THE DEVELOPMENT OF in-vivo BODY COMPOSITION STUDIES AT SWANSEA

by

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ABSTRACT

Measurements were made of organ cadmium contents in hypertensive and normotensive subjects and in occupationally-exposed workers, using a partial-body prompt gamma neutron activation technique based on a ^{252}Cf source. A feasibility study to measure beryllium in the lung by photonuclear reaction is in progress. Future plans include the measurement of silicon by neutron inelastic scattering, and the use of X-ray fluorescence analysis for the measurement of heavy metals.

1. INTRODUCTION

The Swansea research group evolved from a collaboration between the Physics Department of the University College of Swansea and the Medical Physics Department of West Glamorgan Health Authority, based at Singleton Hospital. The original members of the group were Professor J.Dutton and Dr. C.J.Evans of the University and Mr. A.Sivyer and Dr. W.D.Morgan at the Hospital.

Clinical interest was evident from the outset and has developed to such an extent that current medical support is enthusiastic and broad-based through Dr. D.Phillips-Miles, Area Medical Officer, Dr. P.C.Elwood, Director of the Medical Research Council Epidemiology Unit in Cardiff, Dr. R.R.Ghose, Consultant Physician and Dr. A.C.Ames, Consultant Chemical Pathologist.

The first research student, P.E.Cummins, successfully submitted a Ph.D. thesis in 1980, and a second student, P.Ali, commenced work at the end of that year.

Initial interest in the field of body composition studies began in 1976, when some experimental data which had previously been obtained by Dr. Morgan at the University of Birmingham was reviewed. The results, which indicated that a measurement of the oxygen: carbon ratio by fast neutron activation analysis provided a good estimate of the fat: fat-free tissue in the sample, and was a more sensitive indicator of body composition than the dual-energy photon absorptiometry technique (1), were presented at the First European Congress of Nuclear Medicine

and later published by Biggin and Morgan (2). This particular neutron activation method, however, was not applied to human subjects, mainly because of the requirement for high energy neutrons (>16 MeV) for the (n,2n) reaction in oxygen, and also because the dose was expected to be slightly higher than was customary for such studies. Nevertheless, recent measurements of total body oxygen by (n,p) reaction on ^{16}O (3,4) and the possibilities of analysing carbon (5) and oxygen by inelastic scattering reactions, might encourage further work in this direction.

2. CADMIUM - PROJECT NAOME

Apart from this brief incursion into the field of major body element analysis, the main thrust of the Swansea research has been towards the partial-body measurement of minor and toxic elements. A proposal to develop an instrument for prompt-gamma analysis of cadmium and mercury (project NAOME - Neutron Activation of Metallic Elements) was funded by the Welsh Scheme for the Development of Health and Social Research in 1976, and a research student (supported by a Science Research Council CASE Award) commenced work at the end of that year.

The clinical purposes of building this instrument were threefold, relating (a) to the suggested role of cadmium in the aetiology of essential hypertension, (b) to the study of a population in a region some parts of which are heavily polluted as a result of two centuries of metal working (6), and (c) to the study of occupationally-exposed workers.

The primary investigation of cadmium and hypertension was motivated by the conflicting evidence of earlier work. Several studies had been carried out in which blood levels of cadmium were compared between hypertensive and normotensive subjects (7,8), while other workers had analysed post mortem tissues in similar categories of patients (9,10). However, blood and urine analyses are not very good indicators of critical organ concentrations, and furthermore, care has to be exercised in matching the two populations for age, sex and smoking habit (11). It was decided, therefore, to undertake an in-vivo study of renal cadmium concentrations in two groups of carefully matched persons residing in the Swansea area.

2.1. Instrumental design

An instrument was designed and constructed (12) to house a neutron source of sufficient output ($>10^8 ns^{-1}$) that 'normal' levels of kidney cadmium could be detected within an analysis time of about 30 min. After careful consideration, it was decided to use a 200 μg (4.0GBq, 108mCi) ^{252}Cf source of output $4.6 \times 10^8 ns^{-1}$. Although ^{252}Cf has a lower mean neutron energy (2.1 MeV) than an (α,n) source (~4.5 MeV)

and a relatively short half-life of 2.65y, a pilot study using 1 μg ^{252}Cf and an 11.1 GBq (300mCi) ^{241}Am,Be source had shown that the depth distribution of thermal neutron fluence in a water phantom was very similar for the two sources. This was confirmed by a recent study (13) in which collimated beams of ^{252}Cf and ^{238}Pu,Be were compared for partial-body prompt-gamma IVNAA. In addition, the later study showed that a ^{252}Cf source achieved a higher thermal fluence-to-dose ratio, was less damaging to Ge(Li) detectors, and in many countries is subject to less stringent transport regulations than ^{238}Pu,Be. Moreover, the disadvantage of the shorter half-life of ^{252}Cf may be largely overcome by gradually reducing the source-subject distance (SSD) provided that effective collimation and adequate shielding of the detector(s) can be maintained. For example, in Swansea a doubling of the Cd detection limit after 5 years' decay of the ^{252}Cf source is reduced to only a 50% increase in the same period by a gradual reduction in SSD (14).

The original Swansea design was fully described by Evans et al (12), but improvements to the shielding beneath the detector and the calibration measurements necessary for in-vivo analyses were given in Cummins' thesis (15) and at the recent Toronto conference (14). At present, using one 21% efficient Ge(Li) detector, the detection limit (2 SD of the background) is 3.2 mg of cadmium in the kidney and 2.2 μg/g in the liver for an organ dose of 3mSv (300 mrem) delivered in 33 min.

2.2. Clinical studies

2.2.1. Cadmium and hypertension. This study was greatly facilitated by the co-operation of Dr.P.C.Elwood and two general medical practitioners in the Swansea area. They provided 30 cases of long-standing hypertension severe enough to require treatment, and 30 control subjects. The controls, who were checked to ensure that their blood pressures were within the normal range, were selected at random from an age-sex register within the same practice lists and individually matched for age, sex and cigarette consumption. Following a full explanation of the nature of the research and the radiation dose involved, each person who agreed to participate was then invited to complete a questionnaire relating to employment history, smoking habits, and a broad classification of normal weekly diet. Blood and urine samples were taken for routine biochemistry and also cadmium estimations by atomic absorption spectