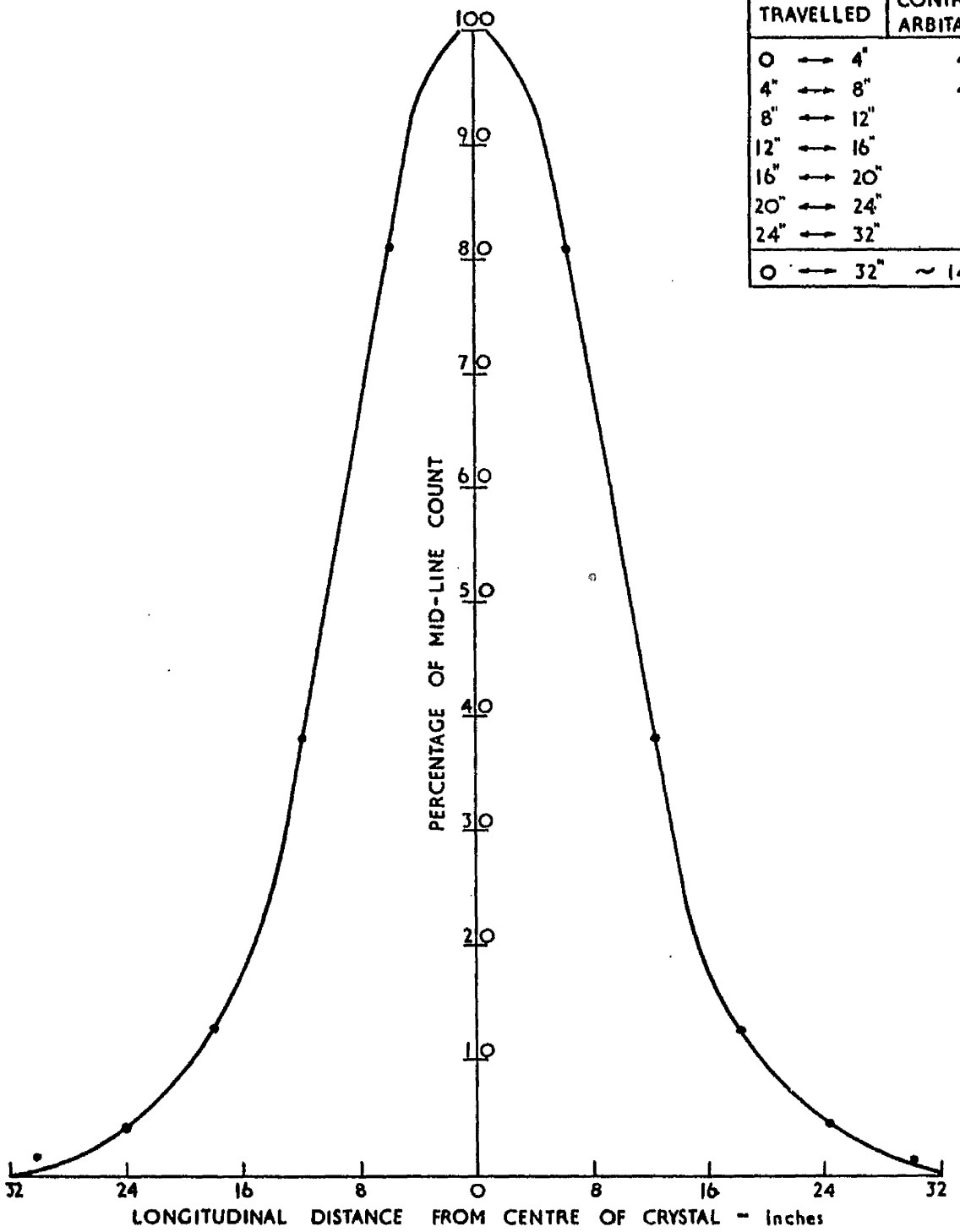
The extreme opposite of this case is that in which the total activity is concentrated at one point, and the worst geometrical position is clearly if the activity is four inches from either extremity of the body. In this case, with the scan again commencing and ending 12, 8 and 4 inches at each side of the crystal centre-line and directly beneath the crystal centre, the retention, compared with that when the source is centrally positioned as when in the intestine following an oral dose, is underestimated by 100(1-2700/2800) °/o = 3.5°/o, 100 (1 - 2560/2800) = 8 °/o 100(1-2300/2800) = 18°/o and 100(1-1900/2800)= 32°/o. Such an extreme case is unlikely to arise in practice; the concentration of iodine in the thyroid gland may be the closest approximation, when the source is, largely,

TABLE 3.13

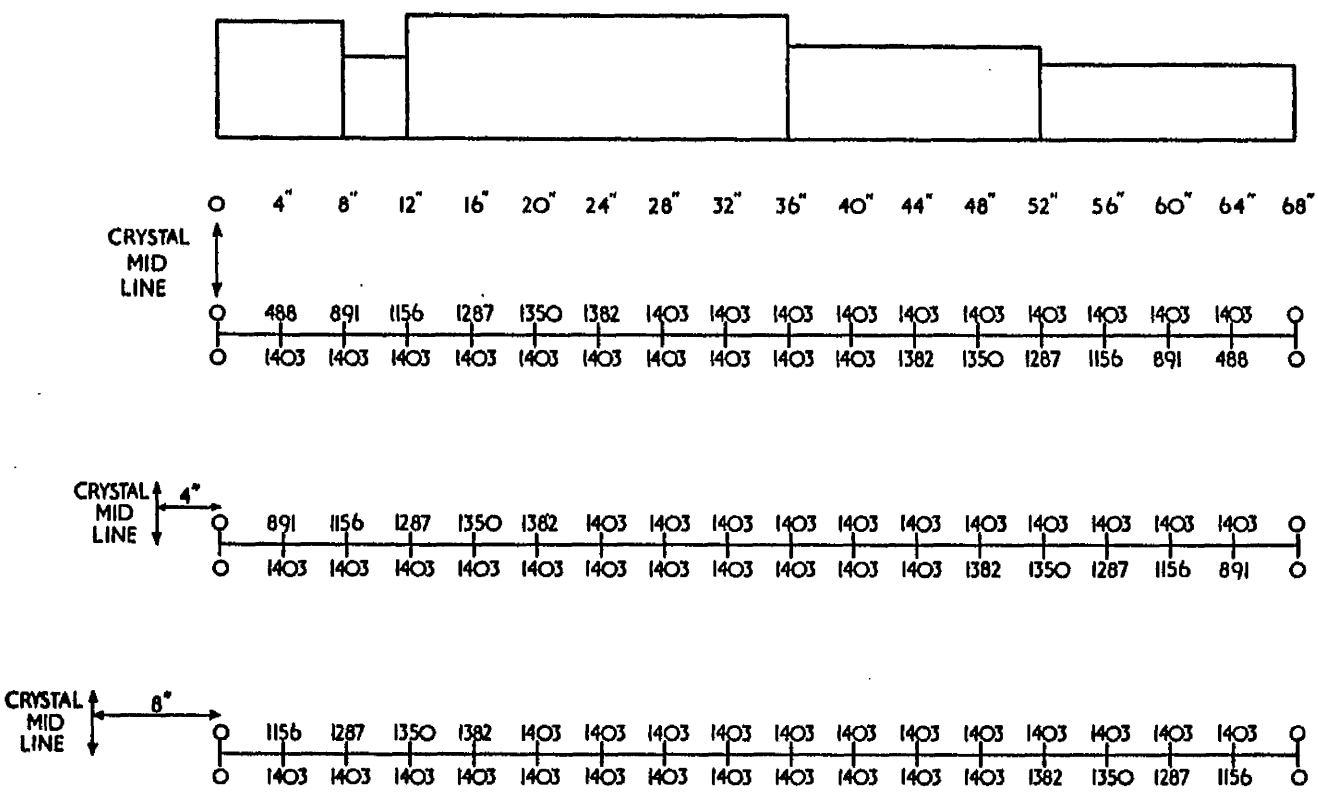
RCE ITION	0.51 MeV photopeak		1.28 MeV photopeak	
	cts in 4 mins	o/o of maximum	cts in 4 mins	o/o of maximum
ath xtal centre	850000	100	300000	100
inches	640000	75	232000	76
inches	300000	35	111000	37
inches	114000	13	45500	15
inches	48000	5.7	19000	6.3
inches	23400	2.8	9100	3.0
inches	13000	1.5	4900	1.6

FIG 3. 10 VARIATION OF COUNTING-RATE (AS PERCENTAGE OF MID-LINE COUNT-RATE) WITH LONGITUDINAL DISTANCE

DISTANCE TRAVELLED	INTEGRATED CONTRIBUTION ARBITARY UNITS
0 ⟷ 4"	488
4" ⟷ 8"	403
8" ⟷ 12"	265
12" ⟷ 16"	131
16" ⟷ 20"	63
20" ⟷ 24"	32
24" ⟷ 32"	21
0 ⟷ 32"	~ 1403



3.11 INTEGRATED COUNTING - RATES OF PHANTOM SCAN - DISTRIBUTED POINT SOURCES



about twelve inches from the top of the head. The corresponding maximum underestimates would then be 0.7, 1.7, 3.5 and 8°/o respectively if all of the iodine was in the gland, compared with the normal fraction of 0.2 (I.C.R.P., 1960). It may be implied, therefore, that the probable distribution of a given isotope should be considered in order to determine at what position a scan should commence and finish. In general, however, the error involved in taking the crystal centre-line as the start-stop point is unlikely to exceed ~ 1-2°/o.

The micro-switch system devised for MERLIN allows counting to start and stop at any distance within 18 inches on either side of the crystal centre-line. At 18 inches start-stop, the longitudinal variation is unlikely to exceed ~1.8°/o in the most extreme case. This flexibility is achieved simply by fixing two microswitches, one at each side of the crystal centre-line and at 18 inches from the centre-line. The switches are placed on the base outside the rail on the opposite side from the driving screw. They are off-set transversely so that each switch is operated by only its own actuator. The actuators are adjustable each with a pointer to a steel-tape measure fixed to the bed and they may be firmly located by a screwed clamp over the side of the bed. With the actuator-pointers set at the head of the bed and at the patient's height, counting begins and ends 18 inches before and after the crystal respectively. The scan is begun and ended beneath the crystal centre-line by setting the actuator pointers at 18 inches from the head of the bed at the patient's height minus 18 inches.

None of the monitors using the scanning technique and listed in the I.A.E.A. Directory of Whole-Body Radioactivity Monitors, 1964, (Tables XIII and XIV) are as flexible as MERLIN in this respect. Only two would appear to have adjustment of either the distance from the shoulder at which the scan commences or the overall length of the scan. Furthermore, the total scan length in MERLIN can exceed 275 cms whereas the maximum scan length of the single detector monitors

is 235 cms. (I.A.E.A. monitor, Vienna) and of the two-detector monitors is 175 cms. (University of Lund, Sweden).

Of the monitors using the multi-detector stretcher technique listed in Tables X and XI (loc. cit.) none would appear to use the detectors outside the extreme lengths of the body. It would also be more difficult and cumbersome to adjust the detectors compared with the simplicity of adjusting the micro-switch actuators in MERLIN.

b) Lateral Variation.

The lateral variation was investigated with a sodium-22 source placed on the phantom mid-line directly below the crystal centre, and displaced horizontally across the monitor at 3 inches and 6 inches on either side of the central position. High and low crystal positions were investigated. The results for the 1.28 MeV photopeak are summarised in Table 3.14. Counts are corrected for background.

The standard deviations for these data are $\sim$ 6.7o/o for the high position and $\sim$9.8o/o for the low position. These estimates are pessimistic as they represent the differences obtained with point sources at discrete distances. In the high crystal position, a point source at the "centre" of the patient and "redistributed" becoming a point source six inches off the mid-line would be underestimated by about 15o/o. Similarly, for the low crystal position, the underestimate would be about 20 o/o.

The extremity of those latter estimates requires emphasis. The source used and the positional limits were not representative of conditions likely to arise in practice. Complete transfer of an isotope from the gut to the kidneys or spleen is probably the closest approximation, but such a situation is highly improbable. The kidneys usually lie closer to 3 inches on either side of the body mid-line than the 6 inches assumed in the extreme case of the phantom. At 3 inches, the underestimates would be about 3o/o and 6 o/o for the high and low positions respectively.

TABLE 3.14

Source osition from centre	Crystal Position.			
	HIGH		LOW	
	Cpm	o/o Centre	Cpm	o/o Centre
6 inches	172,800	85	230,900	79
3 inches	196,400	97	271,100	93
entre	202,200	100	292,400	100
3 inches	196,200	97	273,800	94
6 inches	173,200	85	231,200	79

The standard deviation is smaller with the larger crystal than with the 3 inches x 3 inches detector of the prototype at the same patient-detector distance. It seems likely, therefore, that the lateral variation will be less in monitors using a single large detector or with two or more crystals across the body. No monitor listed in the I.A.E.A. Directory of Whole-Body Radioactivity Monitors (1964) utilises a detector of this diameter in scanning-bed or multiple-detector stretcher geometries. However, the Hanford Mobile Monitor uses an $11\frac{1}{2}$ inches x 4 inches detector (Brady, 1964 Private communication), and the latest monitor at Leeds is particularly flexible since, when completed, it will be possible to use the scanning-bed geometry with 2 crystals, each 6 inches x 4 inches, across the body as well as in a multi-detector stretcher geometry.

c) Depth variation:

In view of the similarity between the depth variations observed for caesium-137 and cobalt-60 with the prototype, (Section 2-5), this investigation was limited to cobalt-60. Measurements were made, however, in the photopeak region and also using a wide energy band of 0.4 - 1.4 MeV.

The source was placed one inch above the bed beneath 7 inches of water and lifted one inch successively until it was beneath only one inch of water, representing variation over the depth of the body to one inch below either surface. The results are presented in Table 3.15.

These counting-rates may represent those in a patient measured in either the supine or prone positions. The standard error is that which might be obtained if the depth of the source varied in a regular manner in successive measurements. Such a situation may be unrealistic but, at worst, a basis for comparison is provided showing, as might be anticipated from experience with the prototype monitor, that the crystal high and using the wide band counting technique (Warner and Oliver, 1966) reduces the standard error.

TABLE 3.15

ource osition	cpm. in wide energy band		cpm in photopeak	
	Crystal high	Crystal Low	Crystal High	Crystal Low
er 7" water	44411	49509	21651	27887
er 6" water	54491	63085	27086	36071
er 5" water	66294	81100	34071	46549
er 4" water	81825	105165	43459	61449
er 3" water	101295	134207	55945	81058
er 2" water	126695	173748	73112	108737
er 1" water	153734	218422	94024	141970
$\sigma' \triangleq$	44.3o/o	52.2o/o	52.5o/o	57.7o/o

The error is, nevertheless, appreciable.

The counting-rates equivalent to measuring a patient in the supine and prone positions may be obtained by summing results, under 7" water + under 1" water, under 6" water + under 2" water, etc. The corresponding values are shown in Table 3.16. The standard errors are reduced by factors of 4 - 5.

With the detector raised to the maximum height, (crystal face to patient mid-line = 29.8 cms), the depth variation was again investigated with the results given in Table 3.17. The standard errors are further reduced. The lateral variations were very similar to those with the crystal in the high position.

The worst case, counting supine and prone, is approached by assuming a source close to the centre line moves entirely to the surface of the body. Overestimates of 27°/o, 21°/o and 17°/o might result with wide band counting with the crystal in the low, high and maximum positions respectively. The results, however, are for a point source at these depths whereas in reality all sources within the body are of finite depth and would "overlap" successive positions of the point source. For example, if initially the source within the body overlapped the "under 4" water positions + "under 3" and 5" water" the aggregate counting-rate represents the mid-line value. The sum of "under 1" and 7" water" + "under 2" and 6" water" approximates to the counting-rate at the surface of the body. The corresponding over-estimates are reduced to approximately 18.5°/o, 14.5°/o and 11°/o.

d) Variation of the initial counting-rate in patients:

In a study of the effects of various proprietary pharmaceuticals on the absorption of iron, (Boddy and Will, 1967), tablets of iron-59 ascorbate were administered to normal and anaemic subjects. Several patients were measured immediately after taking the tablet and successively at intervals of about one hour during the working day. Measurements were made with the detector in the low position and at

TABLE 3.16

Positions summed	summed cpm. - wide band		summed cpm. - photopeak	
	Crystal high	Crystal low	Crystal high	Crystal low
der 1" + 7" water	198145	267931	115675	169857
der 2" + 6" water	181186	236833	100198	144808
der 3" + 5" water	167589	215307	90016	127607
der 4" + 4" water	163650	210330	86918	122898
σ =	9.2%	11.3%	13.1%	14.8%

TABLE 3.17

ource osition	cpm. max. ht.		Positions summed	summed cpm.	
	Wide band	photopeak		Wide band	photopeak
ler 7" water	37042	18034	Under 1" + 7" water	156467	90463
ler 6" water	44761	22227	Under 2" + 6" water	143640	78632
ler 5" water	54469	27793	Under 3" + 5" water	135071	71910
ler 4" water	66923	35411	Under 4" + 4" water	133846	70822
.er 3" water	80602	44117			
.er 2" water	98879	56405			
.er 1" water	119425	72429			
0 =	41.6 o/o	49.6 o/o	0 =	7.3 o/o	11.5 o/c

the maximum height. Typical results are presented in Table 3.18. The standard error is lower using the wide band counting technique compared with measuring only over the photopeak and lower with the detector at the maximum height. These findings are in good agreement with the phantom studies. Overall variations, defined as 100 (Highest count-rate/Lowest count-rate -1), are 12, 10o/o and 9 o/o, 7.5 o/o respectively.

3.7 Comparison with redistribution effects in other monitors:

It is perhaps pertinent to ask, in assessing the performance of this new design of monitor, whether depth variations of this magnitude are likely to be greater or smaller than with other whole-body monitors. The principal factor is clearly the patient-crystal distance. In the maximum position, this distance from crystal face patient mid-line is 29.8 cms. and in the high position is 25.4 cms. and low position 20.3 cms. The I.A.E.A. Directory indicates that monitors using scanning-bed techniques and a single detector use similar distances whilst the two-detector scanning monitors at Lund, Sweden, operate with one detector 45 cms. above the bed but with the other only 25 cms. beneath the bed. On the other hand, most monitors using the multi-detector stretcher techniques operate at distances smaller than those in MERLIN, particularly in the case of detectors beneath the bed.

The tilting-chair geometry is almost inevitably worse than most other geometries. Over the first few hours after administration of iron-59, Price et al. (1962) obtained variations in the counting-rate between 0 and 20 o/o. Naversten (1964) has shown that variations in response of 0.8 to 2.0 for the same activity in different 'organs' of a phantom and using a tilting-chair geometry were reduced to 0.95 to 1.15 using a scanning-bed geometry. It may be inferred that the tilting-chair geometry will be most useful for isotopes which are distributed fiarly uniformly throughout the body at low-levels of activity such as in measuring body potassium. For other isotopes the improvement in sensitivity may be off-set by the geometrical errors. Consequently, MERLIN's tilting-chair geometry will

TABLE 3.18

Detector in low position.						Detector at maximum height			
	Retention (Supine and Prone)					Retention (Supine and Prone)			
	Narrow Band		Wide Band		Time	Narrow Band		Wide Band	
	cpm	o/o	cpm	o/o	Hrs	cpm	o/o	cpm	o/o
	21,816	100	57,073	100	0	13,029	100	28,554	100
	26,482	98.7	55,758	97.7	1	12,647	97.1	28,124	98.5
	26,969	100.6	55,709	97.6	2	13,506	103.7	29,446	103.1
	27,918	104.1	58,220	102.0	3	13,811	106.0	30,249	105.9
	26,545	98.9	56,055	98.2	4½	13,795	105.9	29,873	104.6
	25,880	96.5	54,802	96.0	5½	13,707	105.2	29,577	103.5
	24,936	92.9	53,011	92.9	6½	13,648	104.7	29,569	103.5
=	858	3.24	1,527	2.74	σ =	.411	3.1	690	2.35

largely be confined to measurement of potassium-40 in patients who are unable to lie flat.

In a comparison of the performance of some whole-body monitors in Britain, Glass (1965) showed that the depth variation using a 1.75 metre arc geometry was surprisingly large. Sources were placed on the top of the phantom and then below the phantom, which is more pessimistic than the measurements in MERLIN. Using the wide energy range for iron-59, the top position over-estimated by about 23°/o compared with the sources uniformly distributed and the bottom position underestimated by about 36°/o. Counting prone and supine would apparently reduce the error to about 6.4°/o compared with 11°/o in MERLIN. Sensitivity with the arc, however, is comparatively poor.

Warner and Oliver (1966) have described a shadow-shield monitor in which shielding is confined to two detectors 18 inches on each side of a motorised bed. Collimation is also used to reduce re-distribution effects. Sensitivity is sacrified since the prototype with only a quarter of the crystal volume is about three times more sensitive. The redistribution performance, however, is remarkably good. The depth variation compared with a small central source was quoted as not exceeding -6°/o to + 10°/o which would be equivalent to an overall variation of about 12°/o. The corresponding variation for MERLIN with the detector at the maximum height is about 17°/o. In two patients on whom successive measurements were made without faecal loss between measurements, Warner and Oliver observed a maximum variation of only about 3°/o compared with overal variations of about 7 - 12°/o in MERLIN. The better performance of the former monitor with respect to redistribution is understandable in view of the greater crystal-patient mid-line and the findings described in section 3.6c. On the other hand, the sensitivities of this monitor, as mentioned earlier, is very much less than MERLIN or the prototype monitor. Naversten (1964), using a scanning-bed monitor of high sensitivity with detectors above and below the bed and 70 cm. apart, observed overall variations in phantom studies

of up to 21°/o MERLIN's performance compares not unfavourably, therefore.

3.8 Performance of MERLIN and a comparison with some other Monitors in Britain:

The counting-rates per unit activity have been measured in MERLIN for cobalt-58 and iron-59 in patients to whom these isotopes had been administered. A polythene phantom containing 140 gm of potassium in water was also monitored. The results are summarised in Table 3.19.

Data for potassium-40 measurements in other monitors in Britain are included in the I.A.E.A. Directory of Whole-Body Monitors (1964). Using the equation described in section 2.6 and assuming a total body content of 140 gm. of potassium and a total counting time (background time and subject time) of 100 mins., these data have compared with those of MERLIN in Table 3.20.

The scanning-bed geometry is, apparently, several times more sensitive than the chalk room monitors and virtually identical in sensitivity with the steel room monitors. The tilting-chair geometry is more sensitive.

A comparison in terms of cost shows a startling contrast. As an installed monitor, MERLIN could be established for about £6,500 including the shield (£1,700), an 11½ inches x 4 inches detector £2,600), 100-channel analyser with printer and H.T. supply (about £2,000). The steel room of a commercial monitor costs from about £5,500 to £9,000 and the complete system from £20,000 - £30,000 excluding transport and erection costs and the cost of a special building if this is required to house the monitor.

TABLE 3.19

Isotope	Energy range MeV	cpm/uc	Background cpm
1. Detector at maximum height:			
K-40*	1.36 - 1.56	0.66	126
Fe-59	0.4 - 1.38	14,800	1065
	1.0 - 1.38	6,900	238
Co-58	0.3 - 1.0	23,000	1104
	0.74 - 0.89	8,500	153
2. Detector in low position:			
K-40*	1.36 - 1.56	0.82	137
Fe-59	0.4 - 1.38	27,900	1150
	1.0 - 1.38	13,300	260
3. Tilting-chair geometry:			
K-40*	1.36 - 1.56	1.17	133

* cpm/gmK.

TABLE 3.20

Monitor Location	Background cpm	cpm per gm K.	Subject cpm per 140 gm K.	Standard error o/o
R.P.S., Sutton	90	0.20	28	7.3
Royal Marsden Hosp., Sutton	83	0.11	15.4	12.4
D.E.R.E., Dounreay	220	0.95	133	2.53
A.E.E., Winfrith	175	0.90	126	2.43
A.E.E., Windscale	141	0.872	122	2.30
General Infirmary, Leeds.	80	1.33	186	1.36
A.E.R.E., Harwell	138	1.36	190	1.57
MERLIN - scanning	137	0.82	115	2.40
- chair	133	1.17	164	1.75

CHAPTER 4: The determination of Iron Absorption and Turnover Rates in normal Adult Males.

Introduction:

The earliest method used to measure the retention of iron taken orally was by chemical iron balance studies. Such investigations are both difficult and time consuming, and in chemical measurement procedures, especially with faeces, there is a tendency to lose iron, so that the absorption figures appear greater than they actually are (JOSEPHS, 1958).

Since the introduction of methods based on the use of radioactive iron, balance studies have largely lost favour and iron absorption has been followed either by measuring the percentage of the administered radioactive iron which subsequently appears in the circulating blood as newly synthesised haemoglobin (HAHN et al, 1939) or by determining the amount of radioactive iron which can be recovered in the faeces (DUBACH et al 1948, SMITH and MALLETT 1957, BONNET et al, 1960).

These newer methods are not entirely satisfactory, however. The first requires the assumption that a particular fraction of the absorbed iron has been used for haemoglobin synthesis and also includes the error involved in determining or estimating total blood volume. The second method relies completely on the co-operation of the subject in undertaking accurate stool collection over a prolonged period, and in any event the per cent absorption of iron is often so small that technical errors are magnified. There is also the additional factor of the cost involved in keeping the patient in hospital during the period of the faecal collection.

More recently a limited number of investigations have been reported using whole body monitors (SARGENT 1962, LUSHBAUGH and HALE 1965, McKEE et al, 1965, PRICE et al, 1965, REIZENSTEIN and BRANN 1965). This chapter describes the use of the shadow shield whole body counter to

investigate iron absorption and turnover in a group of normal adult male subjects.

MATERIALS AND METHODS.

The prototype whole body monitor was utilised. The patients were monitored in the supine and prone positions as far as possible.

Care is required in the selection of normal subjects, to avoid the inclusion of non-anaemic but sideropenic individuals. Those accepted as normal subjects were symptom-free adult males in whom there was no clinical evidence of disease or of alimentry blood loss and whose peripheral blood findings fell within the accepted normal range for haemoglobin, packed cell volume (P.C.V.) and mean corpuscular haemoglobin concentration (M.C.H.C.) and whose serum iron, total iron binding capacity and percentage iron saturation levels were also normal. The haemoglobin was estimated by the cyanmethaemoglobin method, the P.C.V. using a microhaematocrit, and the serum iron and total iron binding by the method of RAMSAY (1957). The haematological data for the eight normal subjects selected are summarised in TABLE 4.1.

After fasting overnight, the subject was given an oral dose of 5 micro C. Fe^{59}, in the ferric state, in 5 mg. carrier iron, made up with water to a total volume of 150 ml. After taking the dose the subject continued to fast for a further hour. Measurement of the whole body Fe^{59} radioactivity was made four hours after the administration of the oral dose. Further whole body iron radioactivity measurements were made at intervals of a few days up to the twentieth day after ingestion. The four hour count and the twenty day count were used to estimate the percentage iron absorption.

In five subjects further whole body counts were made at intervals, up to the 159th day post ingestion and the body iron turnover measured.

In five subjects, to measure the effect (on the whole body counting rate) of redistribution of Fe^{59} within the body, measurements were made immediately after the administration of the oral dose and subsequently

TABLE 4.1

HAEMATOLOGICAL DATA FOR THE NORMAL SUBJECTS

ase	Hb G/100 ml.	PCV o/o	MCHC o/o	Serum Fe ug/100ml.	T.I.B.C. ug/100 ml.	Saturation o/o
1.	15.0	44	34	170	330	51
2.	15.7	46	34	120	350	34
3.	16.1	48	34	140	345	41
4.	16.3	47	35	115	345	33
5.	15.1	43	35	145	381	38
6.	14.9	44	33	170	405	42
7.	15.6	46	34	112	381	29
.	14.2	42	34	105	285	37

at intervals up to six hours post ingestion.

RESULTS

The variation in whole body counting rate in the immediate post ingestion period (and the effects of these changes on percentage iron absorption) are shown in Table 4.2. A general trend to lower steady counting rates can be seen. This can be attributed to the small size of the detector which is less efficient when the radioactive material is some inches off the centre line and also to variations of response due to depth. The uncertainty in the percentage absorption values due to the initial variation is trivial, however, compared with the biological variation. The percentage absorption has been calculated for each subject using each initial value. The mean value and spread are given in TABLE 4.2 A maximum spread of + 1.9 per cent was observed compared with a range of 4.3 - 19.4 per cent in the absorption values for these five normal subjects.

The pattern of radio-iron elimination is shown in Table 4.3 in which are listed the serial whole-body radio-iron measurements and percentage Fe^{59} retention values from day 0 to day 20, in five subjects. The major part of the radio-iron excretion occurs between day 0 and day 7. However, from day 8 or day 10 to day 20 the rate of loss iron expressed as a percentage (of day 8 or day 10 value) per day is respectively 1.7, 1.1, 3.7, 1.9, 2.1 per cent per day. These values are an order of magnitude greater than the long-term turnover values shown in Fig. 4.1 and presumably indicate that significant losses are occurring. In particular, the retention between days 4 to 10 is still changing appreciably. Because of these factors, day 20 was selected as the second reference point for calculating iron absorption. The whole-body radio-iron count at day 20, corrected for radioactive decay and expressed as a percentage of the four hour count is taken as the measure of iron uptake. The results obtained in the eight normal subjects are shown in Table 4.4. The mean iron absorption is 12.0 per cent, the range being 5.8 per cent to 19.3 per cent.

TABLE 4.?

Variation in Whole Body Counting Rate in the Post Ingestion Period and its effect on Percentage Iron Absorption Results.

Case.	WHOLE BODY COUNTS				PERCENTAGE IRON ABSORPTION				MEAN ABSORPTION
	Immediate c.p.m.	2 hrs c.p.m.	4 hrs c.p.m.	6 hrs c.p.m.	Immediate o/o	2 hrs. o/o	4 hrs. o/o	6 hrs o/o	
1.	9721	8635	9699	9625	4.2	4.7	4.2	4.2	4.3 ± 0.4
2.	29933	X	34726	26810	14.6	X	12.6	16.3	14.5 ± 1.9
3.	34054	X	32700	X	15.1	X	15.7	X	15.4 ± 0.3
4.	11744	11696	10117	10010	11.9	11.9	13.8	13.9	12.9 ± 1.0
5.	6156	5327	5999	5825	18.1	20.9	19.1	19.2	19.3 ± 1.5

TABLE 4.3

CHANGES IN WHOLE BODY RADIO IRON THE FIRST TWENTY DAYS AFTER INGESTION

	Case	4 hrs	2 dys	4 dys	6 dys	8 dys	10 days	12 dys	14 dys	16 dys	18 dys	20 dys
WHOLE BODY COUNT VALUES	1	30490					5270			4600		4384
	2	31481	11500	11700	3660	3660	3220		3050	3040	2900	2920
	3	1323	1642	311	216	212		161	135	134		116
	4	30141	9000	876	525	467				360		362
	5	34895	7314				1019					801
PERCENTAGE RETENTION OF IRON - 59	1	100					17.3			15.1		14.3
	2	100	36.5	37.2	11.6	10.7	10.2		9.7	9.6	9.3	9.3
	3	100	124	23.5	16.3	16.0			12.2	10.2	10.1	9.8
	4	100	30	2.9	1.75	1.55			1.2			1.2
	5	100		21			2.9					2.3

TABLE 4.4

IRON ABSORPTION IN NORMAL ADULT MALES

Case	Whole Body Fe^{59} Activity		Iron Absorption o/o
	At 4 hours c.p.m.	At 20 days c.p.m.	
1.	30490	4364	14.5
2.	33377	5148	15.4
3.	10947	1403	12.9
4.	31481	2920	9.3
5.	5777	1115	19.3
6.	1323	116.4	8.8
7.	24768	1443	5.8
8.	20920	2005	9.6

TABLE 4.5 illustrates the difficulty in obtaining even a short term total faecal collection in ambulant subjects. In this group, five day stool collections were made and the faecal radio iron content measured. The figure for iron absorption obtained by subtracting the radio iron excreted from the dose administered was compared with the percentage absorption calculated from the day 5 whole body count. It should be stressed that the patients were in a general medical ward, not a special metabolic studies unit, that all of them were freely ambulant and that no special effort was made by the nursing staff to supervise stool collections.

The results of the five long term studies are shown in FIGURE 4.1. The whole body iron counts for each patient from day 20 onwards are shown plotted on a semilogarithmic scale. The total body radio iron loss expressed in this way appears to be linear and the best straight line for each set of readings was computed by least squares fit using a DEUCE computer. The radio iron loss in the five subjects ranged from 0.04 per cent per day to 0.26 per cent per day, with a mean of 0.15 per cent per day.

DISCUSSION.

Factors which influence the percentage absorption of radio iron are the presence of food in the stomach, the amount of carrier iron present, the total volume of the administered dose and, possibly, the nature of the iron ion, i.e. ferrous or ferric. In an endeavour to avoid such induced variations an oral dose which is standard in respect of ionic state, carrier iron content and total volume was used, and which is given with the subject in the fasting state. A dose of iron comparable with the amount of iron available in the normal diet was given. The estimated iron content of a full meal is about 5 milligrams (PIRZIO-BIROLI et al, 1958). The ferric ion has been used as most food iron is in this form (SORENSEN, 1964). The absorption figures obtained are similar to those obtained by other workers using whole body counting techniques (VAN HOEK and

TABLE 4.5

COMPARISON OF TWO METHODS OF MEASURING IRON ABSORPTION

Subject	4 Hour Whole Body Count c.p.m.	5 day Whole Body Count c.p.m.	Fe^{59} Retention at day 5 o/o
1	28326	7319	25.8
2	37588	24060	64
3	40913	5480	13.4
4	37459	667	1.8
5	40405	19769	48.9

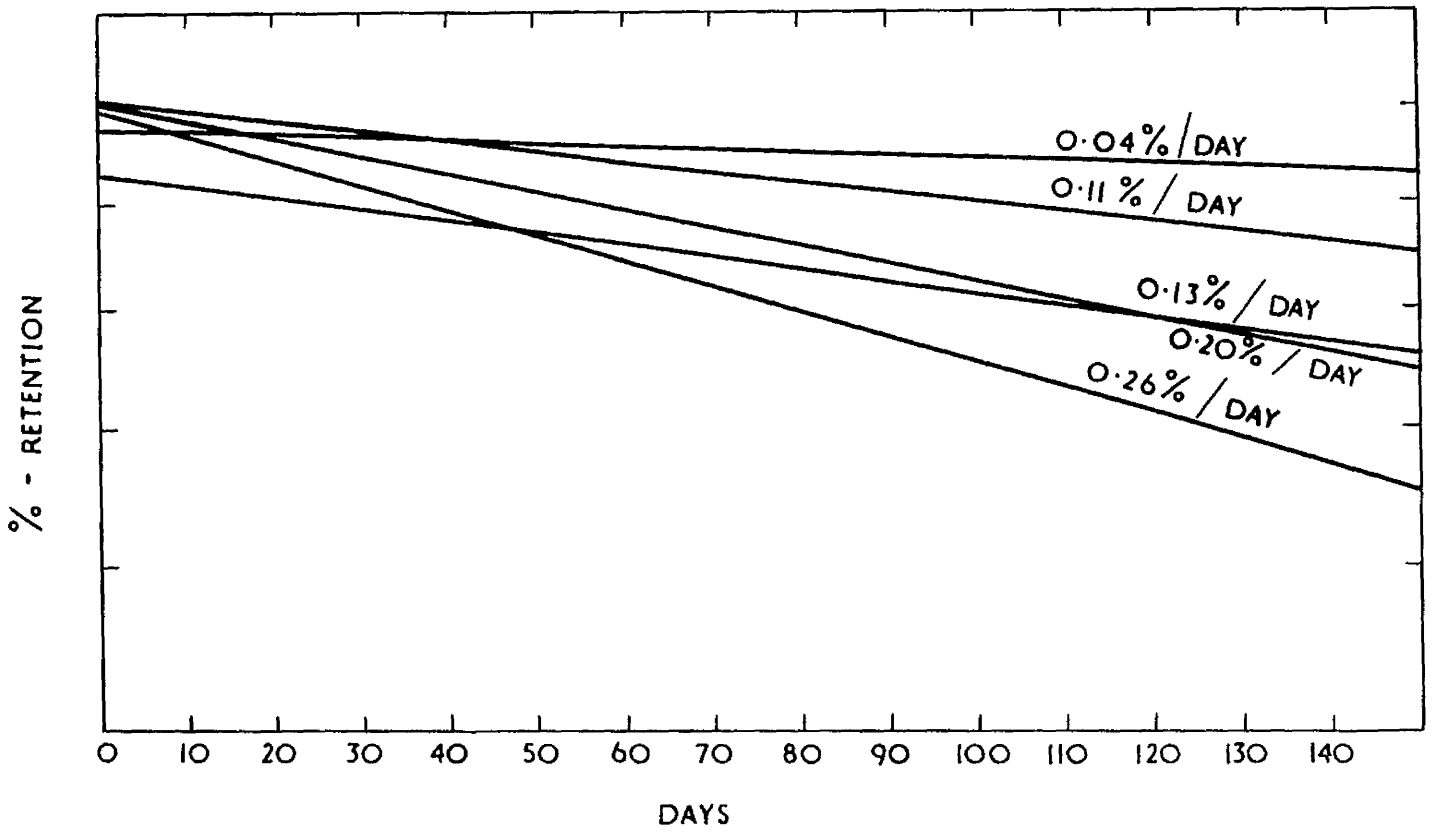
Iron Absorption at Day Five Based on Whole Body Counting.

Subject	Total Radioactive Dose μc	Faecal Radioactivity μc	Fe^{59} Retention at day 5 o/o
1	10	5.78	42.2
2	10	3.92	60.8
3	10	0.69	93.1
4	10	5.93	40.7
5	10	0.79	92.1

Iron Absorption at Day Five Based on Five Day Faecal Collection.

Fig. 4.1.

LONG TERM STUDY OF BODY IRON TURNOVER



and CONRAD 1961, LUSHBAUGH and HALE 1965, McKEE et al, 1965, PRICE et al, 1965). These results are shown in Table 4.6. The practice of these workers has been followed in using the four hours post ingestion count as the 100 per cent value. However, the changes obtained in the present counting system from early redistribution effects did not exceed 16 per cent in any of the subjects studied. This degree of change does not cause a significant alteration in the ultimate iron absorption result so that the 100 per cent value could equally well have been obtained from the immediate count.

If, as suggested by the results reported here, there is a significant continuing loss of iron up to day 20 this may be of considerable practical importance. In particular, the high retention values (Table 4.3) on day 4 compared with those on day 6 would seem to indicate that methods based on a 5 day stool collection, and possibly a 7 day stool collection, may produce over-estimates of the percentage absorption. In view of the limited data obtained, since these were almost incidental to the object of this study, further investigation is being made in measurements currently in progress.

The body turnover results obtained correspond well with those of other workers using whole body counting (McKEE et al, 1965, PRICE et al, 1965, REIZENSTEIN and BRANN 1965). These results are shown in TABLE 4.7. Most workers using whole body counting techniques have expressed radio iron loss as a single exponential function, as we have done. This mode of expression, implying as it does, a single completely miscible total iron pool with a constant rate of absorption and excretion is not strictly correct. It is however, the best approximation which can be made, as accurate mathematical representation of the complex multiple pool system which actually exists, would require observation of total body activity over a period of several years to eliminate the influence of pool shifts on body radio iron loss. This is, of course, impossible because of the short half-life of Fe^{59}.

TABLE 4.6

ORAL IRON ABSORPTION MEASURED BY WHOLE BODY COUNTING

Authors	Ionic Form	Quantity of Carrier iron mg.	Duration of Investigation days	Mean Absorption o/o	Range of Absorption o/o
Van Hoek and Conrad (1961)	Ferrous	1	16 - 23	4.7	0.2 - 10.3
Price et al (1965)	Ferrous	0.25	20	17.1	
Lushbaugh and Hale (1965)	Ferrous and Ferric	12	7	Male 5.3 Female 11.3	Male 1.8-11.7 Female 2.6-23.7
McKee et al (1965)	Ferrous	15	7		2.1 - 13.2
Present Series	Ferric	5	20	12.0	5.8 - 19.3

IRON TURNOVER IN NORMAL ADULT MALES MEASURED BY WHOLE BODY COUNTING

Authors	Duration of study days	Turnover o/o per day	Range o/o per day
Price et al (1965)	100	0.136	0.103 - 0.183
Reizenstein and Brann (1965)	180	0.24	
McKee et al (1965)	270 120 60	0.24 0.06 0.09	
Present Series	80 - 156	0.15	0.04 - 0.26

The development of the whole body monitor has provided a simple and accurate method of measuring the body retention of an administered tracer dose of Fe^{59} making absorption and subsequent long term iron turnover estimations possible in a single clinical study. The investigation makes no great demands on the subject, neither requiring frequent venepunctures nor the collection of excreta and we feel that whole body counting is now the method of choice for studying gastro-intestinal absorption of iron and body iron excretion.

SUMMARY

Oral iron absorption and iron turnover rates have been determined in normal adult males using a shadow shield whole body counter. The ferric ion was used, a dose of five μc Fe^{59} being given in 5 mg. carrier iron.

The four hour and twenty day counts were used to estimate the percentage iron absorption. The reasons for selecting these counts are discussed. In the 8 subjects studied iron absorption ranged from 5.8 per cent to 19.3 per cent with a mean of 12.0.

Iron turnover studies were carried out in 5 subjects, the periods of observation extending from 80 to 156 days. Iron losses ranged from 0.04 to 0.26 per cent per day with a mean of 0.15 per cent.

CHAPTER 5: SUCCINIC ACID and IRON ABSORPTION

In a study of oral iron uptake using solutions of fourteen iron preparations BRISE and HALLBERG demonstrated that there were great differences in the absorbability of different iron compounds (BRISE and HALLBERG 1962.a.). More iron was absorbed from a solution of ferrous succinate than from any other compound, including ferrous sulphate. The absorption of iron from tablets containing ferrous succinate was not greater than from ferrous sulphate tablets, however.

Because of these findings it was suggested that succinic ions per se influenced the absorption of iron and further experiments were carried out to test this hypothesis. (BRISE and HALLBERG, 1962, b.). In these studies the addition of succinic acid to solutions of ferrous succinate was shown to increase iron absorption, the increase being proportional to the amount of succinic acid added. Intravenously administered succinic acid was also shown to increase the absorption of iron from ferrous sulphate solutions given orally.

In an attempt to utilise these observations in practical therapy a commercial preparation, Ferramyn-S, containing ferrous succinate and succinic acid in tablet form has recently become available.

This chapter describes an investigation of the effect of succinic acid on the oral uptake of iron, using Fe^{59} labelled ferrous succinate and the prototype whole body monitor to measure iron absorption.

5.1 Materials and Methods.

Liquid preparations of ferrous succinate were used to avoid the possible effect on iron absorption of variable disintegration of a pill coating. The ferrous succinate was labelled with Fe^{59} so that each dose contained 10 micro C. radioactivity.

Absorption was studied at two levels of iron dosage, 5 mg elemental iron (20 mg ferrous succinate) and 37 mg elemental iron (150 mg ferrous succinate). To one half of the doses of ferrous succinate, free succinic acid was added in amounts based on the optimun ratios (BRISE and HALLBERG, 1962, b) so that there were in all four separate preparations containing:-

1) 20 mg Ferrous succinate
2) 20 mg Ferrous succinate with 15 mg succinic acid.
3) 150 mg Ferrous succinate
4) 150 mg Ferrous succinate with 110 mg succinic acid.

A small quantity of ascorbic acid was added to each dose to prevent oxidation of the ferrous ion.
Non-anaemic, symptomless, adult subjects were selected for the investigation.

The doses of iron were given in the early morning after an overnight fast. The iron solution was taken directly from a small beaker which was then rinsed with tap water and the rinse water also taken. The rinsing procedure was repeated so that the total volume ingested was 150 ml. No food or drink was taken for two hours afterwards. The percentage absorption of iron was calculated from the four hour and twenty day whole body Fe^{59} radioactivity counts as previously described (WILL and BODDY, 1966 and chapter 4).

Each subject was first given a solution containing ferrous succinate only and the iron uptake measured. After an interval of about two months the uptake study was repeated, the subject being given on the second occasion a solution containing the same quantity of ferrous succinate as before but with the appropriate amount of free succinate acid added. The two iron uptake results were then compared.

To study the effect of intravenous succinic acid on oral iron absorption a sterile solution of pH7 containing in each

millilitre 30 mg of succinic acid and 6 mg of solium chloride was used. The subject was first given an oral dose of 5 mg ferric iron labelled with 10uc of Fe^{59} and the percentage iron absorption measured by whole body counting. Two months later a similar oral dose of Fe^{59} labelled iron was given but on this occasion it was preceded by the slow intravenous injection of 5 ml of the succinic acid solution, the injection starting five minutes before the administration of the oral iron dose.

5.2 Results.

The absorption figures of the five subjects who were given the 20 mg doses of ferrous succinate are shown in Table 5.1. In four subjects iron absorption was increased by the addition of succinic acid. The mean absorption from the doses containing ferrous succinate only was 8.5 per cent (range 3.0 to 13.1 per cent) and the mean absorption from the doses containing 15 mg of added succinic acid was 13.0 per cent (range 5.9 to 17.2 per cent). Statistical analysis of the two sets of results using the STUDENT t test gave a value for T of 1.82, which indicates that the differences are not statistically significant.

In six subjects iron absorption from solutions containing 150 mg ferrous succinate was studied. Only two showed increased absorption from the doses containing the added succinic acid. In the remaining four the percentage iron absorption fell. The mean iron absorption from the solutions containing 150 mg ferrous succinate only was 7.2 per cent. (range 0.2 to 15.0 per cent) and the mean absorption from the doses containing 150 mg ferrous succinate plus 110 mg succinic acid was 6.0 per cent (range 2.0 to 8.2 per cent). The results are shown in Table 5.2. The STUDENT t test gave a value for t of -0.46 showing that no statistically significant difference was observed.

The results obtained from the six subjects who took part in the intravenous succinic acid absorption test are shown in Table 5.3. The mean absorption from the 5 mg doses of ferric iron was

TABLE 5.1

The Effect of 15 mg Succinic Acid on the Absorption of 20 mg Ferrous Succinate.

CASE	PERCENTAGE IRON ABSORPTION	
	20 mg Ferrous Succinate	20 mg Ferrous Succinate + 15 mg succinic acid.
1	12.0	17.2
2	10.4	8.7
3	3.0	5.9
4	4.1	16.6
5	13.1	16.5

TABLE 5.2

The Effect of 110 mg Succinic Acid on the Absorption of 150 mg Ferrous Succinate.

Case	PERCENTAGE IRON ABSORPTION	
	150 mg Ferrous Succinate	150 mg Ferrous Succinate + 110 mg Succinic Acid.
1	5.2	2.0
2	2.5	7.3
3	0.2	8.2
4	10.7	8.0
5	9.8	3.9
6	15	6.7

TABLE 5.3

The Effect of Intravenous Succinic Acid on Oral Iron Absorption.

CASE	PERCENTAGE IRON ABSORPTION	
	5 mg Ferric Iron	150 mg Succinic Acid I.V. followed orally by 5 mg Ferric Iron.
1	9.0	13.2
2	14.5	13.4
3	9.3	14.4
4	12.5	2.4
5	19.3	7.6
6	12.1	7.0

12.8 per cent (range 9.3 to 19.3 per cent). When the oral dose of iron was preceded by the intravenous injection of 150 mg succinic acid the subjects showing a decreased iron absorption. The STUDENT t test gave a value for t of -1.12, indicating that any effect was statistically insignificant.

Two patients with rheumatoid arthritis were given oral doses of 5 mg labelled ferric iron both with and without intravenous succinic acid. In one the iron absorption remained virtually unchanged, 1.7 per cent without succinic acid and 1.9 per cent following intravenous succinic acid. The second patient had 10.7 per cent iron absorption from the 5 mg ferric iron alone falling to 0.6 per cent when the oral dose was preceded by intravenous succinic acid.

5.3 Discussion.

The investigation was designed to assess the influence of free succinic acid on the oral absorption of iron at both physiological and pharmacelogical dosage levels.

Five milligrammes was chosen as the physiological dose because this is roughly the iron content of a normal full meal (PIRZIO - BIROLI et al) while 37 mg was regarded as a satisfactory therapeutic dose of iron (KERR and DAVIDSON, 1958).

All doses were of uniform volume and were given to the fasting subject to eliminate as far as possible the influence of local gastro-intestinal factors on iron absorption.

Earlier comparative studies of iron absorption have usually been based on the determination of haemoglobin regeneration in iron deficient patients during iron therapy (FULLERTON 1934, HALER 1952, WILL and VILTER 1954). The haemoglobin regeneration rate is however influenced by many factors, including the severity of anaemia, state of the iron stores, continued bleeding, the presence of infection, which make interpretation of the results difficult. By using a whole body monitor to obtain a direct estimate of iron absorption in non-anaemic subjects these main sources of error have been avoided.

While the present results would appear to contradict those of BRISE and HALLBERG, attention should be drawn to the difference in the methods used to measure iron "absorption". The measurement of iron uptake with the whole-body monitor represents total body uptake. As BRISE and HALLBERG emphasise, their method does not estimate total absorption but measures only the fraction of absorbed iron utilised in haemoglobin formation. In this difference may lie the apparent conflict of the findings. BRISE and HALLBERG'S observed increase in iron utilisation could be explained by succinic acid increasing either the availability of iron to the marrow or the rate of utilisation of iron by the marrow. Their findings that intravenous succinic acid increases the utilisation of orally administered iron also suggests that the effect of succinic acid is not a local one on the gastro-intestinal tract.

The administration of a single tracer dose as in the present studies may require comparison with the ten doses each given on successive days as reported by BRISE and HALLBERG. The possibility that successive doses of succinic acid may have an increasing effect cannot be excluded. Further, these authors showed that individual variations in utilisation may be about $\pm$ 16 o/o with successive doses and they estimated that with single doses the variations may be about $\pm$ 35 o/o. If similar conclusions apply to absorption, the effects of succinic acid may not be sufficiently large compared with the biological variation to be readily detected. To test these hypotheses, a new series of investigations is in progress which will involve the administration of successive daily doses of iron and the simultaneous measurement of utilisation and absorption.

5.4 Summary.

The effects of succinic acid on iron absorption in non-anaemic, symptomless, adult subjects have been examined using a whole body monitor. Two levels of iron dosage, 5 mg. elemental

iron (20 mg. ferrous succinate) and 37 mg. elemental iron (150 mg. ferrous succinate) were studied with oral succinic acid doses of 15 mg. and 110 mg. respectively. The effect on absorption of a slow intravenous injection of 5 ml. of succinic acid solution (30 mg. succinic acid and 6 mg. sodium chloride per millilitre) preceding oral administration of 5 mg. ferric iron was also examined. It is shown that the effect of succinic acid was not sufficiently large compared with the individual biological variation to be statistically significant.

CHAPTER 6: The Retention and Rate of Excretion of Vitamin B_{12} in Patients with Pernicious Anaemia and in a normal subject following Intravenous Administration of Radio-Vitamin B_{12}.

6.1 Introduction:

Administration of radio-vitamin B_{12}, labelled with one of the radioactive isotopes of cobalt, enables the retention and rate of loss of vitamin-B_{12} to be measured for example by urine or faecal monitoring or by whole-body monitoring. When knowledge of the excretion route is irrelevant, whole-body monitoring is the method of choice since the collection of urine and faeces over prolonged periods of time is usually impracticable while, using the whole-body monitor, the patient does not require hospitalisation and can be examined as an out-patient.

The total body content of vitamin B_{12} in normal subjects is about 2000 - 5000 µg (Adams, 1962 and Grasbeck, 1959), while in anaemic subjects the corresponding range is about 200 - 500 µg B_{12} (Grasbeck, 1959).

It has been suggested, (Reizenstein and co-workers, 1962, 1964 and 1966 and Reizenstein, 1966), as discussed in Chapter 7, that, in normal subjects, administration of a tracer dose of labelled B_{12} does not lead to excretion patterns and rates of loss typical of the natural B_{12} pre-existing in the body. The validity of the common assumption of metabolic and isotopic equilibrium was questioned.

If an anaemic patient, whose stores are virtually depleted, receives an intravenous dose of about 5000 ug of labelled vitamin B_{12}, his excretion pattern, after the steady state is established, should closely follow that of natural B_{12} in the normal subject since the fraction retained of the labelled dose (about 10 o/o) is the greater part of his body content of B_{12}. The later

excretion rate, expressed as per cent loss per day, should be of similar magnitude to the rate of loss of natural B_{12} in the normal subject. Therefore, if the "steady-state" is reached in a comparatively short time (say 1 to 2 months) and the subsequent rate of loss can be adequately described by a single exponential term, then it seems reasonable to assume that vitamin B_{12} metabolism approximates more closely to a single-pool system, for which the assumption of isotopic equilibrium is justifiable, than to a multiple-pool system, for which the assumption is not justifiable. Supporting evidence would be obtained if a normal subject, given the same intravenous dose, presented a late excretion rate, as per cent loss per day, of similar magnitude to the rate of loss of anaemic subjects since this implies that the loss is from a single body compartment and is proportional to the level of body stores.

6.2 Methods:

Fourteen patients were studied, one of whom was normal having a normal serum vitamin B_{12} level and no symptoms of anaemia. Thirteen were B_{12} deficient all having subnormal serum vitamin B_{12} level and megaloblastic erythropoiesis on marrow biopsy smears. Some of these patients had presented with symptoms of anaemia; others who were not, or only mildly, anaemic had presented with signs suggesting B_{12} deficiency such as glossitis. Additional diagnostic investigations lead to the diagnosis of post-gastrectomy megaloblastosis due to B_{12} deficiency (Subject McK. 1) and to the diagnosis of Addisonian pernicious anaemia in the others. The pretreatment haematological data are summarised in Table 6.1.

A parenteral dose of about 5000 μg of vitamin B_{12}, labelled with either cobalt-57 or cobalt-58, was administered to each subject. In eight subjects the vitamin was in the form of hydroxocobalamin, in one subject cyanocobalamin and in one subject co-enzyme B_{12}. The remaining four subjects received doses of cyanocobalamin (cobalt -58)

TABLE 6.1

Pretreatment Haematological Data

Subject	Sex	Age Yrs.	Haemoglobin gm o/o	Serum B_{12} uug/ml	Erythropoiesis
H	M	47	10.0	25	Megaloblastic
Mc.D	F	70	6.9	25	"
Mc.K.1.	M	71	10.1	58	"
B.2.	F	34	6.4	25	"
P.	M	57	8.5	25	"
O.	M	51	7.9	26	"
B.1.	F	62	5.1	25	"
4.2.	F	41	11.1	25	"
4.1.	F	66	10.7	59	"
Mc.K.2.	M	74	5.7	25	"
K	F	69	5.6	25	"
L	F	51	12.0	25	"
Ar	M	45	5.1	44	"
A	M	42	14.8	350	"

and of hydroxocobalamin (cobalt-57) providing a double isotope study. Eight subjects had received the dose before this study was established. They were, nevertheless, of interest since the long-term rate of excretion could be measured.

The retention of the administered B_{12} was measured in the prototype whole-body monitor over periods of time presently up to 441 days. Measurements were made with the subject in the supine and prone positions where this was practicable.

6.3 Variation of the initial counting-rate due to redistribution in the body:

It has been suggested (Reizenstein, 1959 b) that the injection of even 0.01 o/o (0.5 ug) of the total body B_{12} is enough to disturb the steady state temporarily, since the total plasma contains only about 0.03 o/o (1.5 ug) of the total body B_{12}. The initial plasma clearance is extremely rapid (Conkite et al, 1959) with a biological half-life of about 2 min. At later times half-lives of about 6 days (Reizenstein, 1959 b) and of 5.14 days (Adams, 1963) have been reported. Consequently the largest variation of the counting-rate due to changes in the distribution of the labelled B_{12} in the body may be expected, in the first few hours after administration. To examine the magnitude of this effect in the prototype monitor, the normal subject was monitored shortly after administration at $2\frac{1}{2}$ hours and at $4\frac{1}{2}$ hours post-administration. For comparison, a urine sample was then passed and collected. The loss of labelled B_{12} was then estimated by a further whole-body measurement and by monitoring the urine. Subsequent counts were made 24 hr and 3 days later and comparison made with the losses estimated from urine collection over these periods. The results are summarised in Table 6.2.

6.4 Results:

The serial counting-rates obtained, and the percentage retention

TABLE 6.2

ne after tial whole- r count	Whole-body (supine and prone) cpm	Loss (o/o total injected)	Urine loss (o/o total injected)	Cumulative Collection Period	Cumulative urine loss (o/o total injected)
hrs	20507	-	-	-	-
hrs	20915	C=2.3o/o	-	-	-
hrs	20902	-	-	-	-
hrs	9594	53.8	46.4	0 - 6 hrs	46.4
hrs	6719	67.7	13.8	6 -30 hrs	60.2
	-	-	3.3	30 -48 hrs	63.5
ays	4920	76.3	2.6	48 -72 hrs	66.1

each represents, are presented in Table 6.3 for the anaemic subjects and in Table 6.4 for the normal subjects all of whom received a single isotope. The results to date of the double isotope studies are given in Table 6.5. For each subject, the regression line and regression coefficients have been computed assuming that the data after about 30 days are adequately described by a single term. The equation obtained, the periods of time covered, the rates of loss (per cent per day) and the standard error of the regression coefficients are summarised in Table 6.6.

A comparison of the retention pattern of the normal subject with that of a typical anaemic subject is shown in Fig 6.1.

6.5 Discussion:

The overall variation in the initial counting-rate (0 - $4\frac{1}{2}$ hrs) (Table 6.1) was about 2 per cent and the standard error was about 1 per cent. As these measurements were made on a normal healthy subject, having an appreciation of the need for reproducibility, the variation for other subjects may be greater. It seems fairly certain, however, that the variations are significantly less than those reported in the discussion of metabolic equilibrium by Heinrich (1964) of about 40 o/o and by Reizenstein et al (1961) of over 20o/o following oral administration of B_{12}.

The general pattern of excretion of the anaemic subjects (Table 6.2) and of the normal subject (Table 6.3) following a single dose of B_{12} are remarkably similar as is shown in Fig 6.1. About 8-10 o/o of the administered dose is retained at about 1-2 months after injection and the subsequent loss with time can be adequately described by a single exponential term (correlation coefficient $\leqslant$ 0.8) with a mean standard error of about 11o/o. The equivalent standard error quoted by Heinrich (1964) was about 33 o/o.

Retention in anaemic subjects following a single intravenous dose of 5000 µg labelled vitamin B_{12}.

(H. -) Hydroxocobalamin (-. M) = Male
(C. -) Cyanacobalamin (-. F) = Female
(E. -) Co-enzyne

Subject McK. 1 (HM)		
Days	cpm	o/o Retained
0	5774	100
2	1321	22.9
7	915	15.8
35	717	12.4
69	612	10.6
97	615	10.6
132	577	10.0
168	527	9.1
196	495	8.6
230	491	8.5
258	484	8.4
296	453	7.9
385	436	7.5
413	433	7.5
441	445	7.7

Subject M.L. (CF)		
7	467	100
35	455	97.4
66	426	91.2
84	393	84.1
112	401	85.9
143	381	81.5
156	365	78.1
199	359	76.8
227	378	81.0
283	382	81.7
304	334	71.5
325	313	67.0

Subject B.1. (HF)		
Days	cpm	o/o Retained
14	2770	100
35	2400	88.8
88	2000	74.0
116	1958	72.5
137	1890	70.0
165	1780	65.9
193	1711	63.4
221	1730	64.1
263	1571	58.2
292	1523	56.4
320	1499	55.5
354	1454	53.8
376	1472	54.5

Subject O (HF)		
7	2730	100
35	2281	83.6
63	2140	78.4
91	1938	71.0
112	1948	71.4
147	1878	69.1
176	1770	64.8
203	1773	65.0
218	1690	61.9
260	1675	61.4
281	1673	61.3
309	1582	58.0
337	1573	57.6
365	1535	56.2

Subject B.2. (HF)		
Days	cpm	o/o Retained
9	2595	100
27	2270	87.4
56	2109	81.2
105	1905	73.5
133	1845	71.1
168	1743	67.2
236	1648	63.5
253	1681	64.9
302	1524	58.7
330	1426	55.0
358	1445	55.7
386	1392	53.7

Subject P (HM)		
7	2820	100
35	2310	81.9
63	2070	73.4
91	2000	70.9
112	1872	66.4
147	1782	63.2
176	1758	62.4
203	1719	60.9
218	1662	58.9
260	1580	56.1
309	1498	53.1
337	1474	52.3
365	1477	52.4

Subject M.2. (EF)		
Days	cpm	o/o Retained
8	1141	100
22	697	61.1
50	516	45.2
85	510	44.7
113	390	34.2
153	330	28.9
176	338	29.6
212	319	27.9
225	306	26.8
253	310	27.1
281	307	26.9
309	301	26.4
337	302	26.4

Subject McK.2 (CM)		
61	784	100
89	712	90.9
117	765	97.5
158	623	79.5
179	634	80.9
197	616	78.6
225	623	79.5
253	606	77.4

Subject H (HM)		
Days	cpm	o/o Retain
73	1405	100
114	1394	99.2
135	1347	95.9
170	1204	85.7
206	1204	85.7
234	1197	85.2
268	1153	82.1
296	1115	79.4
334	1109	78.9
394	1023	72.8
432	954	67.9
488	1031	73.3

TABLE 6.4

Retention in a Normal Subject following a single intravenous dose of 5000 µg vitamin B_{12}.

SUBJECT A (H.M)		
Days	cpm	o/o Retained
0	20774	100
1	6714	32.4
3	4920	23.7
14	3409	16.4
48	2342	11.3
70	2234	10.8
101	1982	9.6
129	1845	8.9
161	1769	8.5
192	1689	8.1
210	1609	7.7
238	1557	7.5
269	1528	7.3
282	1459	7.0
325	1457	7.0
381	1304	6.3
402	1363	6.6
430	1256	6.0

(H, M) = Hydroxocobalamin, male subject.

TABLE 6.5.

Retention in anaemic subjects following double isotope doses of 5000 µg labelled vitamin B_{12}.

	SUBJECT K (F)				SUBJECT (F)			
Days	cpm C	o/o c Retained	cpm H	o/o H Retained	cpm C	o/o C Retained	cpm H	o/o H Retained
0	991	100	1409	100	1172	100	1852	100
3	128	12.9	503	35.7	107	9.1	365	20.0
7	112	11.3	-	-	92.3	7.9	-	-
8	-	-	291	20.6	-	-	-	-
10	104	10.5	-	-	89.5	7.6	-	-
14	-	-	276	19.6	-	-	225	12.1
15	92.0	9.3	-	-	-	-	-	-
21	95.5	9.6	255	18.1	82.0	7.0	210	11.3
28	83.6	8.4	243	17.2	77.0	6.6	208	11.2
35	80.9	8.1	238	16.9	71.5	6.1	195	10.5
42	81.5	8.2	240	17.0	72.0	6.1	193	10.4.
49	79.2	8.0	229	16.2	70.1	6.0	191	10.3
56	78.3	7.9	229	16.2	68.2	5.8	184	9.9
63	76.1	7.6	215	15.3	72.1	6.1	170	9.2
70	77.2	7.8	212	15.0	74.0	6.3	172	9.3
77	74.0	7.5	229	16.2	69.8	5.9	172	9.3
84	75.1	7.6	215	15.2	68.5	5.8	173	9.3
91	73.3	7.4	207	14.7	65.5	5.6	171	9.2
98	73.4	7.4	201	14.3	65.6	5.6	174	9.4
105	74.1	7.4	198	14.1	67.4	5.7	175	9.4
112	71.2	7.2	-	-	67.7	5.8	-	-
119	-	-	193	13.7	-	-	163	8.8
126	75.1	7.6	-	-	63.2	5.4	-	-
147	-	-	201	14.2	-	-	158	8.5
154	72.1	7.3	-	-	58.1	5.0	-	-
182	-	-	195	13.9	-	-	150	8.1
189	52.4	6.2	-	-	60.7	5.2	-	-

c = cyanocobalamin
h = hydroxocobalamin

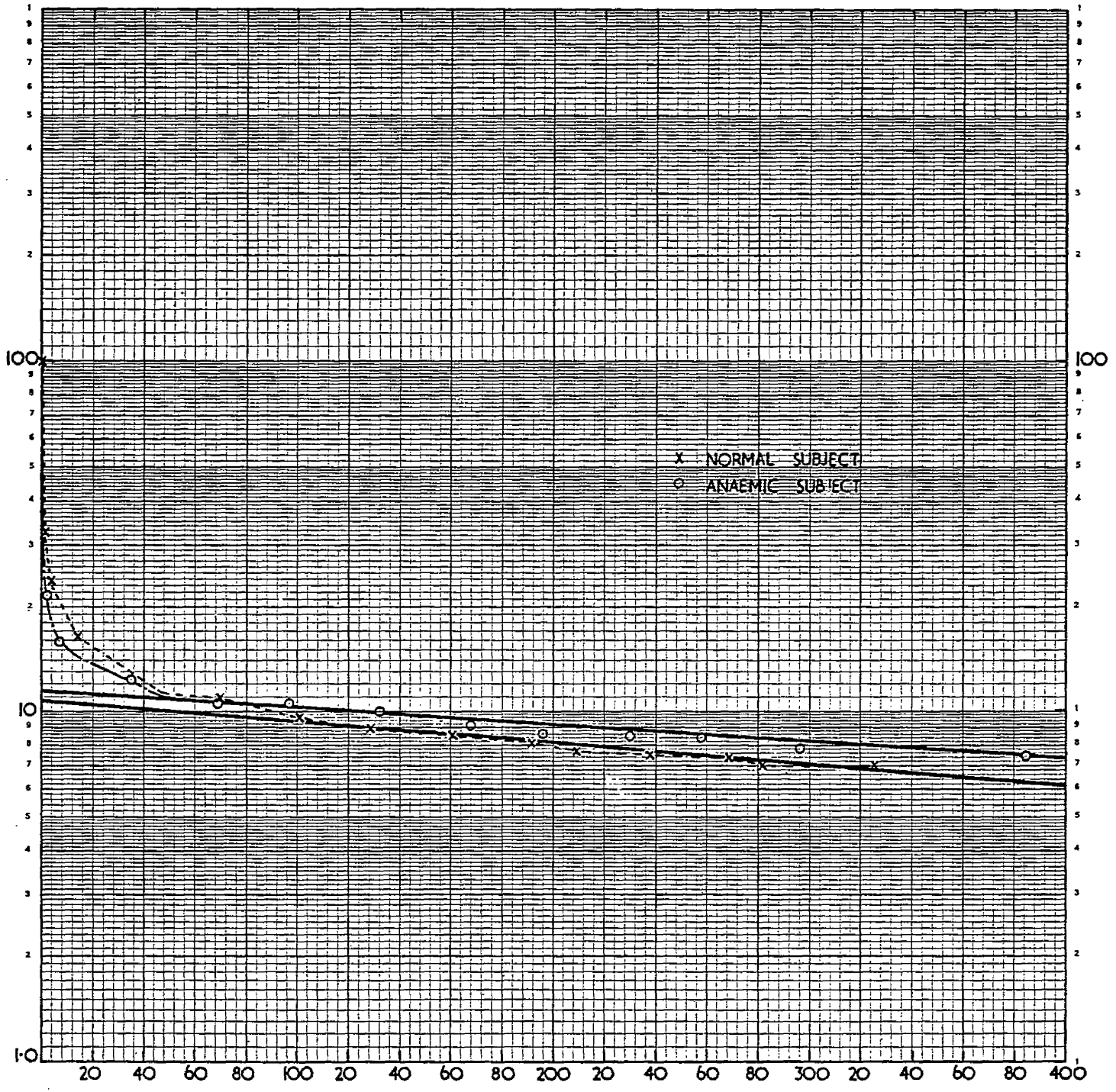
TABLE 6.5 cont'd

SUBJECT Ar (M)						Mc.D. (F)					
)ays	cpm C	o/o c Retained	Days	cpm H	o/o H Retained	Days	cpm C	o/o C Retained	Days	cpm H	o/o H Retained
O	1172	100	O	4896	100	25	271	100	O	11214	100
15	122	10.4	28	700	14.3	59	239	87.7	28	728	6.49
43	107	9.2	56	644	13.2	84	239	87.7	70	650	5.80
71	94.8	8.1	97	635	13.0	122	229	84.4	99	626	5.58
99	81.5	7.0	118	583	11.9	153	228	84.0	127	611	5.45
40	88.0	7.5	146	588	12.0	178	208	76.7	161	566	5.04
61	71.9	6.1	174	558	11.4	206	184	67.8	183	565	5.03
39	84.0	7.2	202	534	10.9	224	217	79.9			
17	73.3	6.2				255	182	67.1			
15	73.2	6.2				283	201	74.1			

TABLE 6.6

ɔject	Time period after administration	Equation of Regression Line	Rate of loss o/o /day	Standard error (o/o) of rate of loss
ıemic subjects, single isotope studies:				
.K.1.	35 - 441	$y = 2.4434-1.11x10^{-3}x$	0.11	± 8.7
..	35 - 376	$y = 4.4479-1.35x10^{-3}x$	0.14	± 7.4
:.	27 - 386	$y = 4.4563-1.27x10^{-3}x$	0.13	± 11.2
..	66 - 325	$y = 4.5523-1.04x10^{-3}x$	0.10	± 13.8
:.	50 - 337	$y = 3.8043-1.91x10^{-3}x$	0.19	± 18.3
	35 - 365	$y = 4.4024-1.09x10^{-3}x$	0.11	± 8.2
	35 - 365	$y = 4.3763-1.30x10^{-3}x$	0.13	± 6.8
K.2.	61 - 253	$y = 4.6663-1.39x10^{-3}x$	0.14	± 20.8
	73 - 488	$y = 4.6577-0.90x10^{-3}x$	0.09	± 9.5
emic subjects, double isotope studies:				
.	28 - 154	$y = 2.1501-1.44x10^{-3}x$	0.14	± 12.1
.	28 - 119	$y = 2.8599-1.59x10^{-3}x$	0.16	± 15.6
.	42 - 154	$y = 1.8948-1.64x10^{-3}x$	0.16	± 14.8
.	42 - 147	$y = 2.3843-1.77x10^{-3}x$	0.18	± 22.9
C.	43 - 245	$y = 2.2134-1.72x10^{-3}x$	0.17	± 26.1
H.	56 - 202	$y = 2.6653-1.34x10^{-3}x$	0.13	± 14.4
).C.	59 - 283	$y = 4.5539-1.10x10^{-3}x$	0.11	± 27.0
).H.	70 - 183	$y = 1.8552-1.36x10^{-3}x$	0.14	± 10.5
nal subject:				
	70 - 430	$y = 2.3861-1.41x10^{-3}x$	0.14	± 7.4

NORMAL SUBJECT AND AN ANAEMIC SUBJECT



6.5.1. Probable significance of retention at 1-2 months:

The initial losses up to about 1-2 months is clearly not significantly influenced by the level of body stores as the retention of the normal subject was the same as that of the anaemic subjects. This finding is almost certainly due to the size of the administered dose (5000 µg) which produces non-physiological conditions. The plasma content of B_{12} is normally about 1.5 µg, and less in anaemic subjects, so that the intravenous dose presumably "floods" the plasma with consequent rapid initial clearance by the kidneys. The large urinary losses of the normal subject (Table 6.2) appear to be in accordance with the latter suggestion which implies that this is the main route of initial excretion. Clearance from the plasma to stores during this time may be limited by the rate at which the body stores can take up B_{12}. Since the uptake by stores is about 10o/o of the administered dose while about 90o/o is excreted, largely by the kidneys, the plasma/stores transfer rate is apparently about 1/10th of that of the plasma/kidney transfer rate. This conclusion may be valid only for the present administered doses and periods of time.

6.5.2 Probable significance of the late excretion pattern.

It is apparent from Fig 6.1, the regression lines and standard errors of the regression coefficients (Table 6.6), that a single exponential term adequately describes the late excretion pattern in the normal and anaemic subjects. Consequently, the loss can be from only a single compartment since it is unlikely that two or more compartments would have identical excretion rates. For a single body compartment, the assumption of metabolic (and isotopic) equilibrium is justified.

The late excretion rates, as per cent per day, range from 0.09 to 0.19 per cent per day. A similar range from whole-body monitoring was reported by Bozian et al (1963) and a more complete comparison is

made in chapter 7. No significant difference was observed between the excretion rates of the anaemic and normal subjects. The quantities of B_{12} exreted per day are apparently proportional to the level of the body stores. It may be inferred for both the normal subject and the anaemic subject with no significant source of addition B_{12} that, at this time, the rate of transfer from stores to plasma is equal to that of transfer from plasma to kidneys. It seems unlikely, therefore, that vitamin B_{12} deficiency or pernicious anaemia, at least in the present subjects, is associated with an obvious fault in B_{12} metabolism.

The retained B_{12} represents almost the total body content of the vitamin in the anaemic subjects. The percent loss per day of the labelled B_{12} should be closely similar to that of the natural B_{12}. If the rate of loss of a tracer dose (about 1 µg B_{12}) does not represent that of natural body B_{12} (Reizenstein et al, 1962, 1964 and 1966 and Reizenstein, 1966) then a different rate of loss would be expected in normal and anaemic subjects to whom a tracer dose of B_{12} had been administered compared with the rates of loss obtained in the present study. In fact, the rates of loss observed by Bozian et al (1963) using tracer doses are virtually identical (0.09 - 0.23 per cent per day) with the present values. Further, in the present studies, the identity of the late rate of loss of labelled B_{12}, of the normal subject equivalent to about 10 per cent of his total body B_{12}, and that of the anaemic subjects also suggests that equilibrium with natural exchangeable B_{12} was indeed established.

6.5.3 Double isotope studies; the retention and the excretion rate of hydroxocobalamin and cyanocobalamin.

Each of the anaemic subjects in the double isotope study received an initial injection of about 5000 µg cyanocoabalamin labelled with cobalt-58 followed at a later time by an injection of about 5000 µg hydroxocobalamin. Allowance was made for the contribution of the Compton region of the cobalt-58 gamma ray spectrum to the photopeak region of the cobalt-57 spectrum. The subject was monitored

immediately priot to the injection of cobalt-57 and the fraction: $\frac{\text{counting-rate in cobalt-57 photopeak region}}{\text{counting-rate in cobalt-58 photopeak region}}$ evaluated from the cobalt-58 whole-body spectrum. Monitoring was repeated shortly after the injection of cobalt-57 and this and subsequent counts were corrected for the cobalt-58 contribution by subtracting the product of the cobalt-58 photopeak and the fraction obtained previously. It is obviously necessary to assume that this fraction is not grossly affected by any subsequent redistribution of cobalt-58 vitamin B_{12}.

Table 6.5 shows that the overall pattern of excretion is similar to that of the single isotope studies. Further, the rate of loss of the initial dose during the month after injection of the second 5000 ug dose does not appear to differ significantly from the rates of loss in the single isotope studies during the equivalent period of time. The rate of loss of the second dose during this time, however, is about four times greater. It seems reasonable to assume, therefore, that at the time of administration of the second dose the major part of the retained initial dose is no longer in the plasma and has, presumably, been transferred to stores. This situation is evidently reached not later than seven days after the initial administration in subjects K and L. This conclusion is in agreement with the results of Mollin (1959) for administered doses of 0.04 µg vitamin B_{12}.

The retention of hydroxocobalamin appears to be significantly better than that of cyanocobalamin, confirming similar findings (for example, Glass, G.B. et al (1961), Killander and Schilling (1961), Adams and Kennedy (1965)). Measurements have not yet been made with the order of administration reversed but if plasma and stores levels affected the observed retentions then it should be the first dose rather than the second dose which is preferentially retained. A comparison of the regression coefficients of the late excretion regression lines using the Student t test shows that the

respective rates of loss, per cent per day, do not differ significantly. Presumably, once the vitamin reaches the stores the subsequent metabolism is essentially independent of the chemical form or the vitamin is transmuted to a common form.

6.6 Conclusions:

a) Following intravenous administration of a single dose of 5000 µg vitamin B_{12}, the retention 1-2 months post-injection was the same (about 10o/o) in the anaemic subjects and the normal subject. No difference was observed in the excretion rates, thereafter, (range 0.09 - 0.19 per cent per day) and a single exponential term adequately describes the late excretion pattern. This implies that metabolic and isotopic equilibrium is then established.

b) The similar excretion rates of normal and anaemic subjects implies that vitamin B_{12} deficiency in these subjects is not attributable to a metabolic fault.

c) Double isotope studies suggest that the retained fraction seven days after administration is largely in the body stores.

d) Hydroxocobalamin is retained to a greater extent than cyanocobalamin.

CHAPTER 7: The Validiity of the Assumption of Tracer Equilibrium with respect to the Excretion of Vitamin B_{12}.

7.1 Introduction:

The validity of the common assumption that the excretion rate of a tracer dose of vitamin B_{12} equals that of the natural B_{12} has been questioned in recent years by Reizenstein and co-workers, (1962), (1964) and (1966), Reizenstein, (1966) and Heinrich (1964) who suggest that equilibrium might not be established even 250 days after administration of the tracer dose. Further, these authors obtain late excretion rates which are significantly different from those of other workers also using whole-body monitors and of others using analysis of excreta.

The suggestion by Reizenstein and co-workers that the assumption of tracer equilibrium is not justified is contrary to their earlier work (for example, Reizenstein, 1959 (a), 1959 (b), Grasbeck, Nyberg and Reizenstein, 1958 Reizenstein et al., 1961, Cohn, Lippincott, Cronkite and Reizenstein (1962)) which provides and cites evidence for, or embodies the assumption of, the early establishment of equilibrium not only with respect to excretion but also between body compartments. The rates of loss from the body of vitamin B_{12} obtained in the earlier work differ significantly from the later estimates of these authors but are in good agreement with those of other workers.

In view of the comparatively large amount of data supporting the assumption of equilibrium and the numerous studies based on the validity of this assumption, evidence to the contrary warrants careful examination.

7.2 Experimental evidence of Reizenstein and co-workers:

The data of Reizenstein and co-workers are self-contradictory in several important respects. To facilitate reference, relevant

data have been collected and are summarised in Table 7.1 with the source of the data.

On the basis of the data in Section A of this table, Reizenstein et al, (1962) conclude that the higher and, apparently changing excretion rate of the tracer shows that "equilibrium is not reached within the time studied".

7.2.1 Examination of premises:

Before dealing with apparent anomalies in the data as a whole, the validity of this conclusion and the premises on which it is based will be considered. Examination of the methods used (Reizenstein, (1959) and Reizenstein et al. (1962)), shows that the quantities of vitamin B_{12} administered in both series of experiments were similar (about 1 µg) and all subjects were classified as normal controls or as having irrelevant diseases. Any perturbation of the steady state resulting from the administered dose of B_{12} can only be due to the presence of additional vitamin and whether it is labelled or unlabelled is irrelevant in this respect. Therefore, whatever the effect of a tracer dose might be on the rate of excretion of vitamin B_{12}, it should be identical for both series of patients. The method of measuring excretion, whole-body or faecal monitoring of labelled B_{12} or microbiological assay should produce identical results, whether equilibrium is established or not, as there is apparently no evidence to suggest that vitamin B_{12} is broken down and the label subsequently lost. This argument leads to the inevitable conclusion that it should be fundamentally impossible to demonstrate a difference in the rates of loss of labelled and non-labelled B_{12} in these particular experiments. The apparent differences shown are then presumably due to experimental errors, inadequacies in the data, biological variations in individuals or groups of individuals, etc.

7.2.2 Apparent anomalies in the data:

The faecal excretion rate of radiovitamin B_{12} (section C, Table 7.1) (Reizenstein, 1959 a) is essentially constant (0.12 o/o /day) at

TABLE 7.1

A			B	C		D					
Comparison of excretion rates of "tracer" amounts of radio B_{12} and cold B_{12} (Reizenstein et al 1962)			Calculated faecal excretion in non-labelled vitamin B_{12} (Reizenstein 1959 c)	Faecal excretion after administration of radiovitamin B_{12} (Reizenstein, 1959a)		Calculations by present author using computed equation[x] of Reizenstein et al (1966)					
Days after Admin.	Radio B_{12} excretion o/o /day	Cold B_{12} excretion o/o /day	ug/day (Mean ± S.E.)	Days after Admin.	Daily faecal excretion o/o[1]	DAYS	o/o Retention 1st Term	2nd Term	3rd Term	TOTAL	Excret rate o/o /day
1-3	3.55		1.1 ± 0.40[a]	37	0.11	30	1.5	Nil	88.4	90	0.12
						60	0.4	-	87.8	87.8	0.05
4-25	0.28	0.03[≡]	1.3 ± 0.55[b]	50	0.12	100	0.1	-	86.2	86.3	0.03
						130	-	-	85.2	85.2	0.03
5-245	0.10		1.6 ± 0.62[c]	63	0.22						
				106	0.07						
				345	0.09						

[1] Per cent of the Radioactivity administered

a E. gracilis
b L. Lechmannu
c E. coli

[≡] Reizenstein et al. use dates of Section B to obtain this value

X Fractional retention =

$$0.0698e^{-0.0485t} + 0.0369e^{-0.650t} + 0.893e^{-0.000362t}$$

least from 37 days onwards to 345 days. A standard error of ± 20 o/o is quoted. In view of the almost inevitable losses which occur in faecal monitoring, the estimated rate of loss is unlikely to be an over-estimate.

The whole-body monitoring data (Reizenstein et al., 1961, 1962, Cohn, Lippincott, Cronkite and Reizenstein, 1962) are in good agreement with those from faecal monitoring. A steady rate of loss is apparent from about 5-20 days after administration and the authors specifically state that "the final slope shows the rate of turnover of the absorbed vitamin B_{12}". The excretion rates can be estimated, from the graphical presentations of Reizenstein et al, 1961, Cohn et al., 1962, as about 0.18 per cent per day in good agreement with that of Reizenstein et al., 1962 (Table 1, Section A). The data are in excellent agreement with those of Bozian and co-workers, (1963), (1964) and (1966) and those of chapter 6, both with respect to the pattern of excretion and the magnitude of the excretion rates.

On the other hand, the interpretation of whole-body monitoring data by kinetic analysis (Reizenstein et al. 1964, 1966) (Table 7.1 section D) apparently suggests that the late excretion rate is about 0.0362 per cent per day and a constant value is approached not later than about 60 - 100 days. This data completely contradicts the assertion of Reizenstein et al. (1962) that "a comparison of the tracer excretion rate with that of unlabelled B_{12} (0.03 per cent per day, Table 7.1 section B) showed a more rapid tracer excretion even 3 years after the administration of B_{12}, indicating that equilibrium had not been reached". The excretion rate of about 0.036 per cent per day is significantly less than those obtained earlier by these authors and, for reasons presented in Section 7.3, is almost certainly an underestimate. Further, the determination of the excretion rate of non-labelled B_{12} (Reizenstein, 1959) involved the use of tracer B_{12} and the assumption that equilibrium was established in about 11 days. It seems illogical, therefore, to argue that equilibrium is not established even after 3 years utilising this data.

7.3 Experimental evidence of Heinrich (1964).

The retention of ^{60}Co cyanocobalamin has been measured in three patients over 671 days using a whole body monitor (Heinrich, 1964). The data from the individual patients were apparently, pooled and an exponential equation of best fit was computed for the data as a whole. Turnover rates calculated by the present author using Heinrich's equation are summarised in Table 7.2 Heinrich suggests that metabolic equilibrium is not established about the 270th day and obtains a final turnover rate of 0.051 per cent per day. On the other hand, these calculations suggest that at 60 days after administration the final exponential term contributes over 93o/o of the retention figure at this time. The turnover rate at 150 days is 0.067 per cent per day compared with a final rate of 0.051 per cent per day. Heinrich (1964) quotes a standard error for Reizenstein's excretion rate of ± 33 o/o, and if Heinrich's standard error is of similar magnitude, it seems reasonable to assume that the rate of loss is constant within the experimental errors not later than 150 days.

7.4 Whole-body monitoring data of other workers.

The retention of ^{60}Co-labelled vitamin B_{12} has been measured in three normal subjects, two patients with irrelevant diseases and eleven patients with pernicious anaemia up to 668 days (Bozian et al., 1963) and up to 1100 days (Heyssel et al 1964 and 1966). Rates of loss obtained are summarised in Table 7.3. These authors find that, "during the first several weeks following absorption or injection of ^{60}Co vitamin B_{12}, there are wide fluctuations of counts which probably correspond to redistribution of the vitamin through various compartments." Further usually after one month and invariably after two months in the case of injected vitamin B_{12}, rate of loss from the body becomes effectively constant.

A similar excretion pattern was observed (Chapter 6) following intravenous administration of about 5000µg of B_{12} in anaemic patients

TABLE 7.2

Retention and Excretion Rate of Absorbed Vitamin B_{12} in Man (Heinrich, 1964) as Calculated by present author from Heinrich's equation: Retention (o/o) = $7e^{-0.072t} + 25e^{-0.028t} + 68e^{-0.00051t}$

Days after intestinal ^{60}Co B_{12} Absorption	o/o RETENTION				Excretion rate (o/o per day)
	1st Term	2nd Term	3rd Term	TOTAL	
30	0.8	9.1	67.0	76.9	0.45
60	0.1	4.7	65.9	70.7	0.24
100	0.1	1.5	64.6	66.1	0.11
150	-	0.4	63.1	63.5	0.067
200	-	0.1	61.5	61.6	0.055
250	-	-	59.9	59.9	0.052

TABLE 7.3

Excretion rates observed by Bozian et al (1963).

Patient condition	ug B_{12} given	o/o loss per day during B_{12} therapy	o/o loss per day after B_{12} therapy
Normal	Dietary	0.12	-
	Dietary	0.15	-
	Dietary	0.09	-
Irrelevant deseases	Dietary + 65/3 wk	0.23	0.21
	Dietary	0.21	-
Pernicious anaemia	3/1 wk.	0.15	-
	7/1 wk.	0.15	0.14
	30/4 wk.	0.11	-
	30/4 wk.	0.09	0.10
	45/4 wk.	0.14	0.11
	45/4 wk.	0.16	0.11
	60/4 wk.	0.17	-
	60/4 wk.	0.14	-
	60/4 wk.	0.11	-
	30/2 wk.	0.13	-
	60/2 wk.	0.12	0.12

and a normal subject, Fig 6.1 and Tables 6.3 and 6.4.

7.5 Rate of loss per day and its probable range:

The final rates of loss per day observed by a number of workers are summarised in Table 7.4 with a note of the measurement technique. The greater part of these data suggest that the range of rates of loss is from about 0.1 - 0.3 per cent per day with a mean of about 0.2 per cent per day. It seems hardly co-incidental that the three values significantly lower than the remainder are those principally cited as evidence against the assumption of metabolic equilibrium with respect to excretion. All of the techngiues involved directly or indirectly the use of labelled vitamin B_{12}. Clearly, it cannot be shown that one range of excretion rates is right and the other wrong, but it is possible to show that one range is more compatible with clinical findings.

7.5.1. Significance of the rate of loss in relation to depletion time:

If the clinical symptoms of vitamin B_{12} deficiency develop as soon as the whole body vitamin B_{12} pool falls below 10 per cent of the normal value, (Heinrich, 1964), then the time required for effective depletion can be calculated using the estimated rate of loss. Comparison can then be made with the range of about 1 - 8 years reported (Maclean and Sundberg, 1956, Paulson and Harvey, 1954) for the development of the haematological and/or neurological symptoms of the B_{12} avitaminosis in patients after total gastrectomay.

On the basis of his estimated rate of loss of 0.051 per cent per day, Heinrich, 1964, has calculated the depletion time as 1764 days of 4.8 years, which apparently is in good agreement with the range quoted above. His calculation, however, is based on the assumption of a linear relationship of retention with time, as he simply divides 90 per cent of the whole body content of B_{12} (= 0.9 x 5000 µg assumed) by the rate of loss per day (=2.55 µg/day on his assumption of a whole body content of 5000 µg) and obtains 4500/2.55 = 1764 days. In fact, the relationship between retention and time is exponential

TABLE 7.4

Final rates of loss of vitamin B_{12}.

uthor(s)	TECHNIQUE	Final rates of loss per cent per day.
izenstein (1959 a and b)	Faecal monitoring-tracer	0.09 - 0.22
izenstein et al (1962)	W.B.M. - tracer	0.10
izenstein et al (1961)	W.B.M. - tracer	0.17
hn et al. (1962)	W.B.M. - tracer	0.17
zian et al (1963)(1964)	W.B.M. - tracer	0.09 - 0.23
yssel et al (1966)	W.B.M. - tracer	0.09 - 0.17
esent work (1967)	W.B.M. - 500 ug labelled	0.09 - 0.19
asbeck et al (1958)	Faecal and urine monitoring - tracer	0.28
onkite et al (1959)	do.	0.23
hloesser et al (1958)	Liver monitoring - labelled	0.16 - 0.21
ass (1958)	do.	0.08 - 0.46
izenstein (1959 c) and izenstein et al (1962)	Non-labelled B_{12} - micro-biological and using tracer B_{12}.	0.03
izenstein et al (1964 and 1966)	Kinetic analysis by computer	0.036
inrich (1964)	W.B.M. - tracer	0.051

(or log-linear) and it is necessary to use the basic equation:

$\frac{A_t}{A_o} = e^{-\lambda t}$ for which, at depletion, At/Ao is assumed to equal 1/10th. Inserting this value and transposing, the depletion time (t) = $\frac{\ln 10}{\lambda}$ = $\frac{2.303}{\lambda}$. Heinrich's value of λ, as the fraction per day, = 0.00051, and hence the depletion time = (2.303/0.00051) = 4,520 days = 12.4 years. This period is much longer than that calculated by the author and than the period (1-8 years) quoted above which he also cites in support of his calculated depletion time. A similar comment was made by Heyssel et al (1966). The analogous calculation for the data of Reizenstein et al. (1966) suggests that the depletion time would be even longer (= 5760 days = 15.9 years).

If a depletion time of 1-8 years is a reasonable estimate, then the corresponding range for the rate of loss is about 0.63 per cent per day to 0.08 per cent per day. This range is in good agreement with that observed by the majority of workers cited in Table 7.4 while the mean rates of loss of Heinrich and Reizenstein (1964 and 1966) would seem to be underestimates. A similar conclusion can be drawn with less specific assumptions.

If the range of whole-body content of vitamin - B_{12} in an adult man is about 2000 to 5000 µg (Grasbeck, 1959, Adams, 1962 and Grasbeck, Nyberg and Reizenstein, 1958) and in patients with pernicious anaemia in relapse is about 200 to 500 µg, then the limiting rates of loss corresponding to 1 year and 8 years depletion times can be calculated. Clearly, subjects with an initial content of 2000 and of 5000 µgs who are depleted at 200 µg and 500 µg respectively correspond with Heinrich's assumption of a 10 per cent level as already discussed. However, subjects with an initial content of 2000 µg who are depleted at 500 µg can provide a rough estimate of the lowest range to be expected. An analogous calculation shows that, even with this more favourable assumption, the range is only 0.38 - 0.048 per cent per day, so that the mean rate of loss obtained by Heinrich (0.051 per cent per day) and by Reizenstein and co-workers (0.036 per cent per day) are at the

lower limit of this range.

7.6 Discussion:

The only direct experimental evidence reported of a difference between the rate of excretion from the body of unlabelled and of labelled vitamin B_{12} is apparently that of Reizenstein et al. (1962). It has been argued (Section 2.1) that it is impossible for fundamental reasons to demonstrate a real difference in the experiments described. Further, the final rate of loss from a later analysis of the whole-body monitoring data (Reizenstein et al 1964 and 1966) is in good agreement with the estimated rate of loss of non-labelled B_{12}. Both of these rates of loss, however, are significantly less than those observed by all other authors in Table 7.4 with the exception of Heinrich (1964). None of the data discussed, including that of Reizenstein et al. and Heinrich, supports the suggestion that the rate of excretion is not effectively constant even after 250 days or longer. Indeed, the data as a whole suggest that it changes little after relatively short times (30 - 60 days or less).

The higher ranges of excretion rates observed are in remarkable agreement with those to be expected from the clinical evidence of depletion times following gastrectomy, while the excretion rates found by Reizenstein (1959 c), Reizenstein et al. (1964), (1966) and Heinrich (1964) are much lower giving depletion times greatly in excess of those reported to date. It seems significant that it is the data yielding the higher excretion rates which also supports the assumption of metabolic equilibrium in a finite (and short) period of time at least with respect to the excretion of vitamin B_{12}.

Heinrich (1964) suggests that the higher values obtained by Bozian et al (1963) might be due to problems in reproducibility of these authors' counting geometry. This is clearly a gross over-simplification since Reizenstein et al used an almost identical counting geometry while Heinrich's own counting geometry shows

increases in the initial counting-rate of over 30 per cent and variations in consecutive counts of up to about 10 per cent even after 200 days (Fig 1 (b) of Heinrich, 1964). Indeed, it is the lower rates of loss which are more critically affected by counting errors. Substituting the excretion rates of 0.04, 0.1 and 0.2 per cent per day in the basic equation $At/Ao = e^{-\lambda t}$, it can be calculated that at 100 days after any chosen reference time, the respective counting-rates would be about 96 per cent, 90 per cent and 82 per cent of those at the reference time. The uncertainty in estimating a loss of only 4 per cent is almost certainly greater than that for losses of 10 to 20 per cent.

If metabolic equilibrium does not occur in a finite time, then, presumably, the level of body stores and the size of the administered dose will influence the excretion pattern and the rate of loss. In anaemic patients, the administered "tracer" dose, if sufficiently large, may be greater than the total body content before administration. The behaviour of the tracer may then typify that of natural B_{12} in normal subjects or, at the other extreme, show gross perturbations compared with natural B_{12} because the "steady state" has been drastically violated. Bozian et al. (1963) and Heyssel et al. (1966) (Table 7.3) found no difference in excretion pattern or rate or loss between normal and anaemic subjects with administered doses ranging from 3 µg to 65 µg total. These doses, however, are small compared with the total body content even of anaemic patients (- 200 - 500 µg of vitamin B_{12}). Intravenous doses of about 5000 µg of labelled vitamin B_{12} were administered to anaemic patients and a normal subject as described in chapter 6. This dose initially is comparable with the total body content of a normal subject and about 10-25 times greater than that of an anaemic subject. The excretion pattern and rates of loss (Fig 6.1 and Tables 6.3 and 6.4) are virtually identical for the normal subject and the anaemic subjects and apart from a larger initial excretion which may be explained by the size of the dose, the data are in excellent agreement with those of Bozian,

Heyssel and co-workers. Apparently, therefore, neither the size of body stores nor of the administered dose influences the general excretion pattern, the time at which the excretion rate becomes effectively constant or the final value of the excretion rate. The assumption that metabolic equilibrium is established in a comparatively short time may not be the only explanation of these findings but, in view of the supporting evidence cited earlier, it would seem to be the most likely explanation.

Reizenstein (1966) implies that a kinetic analysis is needed "to translate the experimental data (in themselves meaningless) into physiologically meaningful terms" in the study of vitamin B_{12} metabolism while only for closed systèms of for single-pool systems is the assumption of isotopic equilibrium justified. The kinetic analysis of Reizenstein et al (1966), however, shows that over 99 per cent of the tracer dose of vitamin B_{12} is contained in a single pool; which would seem to imply that a kinetic analysis is not necessary in this case and that, with the arguments presented above, the assumption of tracer equilibrium with respect to the excretion of vitamin B_{12} is a valid approximation in theory as well as in practice.

CHAPTER 8: In vivo activation analysis of iodine in the thyroid - Preliminary studies and their Adaptation for Clinical Trials.

8.1 Introduction:

The limitations of the indirect methods currently used to measure the exchangeable iodine content of the thyroid and the importance of knowledge of the intrathyroidal stores of iodine have already been discussed (Chapter 1 sections 1.3 and 1.4). As well as providing a direct method of measurement, in vivo activation analysis appears even more suitable for the estimation of the elemental content of specific organs than of the total body content. In particular, the estimation of iodine in the thyroid gland at least has the advantages that the gland is close to the surface of the body and the irradiation area is small compared with whole-body irradiation. Preliminary experiments were conducted using neutrons from the U.T.R. 100 reactor to establish whether measurements in vivo would be feasible with an acceptable radiation dose, subsequently to measure total iodine levels in excised glands (Boddy, 1966). The techniques were subsequently adapted for clinical trials.

8.2 Preliminary studies:

A horizontal beam tube of the UTR-100 reactor was selected as the most convenient facility for preliminary studies. A collimator with a shutter already existed for this beam tube and elementary measurements with gold foils suggested that a neutron flux of at least 10^7 n/cm^2 sec should be obtainable. As thyroid monitoring was not carried out at the Centre, apparatus for this specific purpose had not been established and the prototype whole-body monitor was the most suitable equipment for measuring the induced radioactivity.

8.2.1 Theoretical considerations:

a) Irradiation and induced radioiodine activity:

An estimate of the specific activity of iodine resulting from irradiation of the thyroid by the beam of neutrons was obtained from the equation:

$$S = \frac{0.6\ \Phi\ \sigma \left(1 - e^{-0.693t/T}\right)}{3.7 \times 10^{7}\ A}$$

where S = specific activity as μc of I^{128} per milligram of iodine

Φ = effective neutron flux, in neutrons per cm^2 per sec.

σ = activation cross-section of iodine in barns (= 5.6 barns)

A = Atomic Weight of iodine-127

t = irradiation time.

T = half-life of iodine-128 (= 25 min)

At the irradiation position, the thermal neutron flux was approximately 2×10^7 $n.cm^{-2}.\ sec^{-1}$. For an exposure time of, say, five minutes, the specific activity resulting is about 2m μc/mgm.

b) Detection.

The prototype whole-body monitor has a background counting-rate of about 40 counts per minute over the main iodine-128 photopeak at 0.46MeV. Interpolation from results on the 0.51 MeV photopeak of sodium-22, suggested that for iodine-128 the counting rate would be approximately 4,640cpm/μc. The 5 min. irradiation produces about 2mμc/mgm so the counting-rate is about 9.2 cpm /mg. The minimum detectable quantity, defined as the amount of iodine giving the same number of counts as three times the standard deviation of the background in the same counting time, is then about 0.65 mgs. for a 10 minute count.

The interpolation was confirmed by irradiation of ammonium iodide under the conditions described producint approx. 8.3 cpm/mg.I.

8.2.2 Experimental methods:

A water-filled polythene thyroid phantom was irradiated at the biological shield of the UTR-100 reactor using a collimated beam of neutrons from a horizontal beam tube as shown in Fig. 8.1. The

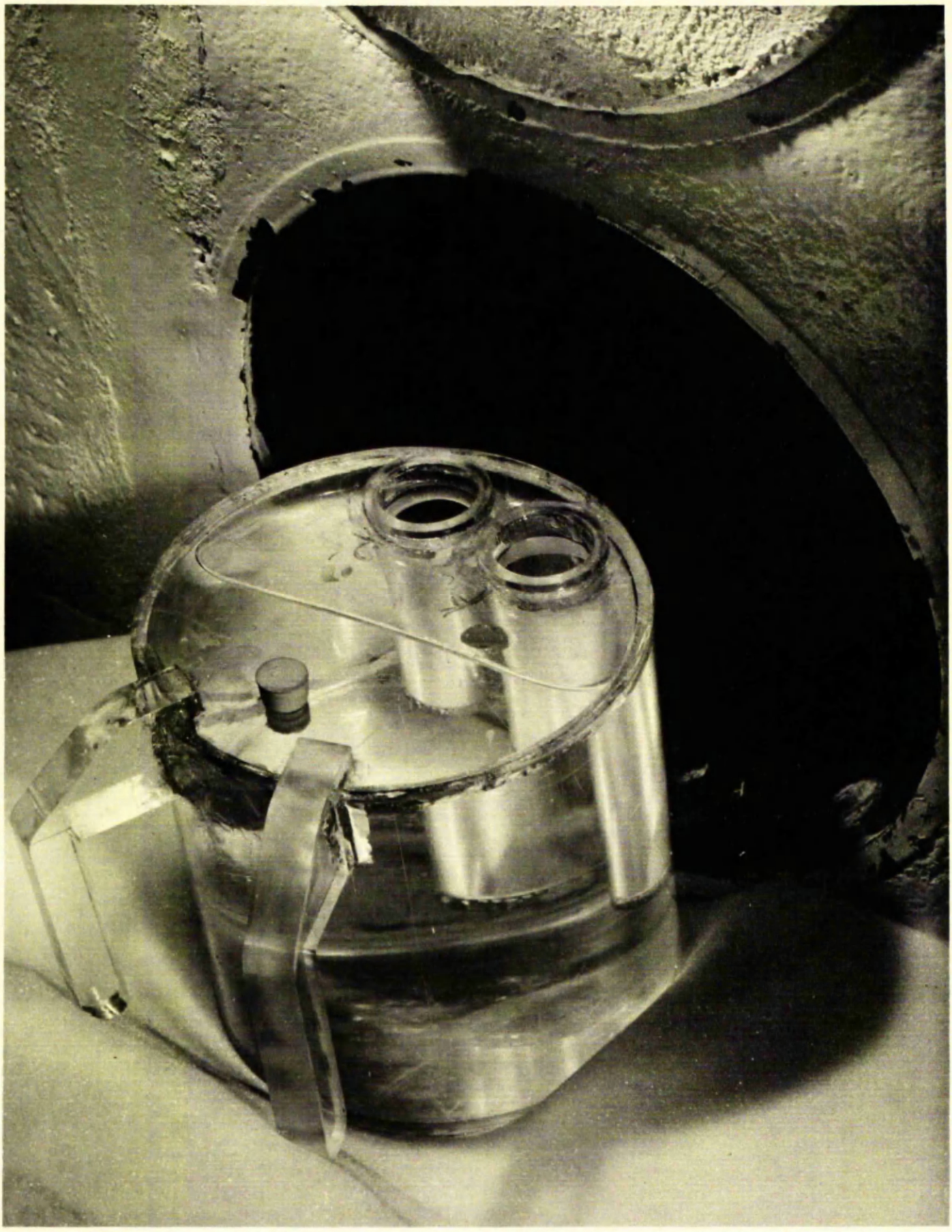


Fig. 8.1. Irradiation Position - Horizontal Beam Tube

phantom bore either a standard comprising 12 mgs of iodine (as ammonium iodide), or an excised human thyroid. Irradiation times were varied from 5 - 20 minutes and the reactor was operated at 100 kW.

Counting was carried out in the prototype whole-body monitor. The neutron energy spectrum was estimated by the use of criticality dosimeters (Dennis J.A. (1964)).

8.2.3. Results:

a) Estimation of iodine content of a human thyroid

Fig. 8.2 shows the gross gamma-ray spectrum from an excised human thyroid after neutron irradiation for 5 minutes. The spectrum clearly shows the principal photopeak of the induced iodine-128 (0.46MeV) and, less prominently the associated peaks at 0.54 MeV, 0.75 MeV and 0.99 MeV.

Peaks due to sodium-24 and chlorine-38 occur at 1.38 and 1.64 MeV respectively and there may be less obvious peaks at about 0.8, 1.1 and 1.27 MeV possibly attributable to copper, magnesium, iron, manganese or silicon which are also present, in the thyroid (Health Physics, Vol.3. (1960)).

The iodine content of the gland was calculated by comparing the area under the 0.46 MeV photopeak with that of the iodine standard irradiated and counted under similar conditions. Due allowance was made for the contributions of sodium-24 and chlorine-38 in the thyroid's photopeak by separately counting a prepared source of each isotope. The integrated thermal flux to the phantom and thyroid were monitored individually with gold foils.

Duplicate measurements were made in vitro on human thyroids removed at autopsy. The results are summarised in Table 8.1. The iodine content of thyroid I was also measured using a biochemical method which gave a value of 8.7 mgs.

b) Dosimetry:

The threshold detectors roughly divide the neutron spectrum

8·2 GROSS THYROID SPECTRUM

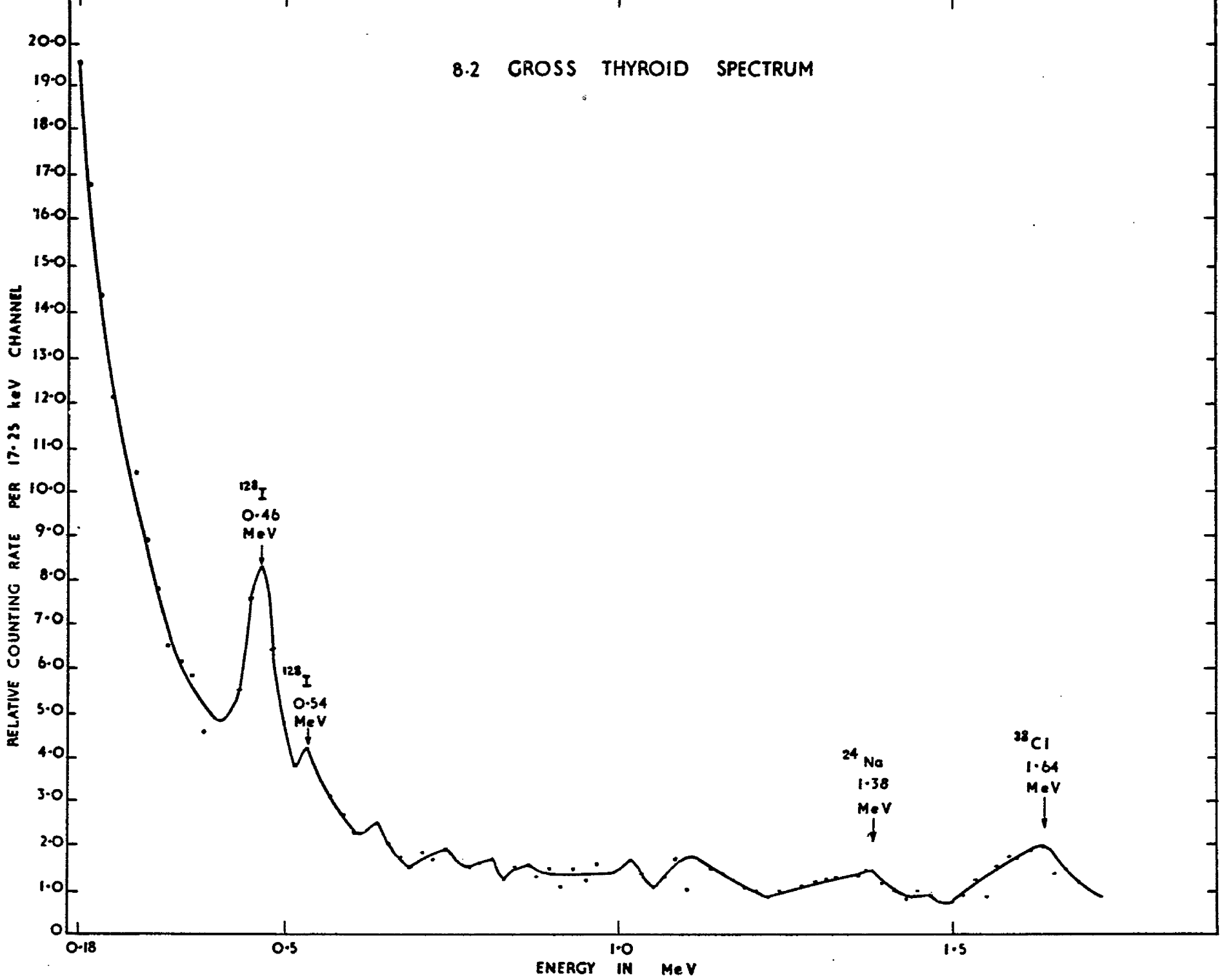


TABLE 8.1

In Vitro Human Thyroid Results.

	Relative counting[1]-rate in iodine photopeak = $\frac{\text{cpm. thyroid}}{\text{cpm. standard}}$	Relative[2] flux = $\frac{\text{n.cm}^{-2} \text{ thyroid}}{\text{n.cm}^{-2} \text{ standard}}$	I content = $\frac{(1)}{(2)}$ x 12 mgs	Mean mgs.
Thyroid I a (30gms)	0.787	1.12	8.43	8.54 ± 0.11
b	0.823	1.14	8.65	
Thyroid II a (13.25gms)	0.876	0.892	11.8	10.0 ± 1.8
b	0.978	1.44	8.2	
Thyroid IIIa (41.11gms)	1.96	0.96	24.6	25.9 ± 1.3
b	2.09	0.93	27.1	
Thyroid IV a (7.2gms)	0.632	1.17	6.49	6.28 ± 0.21
b	0.612	1.21	6.07	
Thyroid V a (21.1gms)	0.911	1.48	7.38	7.48 ± 0.10
b	0.784	1.24	7.58	
Thyroid VI a (23.6gms)	1.68	1.49	11.5	13.9 ± 0.4
b	1.47	1.24	12.1	
Thyroid VIIa (33.7gms)	1.49	1.50	12.0	12.3 ± 0.3
b	1.30	1.26	12.5	

into thermal, intermediate (0.12eV-1MeV) approx and fast (1MeV and above). The results corresponding to a thermal flux of 2×10^7 $n/cm^2/sec.$ and an irradiation time of 1 minute are presented in Table 8.2.

The thyroid dose in a 5 minute irradiation will be about 3.2 rad. With neutron Quality Factors appropriate to acute exposure the rem dose is about 6 rems and with protacted exposure values the rem dose is about 18 rems (see 8.4). This last dose, which is similar to that received by the thyroid in clinical diagnostic tests involving administration of about 12 μcs of iodine-131, is a pessimistic value and almost certainly represents an upper limit.

The remainder of the body, being protected to a large extent by the biological shield of the reactor, would be unlikely to receive a dose in excess of 100 millirem during the five minute irradiation.

8.2.4. Discussion:

The duplicate in vivo measurements are in good agreement mutually and thyroid I agrees well with the result from biochemical assay.

Riggs (Riggs D.S., (1952)), obtained an iodine content of about 8 mgs. for the thyroid gland using chemical methods. In vivo techniques with radioisotopes gave a range of 1.3-18.1 mgs of iodine in the glands of euthyroid patients (Modine J.H. et al (1957)) and a range of 0.9-22.6 mgs. with a mean of 9mgms. for similar patients (Wayne E.J. et al (1964)).

The interference of sodium-24 and chlorine-38 was not a serious embarrassment in the in vitro irradiations, and it seemed likely that the additional yields of these isotopes in the in vivo studies might be offset by their removal in blood.

The technique, however, required some modification before it could be tested clinically. With a patient, irradiation using the horizontal beam tube would have been difficult to arrange and make reproducible. Neutron fluxes of 2×10^7 n/cm^2. sec thermal and

TABLE 8.2

Neutron spectrum and Radiation doses.

Radiation	Flux $n.cm^{-2}.\ sec^{-1}$	Integrated flux $n.\ cm^{-2}$	$rads.n^{-1}.\ cm^{2}$	Rad dose
Thermal n.	2×10^{7}	1.2×10^{9}	6.30×10^{-11}	0.075
Intermediate n.	4.7×10^{6}	2.8×10^{8}	3.55×10^{-10}	0.098
Fast n.	1.45×10^{6}	8.7×10^{7}	3.62×10^{-9}	0.32
Gamma	9r/hr			0.15

TABLE 8.3

Approximate estimated doses to remainder of body during irradiation at the horizontal beam tube.

Part of body	Dose as per cent of thyroid dose.
Thyroid	100
Eyes	20 - 30
Gonads	5 - 10
Feet	1

4.7×10^6 n/cm^2. sec intermediate were only obtainable with the reactor at its maximum power, leaving no margin in hand for modifying the flux spectrum and increasing the effective flux without necessarily increasing the radiation dose to the gland. These difficulties have been overcome to a large extent by the use of the central vertical stringer of the reactor as described in Section 8.3.

While the sensitivity of the prototype whole-body monitor was remarkably good, the small dimensions of the detector seemed likely to lead to difficulties in reproducing the counting geometry with patients. Additionally, the heavy commitments of the monitor in the whole-body monitoring programmes made allocation of time difficult. A shadow shield thyroid monitor was designed and constructed (Chapter 9) to provide a suitable counting arrangement at least until a large detector could be obtained for the prototype whole body monitor and its performance assessed.

In compliance with the requirements of the Site Licence covering operation of the UTR reactor, a submission (Boddy, K., Wayne, E.J., and Alexander, W.D., 1965) was made to the Reactor Safety Committee and approval was granted for clinical measurements in patients.

8.3 Adaptation of the irradiation position:

The central vertical stringer of the reactor has the advantages over the horizontal beam tube that the emergent neutron flux is about 20 times greater for the same reactor power and reproducible alignment of the patient is easier.

A collimator, 57in. in length, was constructed of concrete and lead in a steel shroud designed to fit closely in the central vertical stringer. An aperture 6 in. x 3 in. extends throughout its length. The aperture dimensions were selected on the basis of physical measurements on hospitalised patients (Alexander, W.D. Personal communication, 1965). The patient lies on a moveable bed with the estimated location of the gland on a neck-rest to predetermine position. The bed is moved forward outside of the beam until the neck-rest is roughly in line with the aperture, when the bed is moved

sideways to the irradiation position. A low line of concrete blocks defines the final position of the bed and this lining-up procedure avoids passing the patient's head and eyes through the emergent beam. Fig. 8.3 is a schematic representation of the irradiation position.

8.4 Dosimetry - thyroid gland:

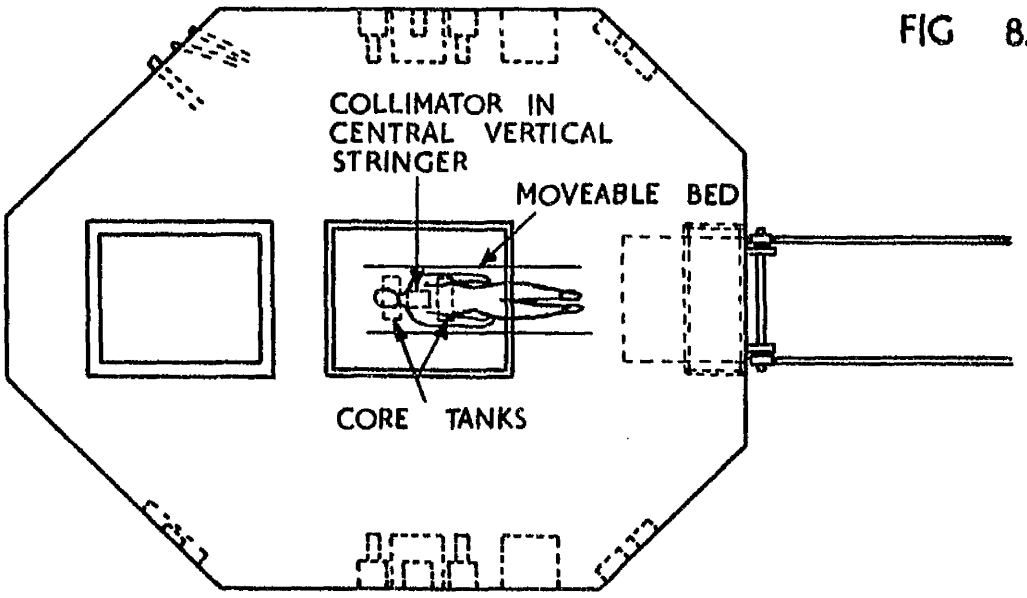
The neutron energy spectrum was again estimated with threshold detectors (Dennis, J.A. 1964) and the results are summarised in Table 8.4 for a reactor power of 20 kW.

The energy spectrum of the emergent neutrons is "harder", or contains a larger proportion of neutrons in the intermediate energy range, than that at the horizontal beam tube (see Table 8.2). This is presumably attributable to the smaller amount of moderator between the fuel tanks of the reactor and the central vertical stringer. The emergent flux per kilowatt of reactor power is about twice as great in the thermal and fast regions and about twelve times greater in the intermediate region.

Before an estimate of the dose in rem can be made it is necessary to assume appropriate values for the Quality Factors or R.B.E. The threshold detectors roughly divide the neutron spectrum into thermal, intermediate (0.12eV - 1 MeV approx.) and fast (1 MeV and above), (Dennis, J.A., Personal Communication and "Neutron Dosimetry" Vol. I. IAEA, 1963). The R.B.E. values for protracted low dose-rate exposures are summarised in Table 8.5 (from N.B.S. Handbook 63, "Protection Against Neutron Radiation up to 30 MeV"). In the intermediate region, the preponderance of neutrons is presumably in the middle of the energy range as the fast and thermal fluxes are about equal. A direct mean R.B.E. of about 7 over the six energy groups of Table 8.5 should represent a pessimistic value for the R.B.E. In the fast region, most neutrons are at the lower end of the range and an R.B.E. of 8 is probably a realistic estimate.

On the other hand, the thyroid exposure is short (5 minutes) and the dose-rates are large, compared with life-time exposures of 100 mrem/week as in Table 8.5. It seems more realistic to assume

FIG 8.3


COLLIMATOR IN
CENTRAL VERTICAL
STRINGER
MOVEABLE BED
CORE TANKS

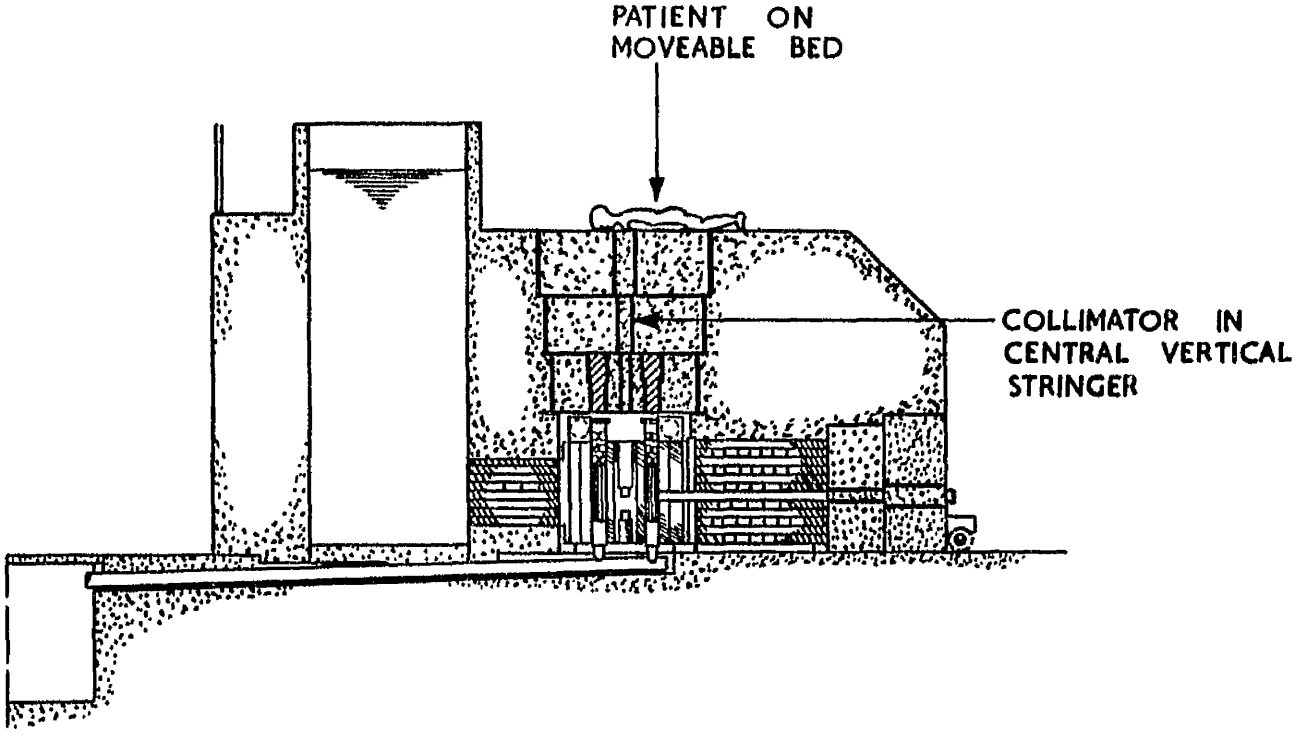

PATIENT ON
MOVEABLE BED
COLLIMATOR IN
CENTRAL VERTICAL
STRINGER

TABLE 8.4

Radiation	Flux n/cm^2. sec	Integrated flux for 5 min. exposure n/cm^2	Rads. n^{-1} cm^2	Rad Dose
Thermal n	7.4×10^6	2.2×10^9	6.30×10^{-11}	0.14
Intermediate n	1.2×10^7	3.6×10^9	3.55×10^{-10}	1.28
Fast n	6.6×10^5	2.0×10^8	3.62×10^{-9}	0.72
Gamma	-	2.4 rad	-	2.4

TABLE 8.5

Thermal region	Intermediate region		Fast region	
R.B.E.	Mev	R.B.E.	MeV	R.B.E.
3	0.0001	2	2.5	8
	0.005	2.5	5.0	7
	0.02	5	7.5	7
	0.1	8	10	6.5
	0.5	10		
	1.0	10.5		

that the exposure more closely approximates an acute exposure for which different values of R.B.E. are applicable (Report of the R.B.E. Committee to the International Commission on Radiological Protection and on Radiological Units and Measurements, reported in full in Health Physics, Vol. 9 pp. 357 - 386, 1963). After discussion of the available biological data, the Committee concludes that "a value of 1 is reasonable for bone marrow failure and associated mortality. It seems probable that the value will be higher, of the order of 2, for intestinal injury and its associated mortality". Data for "variously degraded fission spectra" and "simulating an undergraded fission spectra" are included in the review. The present spectrum is presumably between these extremes. If the thyroid exposure approximates more closely to an acute exposure, then an R.B.E. value of 2 in probably pessimistic. The rem doses equivalent to 5 minute exposure at 20 kW are summarised in Table 8.6 for protracted and acute R.B.E. values.

The more pessimistic estimate of the dose is about 18 rem and probably the more realistic about 7 rem. The higher dose is comparable with that from the routing diagnostic thyroid uptake test using iodine-131 in which about 12 μc of iodine-131 is administered resulting in a dose of about 17 rem.

8.5 Dosimetry - whole-body:

The neutron dose variation along the length of the body was estimated using gold foils placed at intervals along the moveable bed. The bed was then placed in the irradiation position for 5 minutes with the reactor at a power of 20 kW. The gamma dose was measured correspondingly, using integrating ionisation chambers and by dose-rate measurements with an ionisation chamber. Table 8.7 is a summary of the results expressed as percentages of those at the mid-line of the neck-rest. The general pattern, as might be expected, is similar for both types of radiation. It can be seen that the dose to the eyes is unlikely to exceed 10 o/o of the gland dose and the gonad dose is less than 1 o/o of the gland dose.

TABLE 8.6

Radiation	Rad dose	Protracted exposure		Acute exposure	
		R.B.E.	rem dose	R.B.E.	rem dose
Thermal n.	0.14	3	0.52	2	0.28
Intermediate n.	1.28	7	8.96	2	2.56
Fast n.	0.72	8	5.76	2	1.44
Gamma	2.4	1	2.4	1	2.4
		Total = 17.64		Total = 6.68	

TABLE 8.7

Neutron Dose			Gamma Dose		
Distance from mid-line of neck-rest (inches)	Reference	o/o of mid-line of neck-rest	Distance from mid-line of neck-rest (inches)	Reference	o/o of mid-line of neck-rest
7	Eyes	10	7	Eyes	10
1.5	Neck-rest limit	105	1.5	Neck-rest limit	90
-	Neck-rest mid-line	100	-	Neck-rest mid-line	100
1.5	Neck-rest limit	99	1.5	Neck-rest limit	90
3.5		33	7.5		5.2
13.5		2.7	13.5		2.1
19.5		2.0	19.5		1.0
25.5	Gonads	1.3	25.5	Gonads	0.5

8.6 Doses arising from "the maximum credible accident".

For reactor safety assessments, "the maximum credible accident" is conventionally defined as the simultaneous occurrence of an operator error and two instrument failures. Two cases which probably represent the limiting situations of a rapid rise in reactor power and a slow rise in reactor power over the five minute irradiation time are:

a) Sudden insertion of the total available reactivity (0.3o/o) - operator error; failure of automatic control and variable power trip - two instrument failures.

b) Slow power rise which is neither noticed nor corrected - operator error; failure of automatic control and variable power-trip - two instrument failures.

Method of calculation:

If the dose-rate at 20 kW is D_o (r/min) then the integrated dose due to the excursion is given by : $D_{excursion} = D_o \left(\frac{1}{\lambda} e^{\lambda t}\right)_o^t =$ $D_o \left(Te^{\frac{t}{T}}\right)_o^t$ where t mins. is duration of excursion and T mins. is the period.

The reactor power is initially 20 kW and reaches 120 kW before the fixed safety channels cause a reactor scram. The power increases by a factor of 6, equivalent to about 1.8 periods.

The total dose during a normal irradiation is 5 x D_o rem.

Case a) - sudden insertion of total excess reactivity:

The period resulting from the insertion of 0.3o/o reactivity is approximately 6 secs. Taking the limiting period which might not trip the period meter of the reactor, causing a scram at 5 seconds period, as 5.0001 seconds,

Time to shutdown = 1.8 x 5.0001 + Shutdown amplifier time (1 sec)
= 10.0 seconds approximately.

Then $D_{excursion} = D_o \left(\frac{5}{60} e^{\frac{t}{5.0}}\right)_0^{10.0}$

$$\frac{D_o}{12} \cdot (e^{2.0} - 1) = 0.53 \times D_o$$

If the excursion occurred at the end of the irradiation time, the total dose is $5.53D_o$ or about 10 percent higher than the anticipated dose.

Case b) - slow rise in power to 120kW during 5 min. irradiation:

1.8 periods = 5 min.

1 period = 2.78 min.

$$D_{excursion} = 2.78 \ (e^{2.78} - 1) \times D_o = 14D_o$$

The dose is approximately fourteen times the anticipated steady dose.

The unrealistic assumptions embodied in both "maximum credible accidents" require emphasis. No mechanism can be foreseen which could lead to the rapid insertion of the total reactivity of the reactor. A single experiment controlling 0.3 o/o reactivity would not allow criticality. Instantaneous removal of the control rods would presumably require a simultaneous explosion at the base of both separate fuel tanks giving a thrust in exactly the right direction for removal of the rods without causing damage to the tanks and consequent loss of moderator. A slow rise in power would be detected outwith the "scram" controls of the reactor. Installed wall monitors in the Reactor Hall produce audible and visual warnings in the Control Room when a pre-set radiation dose-rate is exceeded. Additionally, the clinician and physicist, who remain close to the irradiation position during patient exposure, continuously monitor the radiation levels using portable monitors. It is apparent that the "maximum credible accidents" are certainly highly improbable.

CHAPTER 9: Development and Performance of a Thyroid Monitor of High Sensitivity using a Shadow Shield.

9.1 Introduction:

In the preliminary studies, the prototype monitor was used as no facility existed at the Centre for monitoring the thyroid gland. Since a collimated detector (for example, Belcher et al. 1964) did not appear to have sufficient sensitivity, a shadow-shield thyroid monitor was developed capable of measuring a few millimicrocuries of iodine-128 in a counting-time of ten minutes. Because of the longer half-life of iodine-131 and the similarity of its principal gamma ray energy (0.36 MeV) to that of iodine-128 (0.46 MeV), this isotope was used for all of the preliminary investigations.

9.2 Construction of the Monitor:

The reduction of the background counting-rate of a 3 inch diameter x 3 inch sodium iodide detector in the energy range 0.42 - 0.48 MeV. (pertinent to iodine -128), was investigated with 2 inches of lead close to the crystal and also in the shadow-shield monitor. Tables 9.1 a and 9.1 b are a summary of the results. The monitor was, of necessity, constructed from materials immediately available on site and the final design is shown without the neck-rest in Fig 9.1. Four inch standard lead bricks form a castle, open at the front, around the detector. The detector is "collimated" by two sections of a castle, normally producing a simple cylinderical collimator extending 2.3 inches in front of the crystal face. A "shadow wall" of four inch lead bricks was constructed 20 inches from the crystal face leaving sufficient space for the patient to be seated in front of the detector. Using the criterion that the centre of the crystal face should be in the "shadow" of the wall, Fig. 9.2, the dimensions required for the wall were calculated by elementary geometry to be about 15 inches on each side of the mid-line.

TABLE 9.1.A

Shield Condition	cpm in range 0.42-0.48 MeV	o/o unshielded counting rate
1. Unshielded	522	100
2. Castle pieces only around X tal.	210	40
3. In 4" lead castle with "Collimator"	50.1	9.6
4. As 3 with shadow-wall.	22.4	4.3

TABLE 9.1.B

Reduction of Background Counting-Rate (0.3 - 0.42 MeV). with size of Shadow - Wall and 4 inches collimation.

Shadow Wall Condition	Background Counting-rate (cpm)
1. Square of 4 lead bricks 4" thick - 4" on each side of crystal axis.	76.9
2. Square of 16 bricks - 8" on each side of crystal axis	48.7
3. Square of 36 bricks - 12" on each side of crystal axis.	49.7
4. Square of 64 bricks - 16" on each side of crystal axis	45.0

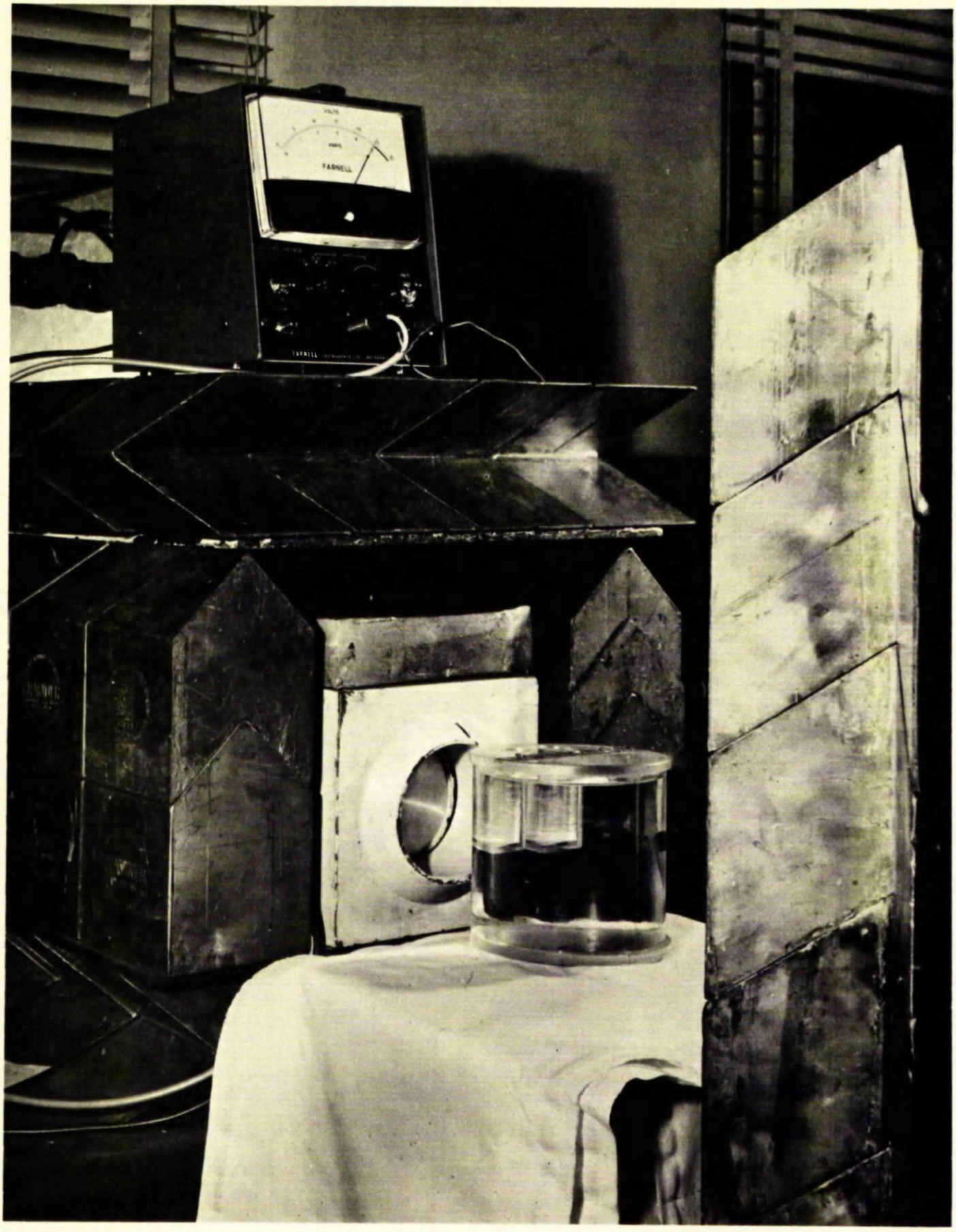
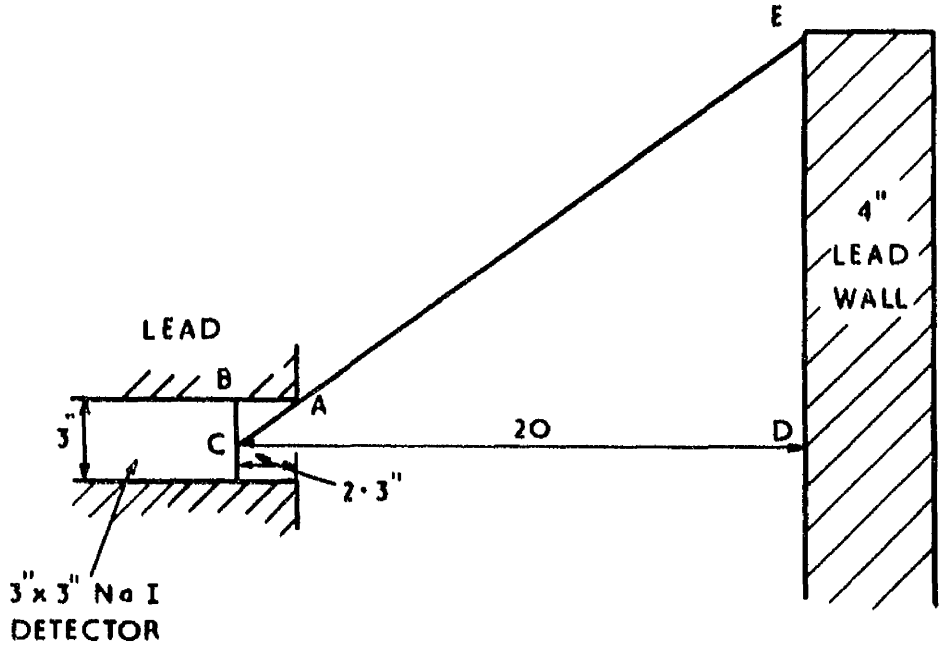


Fig. 9.1. Shadow-shield Thyroid Monitor

Fig. 9.2.

SCHEMATIC PLAN OF THYROID MONITOR



AB = 2·3"
BC = 1·5"
CD = 20"
BY SIMPLE GEOMETRY,
ED = 13" APPROX.

This calculation is clearly a gross over-simplification but seems justified by its effectiveness in practice (Tables 9. a and 9.b)

9.3 Performance of the thyroid monitor:

The total error in measurements arise from geometrical or positional variations and the counting statistics.

a) Geometrical variations:

i) Along the main axis of the crystal:

Ampoules containing 0.68 μc of iodine - 131 were placed in a neck phantom at distances of $3\frac{1}{4}$ inches to $10\frac{1}{4}$ inches from the crystal face. The counting-rate in the region of the 0.36 MeV photopeak was determined for each position, using a T.M.C. 401 pulse height analyser. The results are summarised in Table 9.2 and shown graphically as percentages of the counting-rate at $3\frac{1}{4}$ inches from the crystal in Fig. 9.3. If it is assumed in the first instance that the geometrical uncertainty on this axis due to individual differences in the location of the gland or to patient positioning is approximately $\pm\frac{1}{2}$ inch, then the percentage variations may be roughly estimated by taking the difference from the mean of adjacent results. This has been effected in the penultimate column of Table 9.2.

ii) At right angles to the main axis of the crystal:

The location of the gland may vary from person to person across the neck as well as in depth. Variations in the horizontal plane through the crystal axis were investigated using a single ampoule of iodine - 131 at various angles and distances with respect to this axis (or reference line).

The results, expressed as percentages of those on the reference line at the same perpendicular distances from the crystal face, are summarised in Table 9.3 and shown graphically in Fig. 9.4. If it is arbitrarily assumed that this variation may be represented by the variation of the counting-rate of a point source at $1'' \pm \frac{1}{2}''$ from the crystal axis, the variations given in Table 9.2 may be computed.

TABLE 9.2

istance (inches) rom crystal face	Net cpm	Mean ±	Variation o/o	Sensitivity (uc) in 10 min. count
$3\frac{1}{4}$	18321			2.9×10^{-4}
		15449 ± 2872	± 18.6	
$4\frac{1}{4}$	12577			4.2×10^{-4}
		10885 ± 1692	± 15.6	
$5\frac{1}{4}$	9193			5.8×10^{-4}
		8123 ± 1070	± 13.2	
$6\frac{1}{4}$	7052			7.5×10^{-4}
		6316 ± 736	± 11.6	
$7\frac{1}{4}$	5579			9.5×10^{-4}
		5062 ± 517	± 10.2	
$8\frac{1}{4}$	4544			1.2×10^{-3}
		4127 ± 417	± 10.1	
$9\frac{1}{4}$	3709			1.4×10^{-3}
		3395 ± 314	± 9.3	
$10\frac{1}{4}$	3081			1.7×10^{-3}

VARIATION OF COUNTING RATE ALONG CRYSTAL AXIS

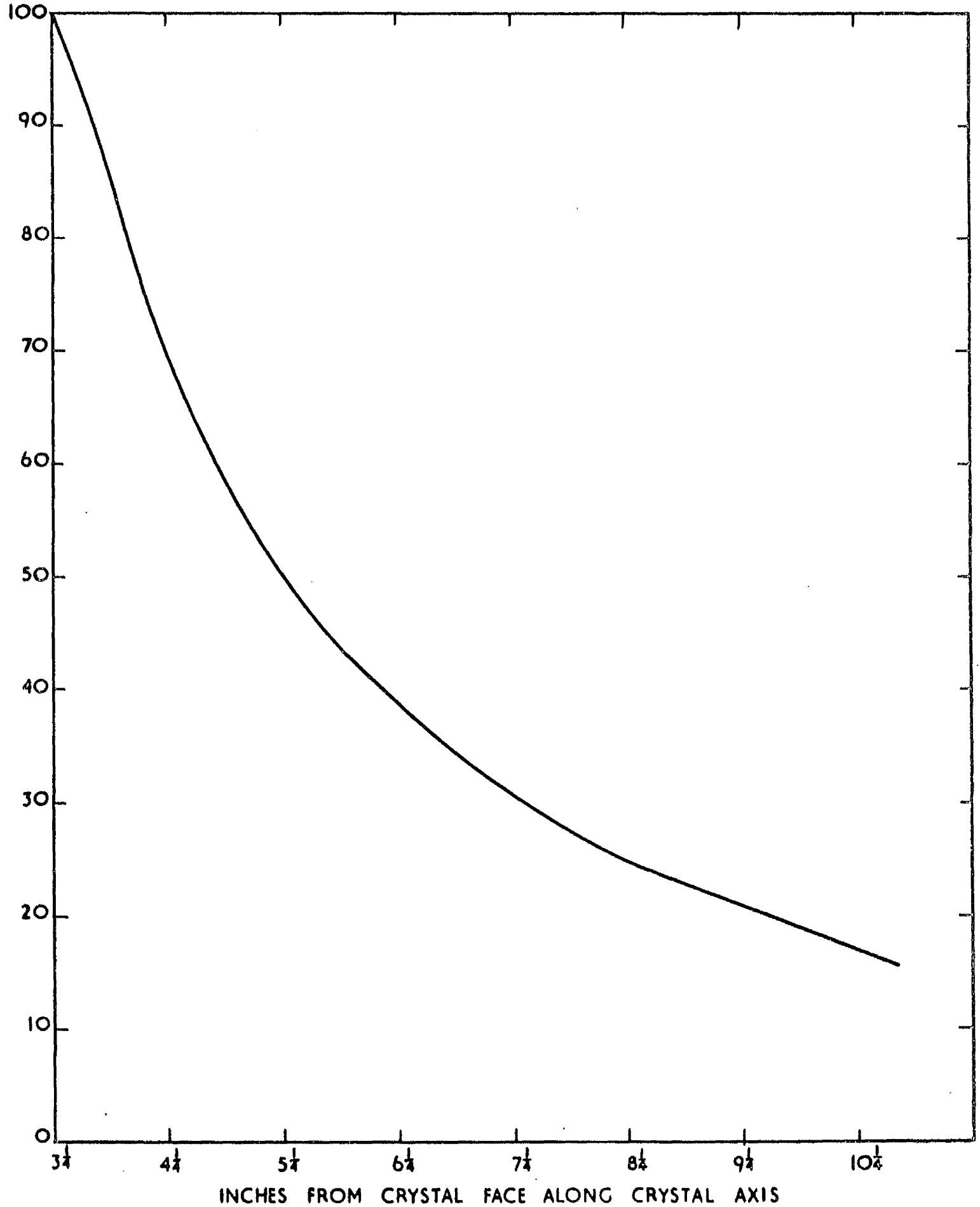


TABLE 9.3

Angle with respect to crystal axis (degrees)	Percentage of counting-rate on crystal axis at same perpendicular distance from crystal face.
8.0	100
11.5	100
16.0	95.5
24.0	80
30.0	52.5
34.0	30
39.0	12.5

Fig. 9.4.a.

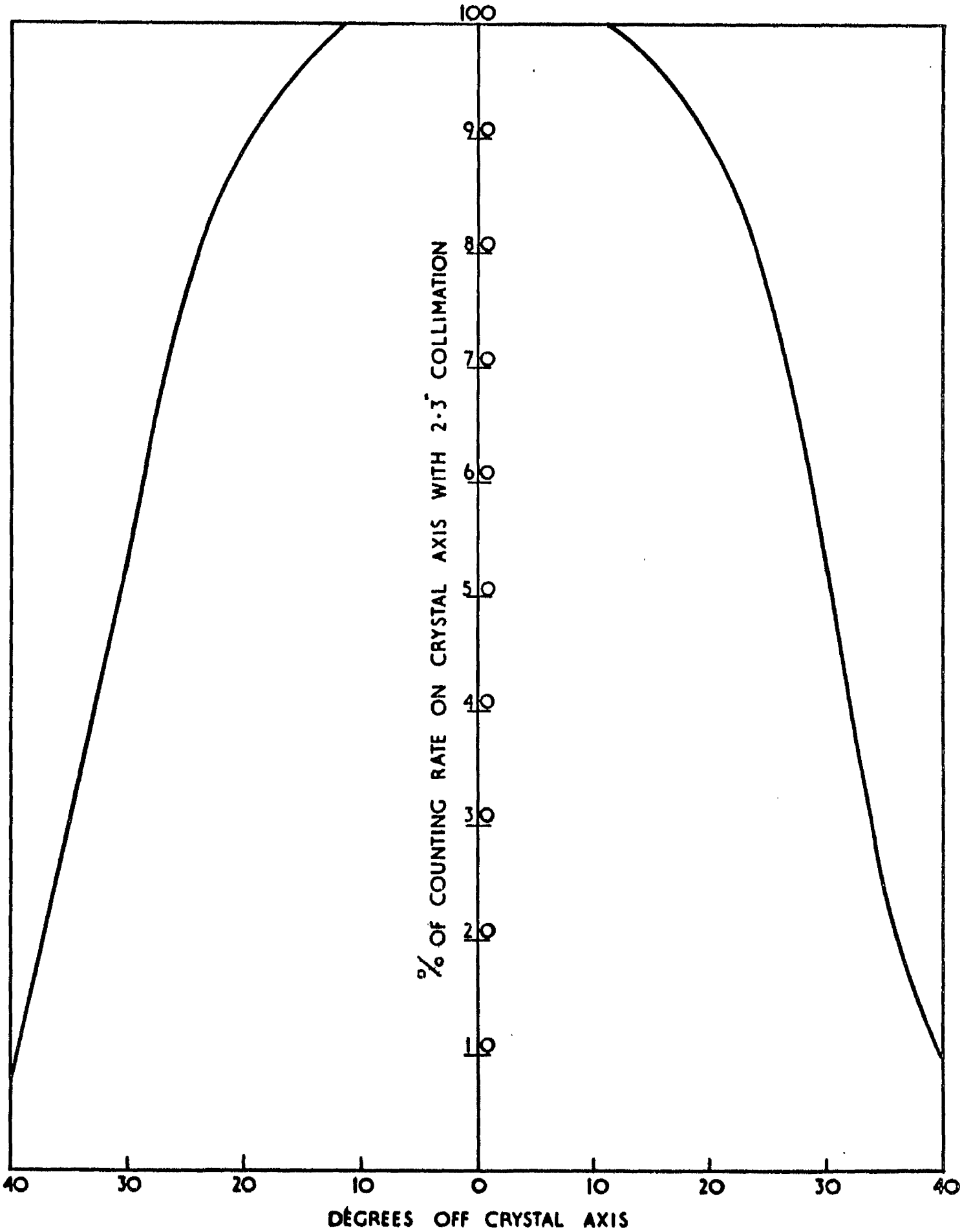
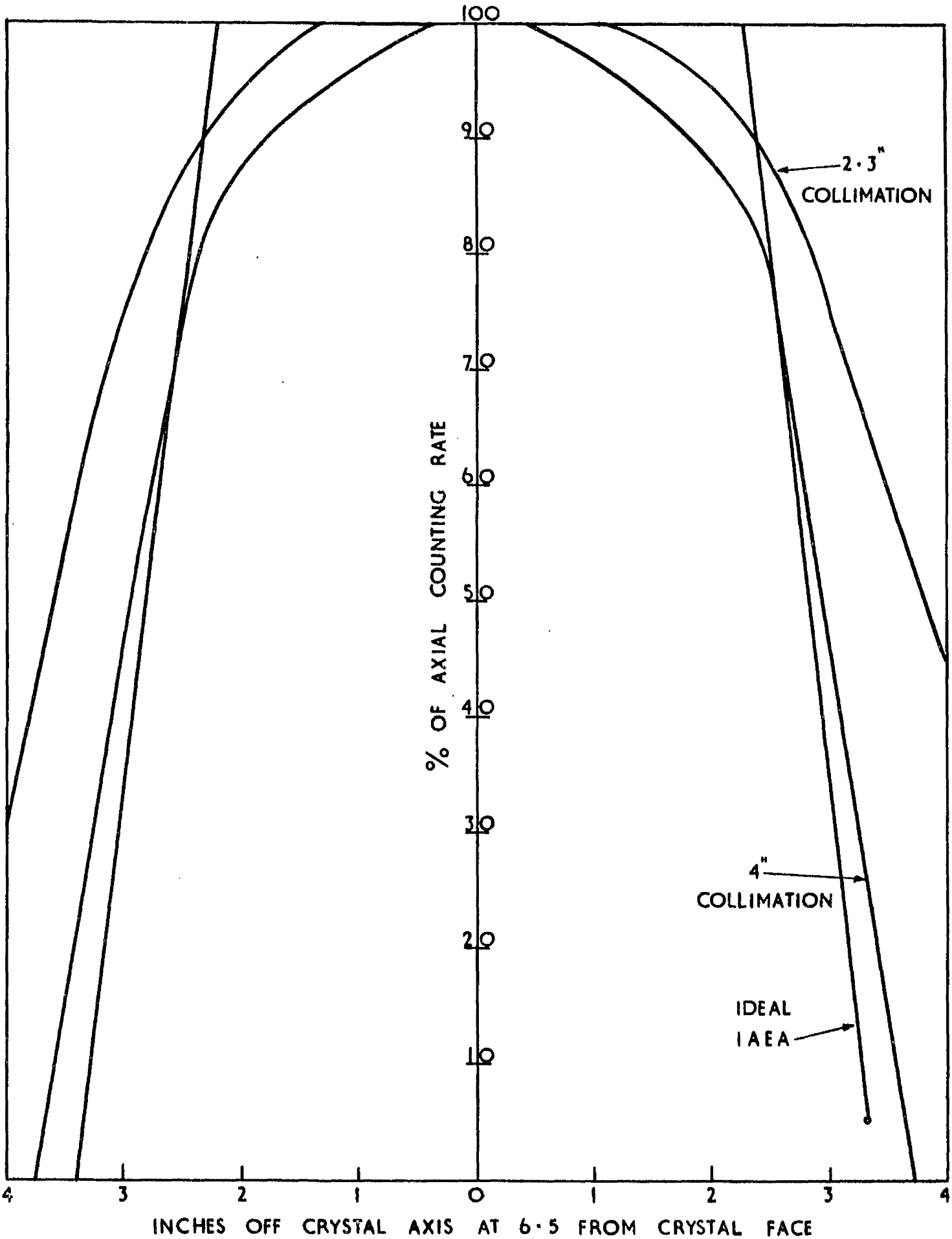

100
90
80
70
60
50
40
30
20
10
% OF COUNTING RATE ON CRYSTAL AXIS WITH 2·3° COLLIMATION
40
30
20
10
0
10
20
30
40
DEGREES OFF CRYSTAL AXIS

Fig. 9.4.b.


100
90
80
70
60
50
40
30
20
10
% OF AXIAL COUNTING RATE
2·3" COLLIMATION
4" COLLIMATION
IDEAL
IAEA
4
3
2
1
0
1
2
3
4
INCHES OFF CRYSTAL AXIS AT 6·5 FROM CRYSTAL FACE

b) Sensitivity:

The sensitivity of a counting system may be defined as the activity of a given isotope which produces a count equal to three times the standard deviation of the background count recorded in the same counting-time (Trott 1965). For iodine-131, taking an energy range of 0.30-0.42 MeV, the background-rate was 67 counts per minute. Using the data presented in Table 9.2 and assuming a counting-time of 10 minutes, the sensitivity at each distance from the crystal face may be calculated. The results are given in the final column of Table 9.2.

9.4 Discussion:

The variation with distance from the crystal face (Table 9.2) is largest, as might be anticipated, at the closer distances. At working distances of about 5 3/4 inches and greater, the reduction in variation with distance is scarcely sufficient to off-set the loss of sensitivity. The variation reduces only from about 13.2o/o to 9.3o/o while sensitivity worsens by a factor of 3. Variation off the crystal axis at each distance is smaller than that along the axis, presumably due to the crystal diameter of 3 inches and "nominal" collimation. At 4 inches from the crystal face the "off-axis" variation is only 5.3 o/o decreasing to zero at just over 6 inches. A working distance of 6.5 inches was chosen as the best compromise.

The performance of the monitor may be compared with the recommendations of a Consultants' Meeting on the Calibration and Standardization of Thyroid Radioiodine Uptake Measurements to the I.A.E.A. (Int. of appl. Rad. Isotopes 13,167 (1962). The visual field, defined as the region within which the counting-rate from a point source of I^{131} does not fall below 90 per cent of the value recorded at the centre of the field if the point source is moved at the working distance, should be preferably 12 and certainly not greater than 15 cm.in diameter in adults and proportionately smaller in children (3.2.1). The counting-rate of the monitor falls to 90 o/o at 20° off the crystal axis and a visual field 12 cmx in diameter can be shown by simple geometry to

coincide with the chosen working distance of 6.5 inches. Although this recommendation is satisfactorily met, the counting-rate at this working distance does not decrease beyond the edge of the visual field as rapidly as suggested in the recommendations. At 1.2 and 1.4 times the radius of the visual field, the counting-rate has fallen to only about 81 o/o and 65 o/o respectively compared with the recommended values of 50 o/o and 5 o/o. This is of minor importance in the in vivo studies where neutron irradiation is confined almost entirely to the thyroid gland by collimation of the beam and extrathyroidal iodine - 128 is unlikely to make a significant contribution.

If the specific activity of iodine-128 induced in the gland is about 2 mμc/mg of iodine (Section 8.2.1) then the sensitivity of the monitor for iodine-128 can be roughly estimated by assuming identical detection efficiency for the principal gamma rays of iodine-131 (0.36 MeV) and iodine-128 (0.46 MeV). The sensitivity (μc) for iodine-128 can then be obtained by multiplying the appropriate iodine-131 sensitivity in Table 9.2 by the ratio of the respective gamma-ray percentage yields per disintegration (viz 80 o/o 17o/o = 4.7). The sensitivity in milligrams of iodine is then: $\frac{4.7 \times \text{Sensitivity of iodine-131 (Table 9.2)(mμc}}{2\ (\text{mμc/ mg.I})}$

At about 6 inches from the crystal face, the corresponding sensitivity is about 1.5 mg. iodine. This is worse than the prototype monitor by about a factor of 2 but is about 12 times more sensitive than the diagnostic uptake monitor (Shimmings, J., Private communication) routinely used in the hospital. Reproducibility, with respect to the patient-crystal geometry, could be checked more readily than with a detector of the same size in the prototype whole-body monitor. The better sensitivity of the latter makes it the method of choice, particularly with a large diameter detector where axial alignment is much less critical, but, in view of whole-body monitoring committments, its availability was limited. The shadow-shield thyroid monitor was consequently used for the preliminary clinical trials.

CHAPTER 10: Clinical Trials of In Vivo Activation Analysis of Iodine in the Thyroid Gland and Modifications of the Technique from the Experience Gained.

10.1 Introduction:

A preliminary series of clinical trials has been conducted to examine the feasibility of the technique in practice and to ascertain the problems remaining. Eleven patients with non-toxic goitre have been examined and the results compared with those from in vivo measurements of exchangeable iodine using the method of Nodine et al, (1957), in vitro activation measurements on the same gland following thyroidectomy and biochemical analysis of the excised gland.

10.2 Methods and Materials:

a) Analysis of data:

As discussed in Chapters 1 and 8, neutron irradiation is not specific in the sense that only the element(s) of interest is rendered radioactive. Experience from the preliminary experiements suggested that the principal interfering isotopes, produced incidentally, are sodium-24 and chlorine-28. To determine the amount of iodime present in the gland involves solving an equation of the form:

$$\text{T.I.I. (mg)} = \frac{1}{\bar{K}} \left(\Sigma \text{ I-128} - f_{I/Cl} \left(\Sigma \text{ Cl-38} - f_{Cl/Na} \Sigma \text{Na - 24} \right) - f_{I/Na} \Sigma \text{ Na - 24} \right)$$

where T.I.I. = Total intrathyroidal iodine (mg).

$\bar{K}$ = cpm/mg. of iodine.

Σ x = Integrated net counting-rate (cpm) in photopeak of isotope X

$f_{y/x}$ = Fractional Compton scatter coefficient of isotope X in photopeak of isotope y.

viz. $f_{y/x} \Sigma$ x = Compton contribution of isotope x to the photopeak energy region of isotope y.

Clearly, if other isotopes also make a significant contribution in the iodine - 128 photopeak region, further corresponding terms must be included.

b) Experimental procedure:

The irradiation situation described in section 8.3 and the shadow-shield thyroid monitor (chapter 9) were used. A five inches diameter x five inches detector, kindly loaned by Quartz et Silice, Paris, was available for part of the trials.

For all patients, but the first, an initial background count of 10. min. duration was made, which permitted adjustment of the chair height to align the thyroid gland of the individual patient with the neck-rest (crystal mid-line) and which ensured that the gland does not contain residual iodine-131 from uptake or similar tests. The short half-life of iodine-128 (25 min) and the small quantity of iodine-128 induced imply that preparations and adjustments such as these should be as complete as possible before irradiation.

Following the background measurement, a small gold foil was attached by adhesive tape to each side of the neck over the estimated position of each lobe of the thyroid. The neutron dose was estimated by counting the foils in a low-background beta counter. Irradiation times of five minutes at a reactor power of 20 kW were used. The monitoring foils were removed after irradiation and from 1 to 3 measurements were made of the induced radioactivity. A standard sample, containing a known amount of iodine, and others containing sodium carbonate and ammonium chloride, were irradiated and monitored in an identical manner. The iodine content of the excised glands of three patients has been estimated by biochemical analysis and, on two of these glands, by in vitro activation analysis.

It was assumed, for the first patient that her background counting rate would be closely similar to that of careful phantom measurements and, in view of other circumstances, this initial measurement was dispensed with. That the assumption was erroneous

became obvious in the first post-irradiation measurement when a small amount of residual iodine-131 could be detected which obscured the iodine-128 contribution after the first measurement. A rough estimate of the total iodine content of the gland could still be made as shown in Table 10.1.

The in vivo results for eight of the patients are presented in Table 10.2 along with estimates of the exchangeable iodine using Nodine's method, or of the total iodine content from biochemical analysis of the gland following thyroidectomy.

Table 10.3 is a summary of the in vivo activation analysis measurements for the two remaining patients, the in vitro activation analysis measurements on the glands following thyroidectomy and the results of biochemical analysis on the excised glands.

10.4 Discussion:

a) Comparison of activation analysis measurements with those using other methods and the possible significance of differences in the results:

The estimated range of the iodine content of the thyroid gland was suggested (see 8.2.4) as about 0.9 - 22.6 mg. The results of in vivo activation analysis all fall within these limits (range 2.8 - 14.4 mg).

With the exception of patient B, all of the activation analysis results are greater than those from Nodine's method. This is to be expected since the present method measures the total iodine content while that of Nodine measures only the exchangeable iodine. Further the ratio of total to exchangeable iodine is not constant which, if this finding is confirmed, implies that the measurement of exchangeable iodine gives no information relating to the total iodine content. The assumption of a mean level of intrathyroidal stores is clearly not justified so that the iodine-131 uptake test would appear to be entirely empirical, at least in the present patients.

The in vivo and in vitro activation analysis results for patients

TABLE 10.1

Time after irradiation mins.	Iodine-131 photopeak cpm.	Iodine-128 (0.40 - 0.52 MeV) cpm	Rationalised Iodine - 128 cpm	Net Iodine-128 cpm	K cpm per Mg. I
3.5	8290	858	858	58	11.8
27	9130	876	795	-	
52	8520	826	804	-	

Assuming iodine-128 contribution is negligible in the second and third measurements, then the variation is due to geometrical errors. The iodine-128 counting-rates can be rationalised to the initial iodine-131 counting-rate. The "Background" counting-rate in the iodine-128 photopeak is taken as the mean of the second and third rationalised results (= 800 cpm). Then, Iodine content = 5 mg. approx.

Patient	Pre-irradiation Background (cpm)			Post-irradiation Gross cpm.			K cpm/ mg. $\bar{I}$	$f_{I/Na}$	f cl/ Na	fI/ Cl	In vivo $I_{\approx}$ content mg$^{\approx}$	$I_{\approx}$ content (mg) from other method $\neq$
	I	Cl	Na	$\bar{I}$	$\bar{Cl}$	$\bar{Na}$						
a) 3" x 3" detector:												
M 1st	88,4	6.3	2.0	153.7	63.3	50.6	5.04	0.641	0.373	0.443	3.4	
(t + 24) 2nd	88.4	6.3	2.0	120.5	34.3	28.2	5.04	0.641	0.373	0.443	2.8	0.09^{N}
(t + 45) 3rd	88.4	6.3	2.0	111.0	21.4	24.3	5.04	0.641	0.373	0.443	3.7	
R	87.4	7.3	3.1	166.4	62.1	46.1	5.04	0.641	0.373	0.443	6.4	0.86^{N}
McI.	83.1	5.5	2.0	176.9	70.7	54.9	5.04	0.641	0.373	0.443	7.9	3.45^{N}
b) 5" x 5" detector:												
C^{x}	286.0	103.5	165.3	718.7	469.6	712.2	14.7	0.526	0.504	0.238	10.4	5.66^{N}
B^{x}	260.7	90.9	138.8	672.0	556.5	861.2	14.7	0.526	0.504	0.238	3.0	6.3^{N}
H 1st	217.4	50.5	22.8	513.6	206.8	246.2	14.7	0.78	0.45	0.51	2.9	
(t + 25) 2nd	202.0	32.4	11.1	338.1	108.0	147.0	14.7	0.78	0.45	0.51	3.1	2.3^{N}
Mic.	340.5	55.7	39.0	534.4	159.4	120.8	14.7	0.78	0.45	0.51	6.5	3.34^{B}
W 1st	343.2	64.6	43.9	608.9	133.1	123.0	14.7	0.78	0.45	0.51	12.8	2.8^{N}
(t + 25) 2nd	166.7	10.8	6.4	274.7	41.3	43.5	14.7	0.78	0.45	0.51	13.6	

$\neq$ N = Nodines' method,
B = Biochem analysis.

x Different energy ranges for Compton scatter coefficients.

$\approx$ Corrected for gold foil count (= integrated neutron flux) relative to foil count for phantom.

TABLE 10.3

Comparison of in vivo and in vitro activation activation analysis with biochemical analysis.

Patient	Pre-irradiation background (cpm)			Post-irradiation Gross cpm			K cpm/ mg.I.	$f_{I/Na}$	$f_{Cl/Na}$	$f_{I/Cl}$	In vivo I content mg ※	In vitro I content mg.	Biochem analysis mg.
	I	Cl	Na	≷I	≷Cl	≷Na							
Ha 1st	400.1	28.4	17.0	742.2	134.1	153.3	20.1	0.78	0.45	0.51	15.8	13.5	8.3
t+ 16½ min	365.8	21.4	12.5	579.6	94.7	110.0	20.1	0.78	0.45	0.51	15.5	10.4	7.8
2nd													
3rd												13.2	
Cr 1st	393.2	31.1	22.4	938.6	270.7	244.1	20.1	0.78	0.45	0.51	14.4	7.1	8.3
t + 17½ min	354.9	20.5	18.6	625.7	146.3	143.1	20.1	0.78	0.45	0.51	10.7	9.8	8.3
2nd													
t + 34 min	354.9	20.5	18.6	541.5	110.1	117.3	20.1	0.78	0.45	0.51	10.6	8.5	
3rd													

※ corrected for gold foil count (integrated flux)

Patient Ha: $\frac{\text{phantom foil (cps/mg)}}{\text{patient foil (cps/mg)}} = 1.54$ (see text)

Patient Cr: $\frac{\text{phantom foil (cps/mg)}}{\text{patient foil (cps/mg)}} = 0.97$

Patient Ha; mean values: in vivo = 16.2 mg.I
in vitro = 12.4 mg.I
Biochem = 8.1 mg.I

Patieng Cr; mean values: in vivo = 11.6 mg. I
in vitro = 8.5 mg. I
Biochem = 8.3 mg. I.

G and Ha (Table 10.3) are in good agreement bearing in mind that about 75 - 90 o/o of the gland is removed in thyroidectomy. Consequently, the in vitro activation analysis result and that of biochemical analysis should always be proportionately less than the in vivo result. The foil correction factor is unusually large for patient Ha but this was not entirely unexpected as the patient was known to have moved during irradiation. Nevertheless, the in vivo result is compatible with the in vitro estimates on the excised gland. Excellent agreement was obtained between the in vivo, in vitro and biochemical analysis results for patient G. The agreement between the results of in vivo activation analysis and biochemical analysis is reasonable also for patient Mic. (Table 10.2) since, again, the complete gland was not removed. Although the results of both activation methods are in good agreement for patient Ha, biochemical analysis produced significantly smaller estimates which were mutually in excellent agreement. The possible reasons for this discrepancy have been investigated.

b) Experimental difficulties and sources of error:

If biochemical analysis underestimates the iodine content, the two most probable explanations might be incomplete oxidation of the tissue so that all of the iodine is not liberated or iodine losses in dilution, etc. Both causes have been examined with negative findings, although an additional oxidation stage produced an increase in one result of about 7 o/o.

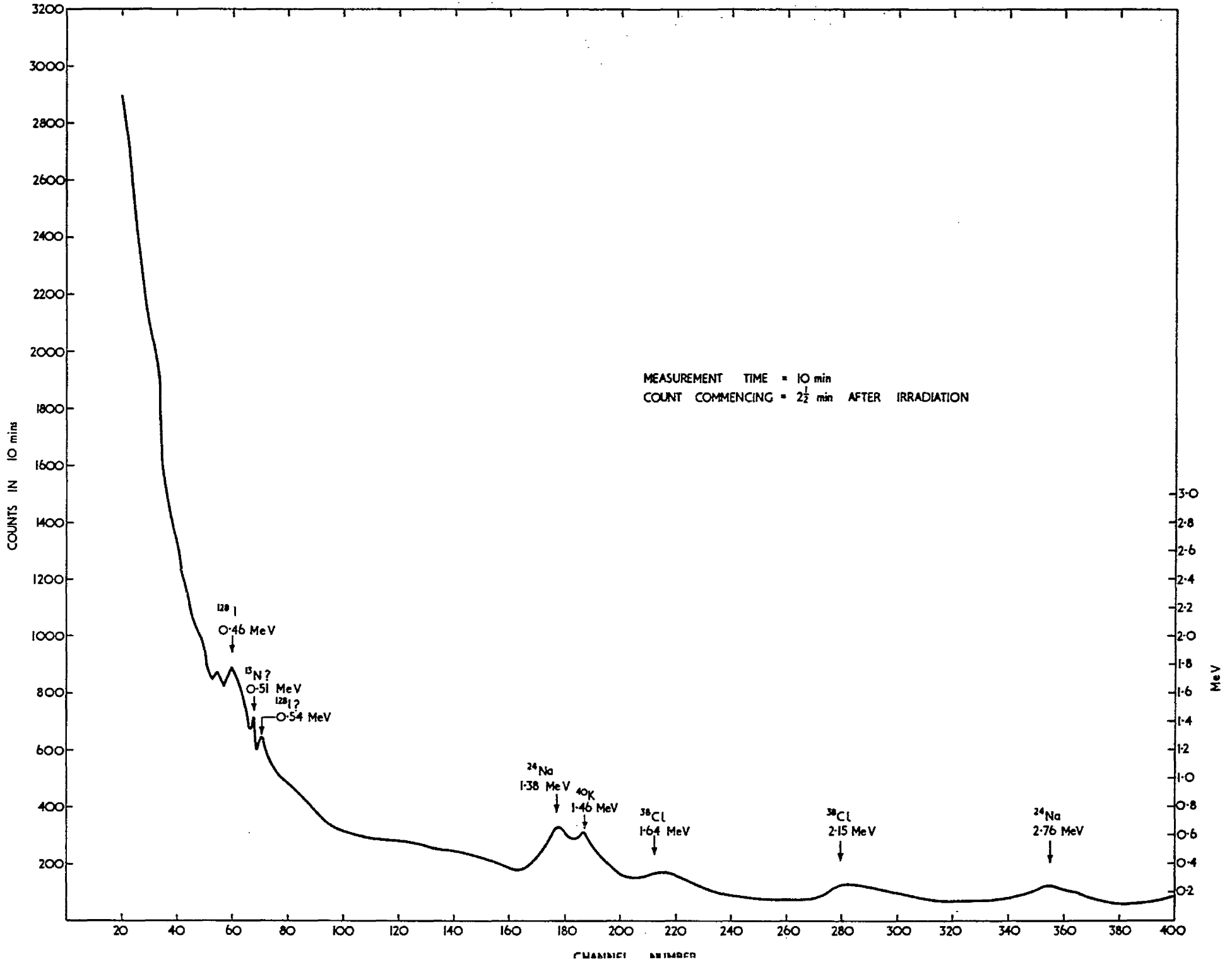
Experience with the in vivo activation analysis technique showed that the effect of the emergent beam and residual radiation from the central vertical stringer of the reactor on the monitor background was more pronounced than when using the horizontal beam tube. This may be accounted for almost entirely by the absence of a beam trap which would have been difficult to arrange and would have increased the patient dose because of back-scatter. The conditions were examined for each in vivo measurement to determine the appropriate background counting-rate as far as possible.

The advantage of the higher counting-rates obtained with the 5 inches x 5 inches detector was off-set to some extent by gain drift shown to be associated with the photomultiplier. Since the principal photopeak of iodine-128 has an energy of 0.46 MeV which is close to the annihilation peak at 0.51 MeV, gain stability is very important and merits even more attention than it received in the present studies.

The interference of sodium-24 and chlorine-38 was not a serious problem but it was clearly a source of error which could be diminished if the quantities of these isotopes could be reduced (see 10.5).

The estimated quantities of total iodine appear too great from in vivo measurements compared with biochemical analysis. Standards were checked for reproducibility. The gland was unlikely to have smaller dimensions than the ampoules used for the standards and comparison with the excised glands confirmed this conclusion. Neutron flux depression due to self-shielding would consequently be less for the standard and should lead to an under-estimate rather than an overestimate of the iodine content. Positioning of the phantom containing the standard in the emergent collimated beam could obviously be achieved more precisely and easily than could the patient's gland. A reduced neutron exposure of the patient's gland, however, would again yield an underestimate of its iodine content. Similarly, positioning of the patient at the monitor would lead to a low value. The only likely cause of an over-estimate of the gland's content appears to be contributions in the iodine-128 photopeak from incidental isotopes apart from sodium-24 and chlorine-38 for which allowance is already made. The gross spectrum of patient H is shown in Fig. 10.1 and inspection has failed to suggest what, if any, other isotopes may be contributing significantly. At the present time, no single factor can be cited as the principal cause of the difference in the estimates from the activation and biochemical analyses.

10.5 Subsequent improvements in the technique:


COUNTS IN 10 mins
MeV
CHANNEL NUMBER
MEASUREMENT TIME = 10 min
COUNT COMMENCING = 2½ min AFTER IRRADIATION
128 I
0·46 MeV
13N ?
0·51 MeV
128I ?
0·54 MeV
24Na
1·38 MeV
40K
1·46 MeV
38Cl
1·64 MeV
38Cl
2·15 MeV
24Na
2·76 MeV

a) Reduction of the post-irradiation dose-rates:

A lead plug has been specially designed and constructed to fit the collimator. The plug, some eight inches deep, can easily be inserted, using the reactor crane, during the transit time of the patient to the monitor.

b) Modification of the neutron spectrum:

Examination of the variation of the iodine-127 neutron capture cross-section with neutron energy shows that large resonances occur between about 0.1 eV and 100 eV which presumably make a highly significant contribution to the total iodine-128 produced on irradiation. Sodium and chlorine cross-sections do not have equivalent resonances and the majority of induced sodium-24 and chlorine-38 is due to neutrons in the thermal energy region. A simple method of modifying the neutron spectrum to take advantage of the differences in cross-section behaviour appeared to be that of introducing an absorber, such as cadmium or boron, which is "black", or has a huge capture cross-section, for neutrons of thermal energies but for which the "cut-off", or fall in cross-section, is extremely rapid at about 0.1 eV. Studies have been carried out to test the effectiveness of this procedure.

Standard samples containing iodine or sodium or chlorine were prepared. A standard of each element was irradiated, using the collimator, by the unmodified neutron spectrum and then with a cadmium absorber in the beam and then a boron absorber. The counting-rates, in the appropriate photopeak energy ranges, were measured using the shadow-shield thyroid monitor. The results are summarised in Table 10.4.

It can be seen that, as predicted, the amount of iodine-128 induced is affected much less significantly than the amounts of chlorine-38 and sodium - 24 which are reduced to about 10 - 20 o/o of the amounts produced using the unmodified spectrum. If the "advantage factor" for each absorber is assumed to be the counting-

TABLE 10.4

Isotope	Net cpm in photopeak for absorber:			Percent of unmodified counting-rate		Advantage Factor I o/o / X o/o.	
	None	Cd	B	Cd	B	Cd	B
^{128}I	4367	3287	2702	75	62	-	-
^{38}Cl	1822	332	207	18	11	4.1	5.9
^{24}Na	1974	311	241	16	12	4.8	5.2

rate of iodine-128 expressed as a percentage of the counting-rate with the unmodified spectrum divided by the equivalent percentage for each of the other isotopes, then boron is slightly better than cadmium but it also reduces the iodine-128 counting-rate to a greater extent. This latter feature needs careful consideration since it involves a greater sacrifice in sensitivity. In view of the promise of this procedure, its effect on the neutron spectrum, and hence the radiation doses, was examined using threshold detectors (Dennis, J.A., 1964). The results are summarised in Table 10.5 with the corresponding neutron doses. The thermal neutron flux is reduced to a negligivle level with cadmium and boron absorbers in the emergent beam. However, the total neutron dose is not greatly reduced. Excellent agreement was obtained with the threshold detector measurements of neutron dose and confirmatory measurements using a REM counter (Anderson, I.O. and Braun, 1963). This counter reads in rem units using protracted low-level R.B.E.s. At a reactor power of 100 watts and with boron or cadmium in the beam, the corrected dose-rate was 0.83 rem/hr. The corresponding integrated dose for a five minute exposure at 20 kW is 13.8 rem.

c) Monitoring technique:

In response to a grant application, the Hospital Endowments Research Trust has kindly agreed to provide a sodium iodide detector assembly 11½ inches diameter x 4 inches for the prototype monitor. Consequently, the monitoring time per patient will be reduced. If the availability of MERLIN off-sets the anticipated increase in the body-monitoring programme of the prototype monitor, then it should be possible to utilise the monitor in the in vivo activation analysis studies also. In anticipation, preliminary measurements were made using MERLIN. With the monitor in the scanning-bed geometry and the detector protruding through the steel plate (by 1 3/4 inches), a lead wall was constructed across the monitor to reduce the background counting rate. Standards containing 10 mg., 5 mg., and 1 mg., of iodine were irradiated and monitored. The mean counting-rate per milligram of iodine was 28 cpm/mg. and the background

TABLE 10.5

Spectrum Condition	Neutron Energy Region	Flux $n.cm^{-2}$ sec^{-1} at 20kW	Integrated flux (n: cm^{-2}) 5 min at 20 kW	Rad dose	Protracted R.B.E. dose (rem)	Acute R.B.E. dose (rem)
1. Unmodified	Thermal	7.4×10^{6}	2.2×10^{9}	0.14	0.52	0.28
	Intermediate	1.2×10^{7}	3.6×10^{9}	1.28	8.96	2.56
	Fast	6.6×10^{5}	2.0×10^{8}	0.72	5.76	1.44
			Total =	2.14	15.24	4.28
2. Cd. absorber	Thermal	8.3×10^{4}	2.5×10^{7}	1.1×10^{-3}	3.3×10^{-3}	2.2×10^{-3}
	Intermediate	1.2×10^{7}	3.5×10^{9}	1.25	8.75	2.5
	Fast	5.0×10^{5}	1.5×10^{8}	0.55	4.4	1.1
			Total =	1.80	13.15	3.6
3. B. absorber	Thermal	Nil	Nil		Nil	Nil
	Intermediate	8.0×10^{6}	2.4×10^{9}	0.90	6.3	1.8
	Fast	7.0×10^{5}	2.1×10^{8}	0.75	6.0	1.5
			Total =	1.65	12.3	3.3

counting-rate was about 190 cpm. The sensitivity (Trott, 1965) for a counting-time of 10 minutes is then about 0.46 mg. of iodine. This is significantly better than the thyroid monitor and, with the larger detector, off-axial reproducibility should not prove to be a problem.

10.5 Summary:

The preliminary clinical trials have shown the feasibility of the technique and significant improvements have been made in the light of this experience and subsequent experimentation. With delivery of the second large detector, further in vitro measurements on excised glands followed by biochemical analysis are proposed. The cause(s) of the small, but significant, difference observed in the iodine content as estimated by the two methods may then be apparent or eliminated. Satisfactory conclusion of these investigations will be followed by the clinical application of the technique.

APPENDIX I

A.1 Introduction:

Elementary theoretical calculation of the initial MERLIN shielding.

The construction and performance of the prototype monitor led to the conclusion that the shield weight was excessive as the final stages of the base and walls provided little further reduction in the background counting-rate. It was apparent that the shielding in the vicinity of the detector was of principal importance. A fairly complicated and rigorous theoretical treatment, aimed at optimising the shield for MERLIN seemed scarcely justifiable in view of the experimental approach for the prototype shield and the amount of data, and possibly computer time, likely to be needed in a sophisticated analysis. Consequently, a highly approximate, but reasonably effective, "line of vision" analysis was developed the fundamental assumptions of which were that the centre of the detector face could "see" incoming gamma rays only after their passage through the chosen thickness of lead and that, secondly, gamma rays reaching the detector travelled in straight lines to do so. The first assumption is clearly a gross oversimplification of the conditions in which an optimum is approached while the second assumption is strictly applicable only for those gamma rays passing through the shield without being scattered! The principal justification of the analysis is the surprisingly good agreement between the results it yields and those obtained experimentally (for example, Chapter 9, Tables 9.1.A and 9.1.B), while the mathematics it employs are extremely elementary.

The criterion was adopted of an "effective" thickness of lead of 6 inches, with the exception of the turret where the weight increase (from 4 inches thickness) and the complexity of construction were impracticable.

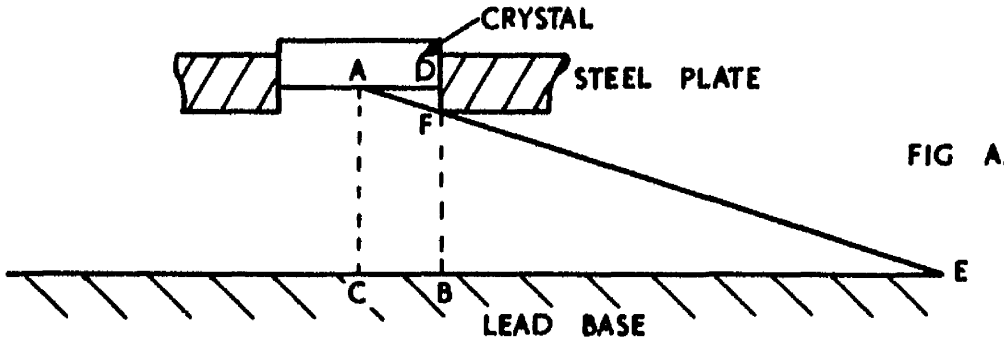


FIG A.1

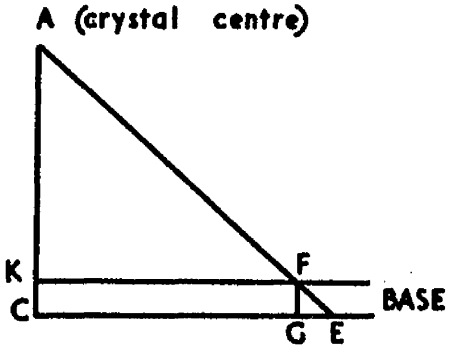


FIG A.2

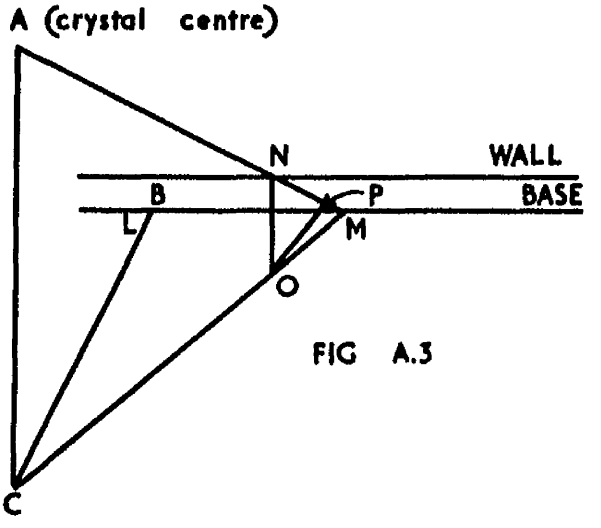


FIG A.3

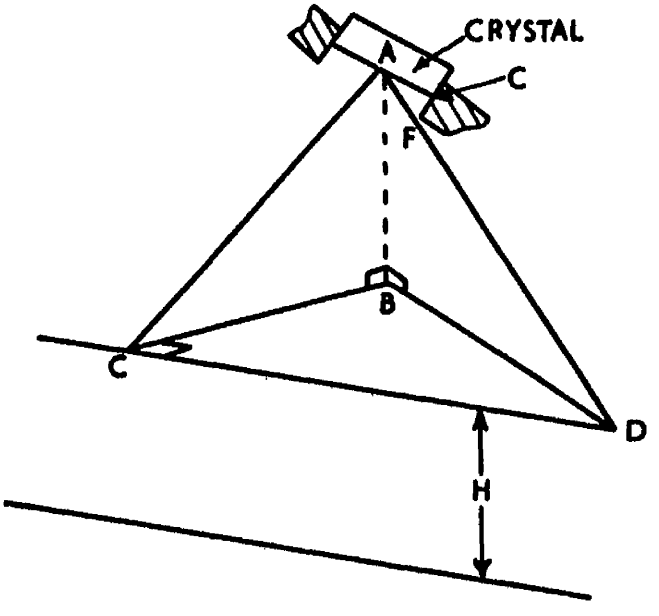


FIG A.4

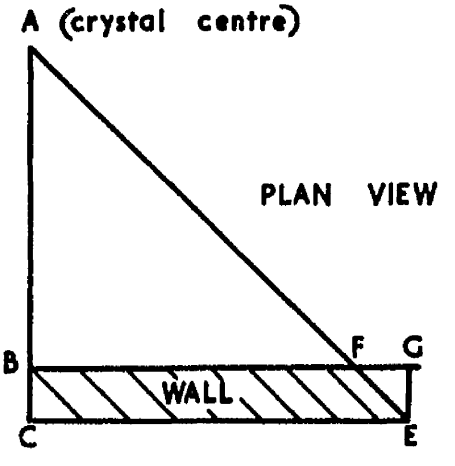


FIG A.5

A.2. Crystal height in steel plate:

The steel supporting plate provides "collimation" or a partial shield. In accordance with above criteria, the height of the crystal face above the base of the steel plate should be such that the centre of the crystal cannot "see" beyond, or is in the "shadow" of the base. This situation is shown schematically in Fig. A.1. Assuming that a lead base of a total length of 12 ft. is adequate, then;

$$CE = 72"$$

$$CB = AD = \text{Crystal radius} = 5.75"$$

$$\therefore BE = 66.25"$$

$$FB = 14" \text{ (as in the prototype monitor)}$$

$$\therefore DF = \frac{FB}{BE} \times AD = \frac{14}{66.25} \times 5.75 = 1.22"$$

Required height above base of steel plate = 1.22".

A.3. Base equivalent to six inches of lead:

Although the actual thickness of the base may be only 4 inches or 2 inches of lead, the "effective" oblique thickness at some distance along the base is 6 inches (see Figs. A.2 and A.3.). The thickness of the base directly beneath the detector must be six inches but at these distances the actual thickness can be reduced to 4 inches and 2 inches thus saving shield weight, while the "effective" thickness is never less than 6 inches.

The limiting positions are i) the centre line of the base and ii) at the outer wall.

i) On centre line of base (Fig. A.2)

AC = Crystal face to floor = 18"

AK = Crystal face to top of base = 18" - 4" or 2".

FG = Base thickness = 4" or 2".

FE = "Equivalent" thickness

KE = Distance at which base thickness can be reduced.

$$GE = (FE^2 - FG^2)^{\frac{1}{2}}$$

$$\text{and } KF = \frac{AK}{FG} \times GE$$

Hence for 4" base, KF = 17"

and for 2" base, KF = 49"

ii) At outer wall (Fig. A.3.)

BC = Half base width = 12"

ON = Actual base thickness (4" or 2")

NM = "Equivalent" thickness = 6"

$$MO = (NM^2 - ON^2)^{\frac{1}{2}}$$

$$CM = \frac{AC}{NO} \times MO$$

$$EM = (CM^2 - BC^2)^{\frac{1}{2}} \text{ and } PM = \frac{MO}{CM} \times EM$$

so that BP = required distance = EM - PM

Hence for 4" base, BP = $14\frac{1}{2}$"

and for 2" base, BP = 48"

This difference between the distances in the two cases is small, amounting to a saving of only about 3 of the four inches standard bricks. To attempt to "stagger" the bricks was, therefore, not considered worthwhile.

A.4. Wall height: (Fig. A.4.)

With the crystal at the calculated height above the base of the supporting plate, the distances for wall heights over which the crystal face centre cannot "see" were computed as follows:

AB = Crystal ht. above top of wall = (19.22 - h")"

EF = Crystal ht. above base of plate = 1.22"

AE = Crystal radius = 5.75"

AC = Half base width = 12"

$$BD = \frac{AB}{EF} \times AE \qquad \text{and } CD = (BD^2 + BC^2)^{\frac{1}{2}}$$

A.5. Wall thickness: (Fig. A.5)

The most pessimistic calculation of the distances at which the path lengths through 4" and 2" wall thicknesses are equal to 6" is made by assuming a constant wall height equal to that of the crystal. All positions of the wall, other than the top, then have an equivalent thickness greater than 6" and the weight difference compared with distances for mid-wall or base of wall are again trivial.

AB = Half base width = 12"

BC = EG = Actual wall thickness = 4" or 2"

FE = Equivalent thickness = 6"

$FG = (FE^2 - EG^2)^{\frac{1}{2}}$

and $BF = FG \times \frac{AB}{GE}$

Thickness	Distance
4"	13.4"
2"	33.9"

A.6. Summary:

The shield based on these calculations is shown diagrammatically in Fig. 3.1. Tenders were requested for this configuration but with maximum flexibility for subsequent modification.

REFERENCES

1. Adams, J.F. 1962, 2nd European Symp. on Vitamin B_{12} and Intrinsic Factor, Hamburg, P.628.

2. Adams, J.F. 1963, Nature, 198, 4876, 200.

3. Adams, J.F. and Kennedy, E.H., 1965, J. Lab. and Clin. Med., 65, 3, 450.

4. Anderson, J., Osborn, S.B. Tomlinson, R.W.W., Newton D., Rundo, J., Salmon, L. and Smith, J.W., 1964, The Lancet, pp. 1201 - 1205.

5. Anderson, I.O. and Braun, J., 1963 Proc. Symp. on Neutron Dosimetry, I.A.E.A. p.87.

6. Belcher, E.H., Gomez-Crespo, G., Trott, N.G. and Vetter, H., 1964, Nuclear Medicine, Vol. IV 1, April.

7. Boddy, K., 1965, Paper VII. 6, Conf. on Low Level Radioactivity Measurements: Limitations and New Techniques, 5-6 July, London.

8. Boddy, K., 1966, Proc. of Seventh Int. Symp. on Radioactive Isotopes in Clinical Medicine and Research, Bad Gastein. (In Press).

9. Boddy, K., 1967, Phys. Med. Biol., 12, 1, 43.

10. Boddy, K. and Adams, J.F. 1967, (In preparation).

11. Bonnett, J.D. Hagendorn, A.B., Owen, C.A. 1960 Blood, 15, 36.

12. Bozian, R.C., Ferguson, J.L. Heyssel, R.M. Meneely, G.R., and Darby, W.J., 1963, Am. J. Clin. Nutr., 12, 117.

13. Brise, H., Hallberg, R. 1962, a Acta Med. Scand. Supp. 376, 23.

14. Brise, H., Hallberg, R. 1962, b Acta Med. Scand. Supp. 376, S9.

15. Burch, P.R.J. and Spiers, F.W., 1953, Nature, 172, 519.

16. Burch, P.R.J. 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A. Vienna), p. 143.

17. Bush, F., 1946, Britt, J. Radiol., January.

18. Cohn, S.H., Lippincott, S.W., Cronkite, E.P., and Reizenstein P.G., I.A.E.A. Symp. on Whole-Body Counting, Vienna, 1962.

19. Cronkite, E.P., Henley, E. Driscoll, D.M. Meyer, L.M., Dohan, F.C., Rubini, J.R. Wollins, W., 1959, Haematol. Latine, 2, 265.

20. Darby, W.J., Jones, E., Clark, S.L., Jr., McGanity, W.J. Dutra de Oliveira, J, Perez, C., Kerany, J. and le Brocquy, J, 1958, Am. J. Clin. Nutrition, 6, 513.

21. Dennis, J.A., 1964, A.E.R.E. - R 4365.

22. Dubach, R., Callender, S.T., Moore, C.U., 1948 Blood 5, 526.

23. Exmans, A.M., Bastenie, P.A., Galperin, H., Beckers, C., van den Schriek, H.G. and de Visscher, M., 1961, J. clin. Endoer, 21, 996.

24. Evans, R.D., Amer, J. Roentgenol, 1937, 37, 368.

25. Fullerton, H.W. 1934 Edinburgh Med. J. 41, 99.

26. Glass, G.B.J., III. J. Lab. and Clin. Med 52, 875, 1958.

27. Glass, G.B.J. Skeggs, H.R., Lee, D.H. Jones, E.L., and Hardy, W.W. 1961, Blood, 18, 511.

28. Glass, H.I., 1965, Private Communication.

29. Grasbeck, R., Nyberg, W. and Reizenstein, P., 1958, Proc. Soc. Exp. Biol. Med., 97, 780.

30. Grasbeck, R., 1959, Scandinav. J. Clin. and Lab. Invest, 11, 250.

31. Hahn, P.F., Bale, W.F., Lawrence, E.O., Whipple, G.H. 1939 J. Exper. Med, 69, 739.

32. Haler, D., 1952 Brit. Med. J. 2, 1241.

33. Hess, V.F. and McNiff, W.T., Amer. J. Roentgenol. 1947, 57, 91.

34. Heinrich, H.C., 1964, Seminars in Hematology, Vol. 1. pp. 199 - 249, (New York, Grune and Stratton, Inc.).

35. Heyssel, R.M. Bozian, R.C., and Darby, W.J. 1964, Dynamic Clinical Studies with Radioisotopes, pp. 331 - 342, Oak Ridge, Tern., U.S. Atomic Energy Commission.

36. Heyssel, R.M. Bozian, R.C. Darby, W.J. and Bell, M.C., 1966, Am. J. Clin. Nutrition, 18, 176.

37. Hill, R., 1965, Private communication.

38. Hine, G.J., Jagger, P.I. and Burrows, B.A., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p. 413.

39. I.A.E.A. Directory of Whole-Body Radioactivity Monitors, Vienna, 1964.

40. International Commission on Radiological Protection, 1960, Report of Committee III on Protection Against X-rays up to Energies of 3 MeV and Beta-and Gamma-Rays from Sealed Sources. London.

41. Josephs, H.W., 1958, Blood 13.1,

42. Kantele, J., 1965, Private Communication.

43. Kerr, D.N., Davidson, L.S.P. 1958 Lancet 2, 489.

44. Killander, A., and Schilling, R.F., 1961, J. Lab and Clin. Med., 57, 553.

45. Koutras, D.A., Alexander, W.D., Buchanan, W.W. Crooks, J. and Wayne, E.J., 1961, Acta endocr. (Kbh) 37, 597.

46. Le Gallic, Y., 1965, Private Communication.

47. Liden, K.V.H., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p. 142.

48. Lushbaugh, C.C. Hale, D.B., 1965 Radioactivity in Man, G.C. Thomas, Springfield, Illinois, p. 417.

49. Maclean, L.D. and Sundberg, R.D., 1956, New Engl. J. Med., 254, 885

50. May, H. H., 1965, Private communication.

51. May, H.H., and Marinelli, L.D., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A.: Vienna), p.15.

52. McKee, I.C., King, J.A. Hartmann, R.C. Heyssel, R.M. 1965 Radioactivity in Man, G.C. Thomas, Springfield, Illinois, p. 402.

53. Miller, C.E., 1958, Proc. 2nd UN Int. Conf. PUAE 23, 113-123.

54. Miller, C.E., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p.81.

55. Mollin, D.L., 1959, Brit-med. Bull, 15, 1, 8.

56. Naversten, Y, 1964, Proc. Symp. on Assessment of Radioactivity in

Man, (I.A.E.A., Heidelberg).

57. Nodine, J.H., Channick, B.J., Sokhos, D., Tassoni, S.D. and Perloff, W.H., 1957, J. Clin. Endocr. 17, 832.

58. Palmer, H.E. and Roesch, W.C., 1965, Health Phys. 11, 1213.

59. Paulson, M. and Harvey, J.C., 1954, J.A.M.A., 156, 1556.

60. Pirzio-Biroli, G., Bothwell, T.H., Finch, C.A., 1958 J. Lab. Clin. Med. 51, 37.

61. Price, D.C., S.H., Wasserman, L.R., Reizenstein, P.G., and Cronkite, E.P., 1962, Blood, 20, 517.

62. Price, D.C., Cohn, S.H. Cronkite, E.P., 1965 Radioactivity in Man, G.C. Thomas, Springfield, Illinois, p. 377.

63. Rajewsky, B., Strahlentherapie, 1941, 69, 438.

64. Ramsay, W.N.M., 1957 Clin. Chim. Acta. 2, 214.

65. Reizenstein, P. Cr., 1959 a, Acta Med. Scand., 165, 467.

66. Reizenstein, P. Cr., 1959 b, Acta Med. Scand., 165, suppl. 347.

67. Reizenstein, P. Cr., 1959 c, Acta Med. Scand., 165, 313.

68. Reizenstein, P. Cr., Cronkite, E.P. and Cohn, S.H., 1961, Blood, 18, 1.

69. Reizenstein, P. Cr., Cronkite, E.P. and Robertson, J., 1962, Vitamin B_{12} and Intrinsic Factor (Stuttgart, Enke) p. 404.

70. Reizenstein, P. Cr. Matthews, C.M.E. and Ek, Cr., 1964, Nutrition, Proc. VI Int. Congr., Edinbrugh, (Edinburgh, Livingstone), p. 416.

71. Reizenstein, P.G., Ek, G. And Matthews, C.M.E., 1966, Phys. Med. Biol. 11, 2, 295.

72. Reizenstein, P., Brann, I., 1965 Radioactivity in Man, G.C. Thomas, Springfield, Illinois, p.391.

73. Reizenstein, P.G., 1966, Blood, 27, 5.

74. Riggs, D.S., 1952, Pharmacol. Rev. 4, 284.

75. Rosenblum, C., Williqan, D.A., Neriwether, H.T. and Cronkite, E.P. 1960, Proc. Soc. Exp. Biol. Med., 105, 142.

76. Rundo, J., J. sci. Instrum. 1955, 32, 379.

77. Rundo, J., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p. 142.

78. Rundo, J., 1965, Conf. on Low Level Radioactivity Measurements: Limitations and New Techniques, 5 - 6, July, London.

79. Sargent, T.W., 1962 Whole Body Counting, I.A.E.A., Vienna, p.447.

80. Schloesser, L.L., Deshpande, P. and Schilling, R.F. 1958, Arch. Int. Med. 101, 306.

81. Schlundt, H., Barker, H.H. and Flinn, F.B., 1929, Amer. J. Roentgenol. 21, 345.

82. Schlundt, H., Nerancy, J.T. and Morris, J.P. 1933, Amer. J. Roentgenol, 30, 315.

83. Shevick, P., 1965, Private Communication.

84. Sievert, R.M., Ark. Fys., 1951, 3, 337.

85. Sievert, R.M., Proc. UN Int. Conf. PUAE, 1955, 13, 187.

86. Sievert, R.M., Strahlentherapie 1956, 99, 185.

87. Smith, M.D. Mallett, B.J., 1957 Clin. Sci., 16, 23.

88. Sorensen, E.W., 1964 Acta. med. Scand., 175, 763.

89. Spiers, F.W., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna). p.3.

90. Spiers, F.W. 1965, Paper WBC/3, Meeting on Use of Whole Body Radiation Counters, M.R.C., London (May, 1965).

91. Trott, N.G., 1965, Proc. 5th. Int. Symp. on Radioactive Isotopes in Clinical Medicine and Research, Bad Gastein.

92. Van Hoek, R., Conrad, M.E. Jr. 1961 J. Clin. Invest., 40, 1153.

93. Van Wambeke, L., 1965, Euratom, IV, 3, 80.

94. Veall, N., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p. 397.

95. Vennart, J., 1962, Proc. Symp. on Whole-Body Counting, (I.A.E.A., Vienna), p. 142.

96. Vennart, J., 1965, Conf. on Low Level Radioactivity Measurements: Limitations and New Techniques, 5-6 July, London.

97. Warner, G.T. and Oliver, R., 1966, Phys. Med. Biol., 11, 1, 83.

98. Watt, D.E. and Ramsden, D. 1964, High Sensitivity Counting Techniques, Pergamon Press.

99. Wayne, E.J., Koutras, D.A. and Alexander, W.D., 1964, Clinical Aspects of Iodine Metabolism, Blockwell.

100. Weller, R.I., Anderson, E.C. and Barker, J.L., 1965, Nature, 206 4990, 1211.

101. Will, G., Vilter, R.W., 1954 J. Lab. Clin. Med. 44, 499.

102. Will, G. and Boddy, K., 1967, Scottish Med. J. (in press).

103. Wilson, A.R., Thesis, University of Leeds, 1964.

104. Wilson, G.M., 1963, in the Thyroid and its Diseases. Ed. A.S. Mason, Lipponcott.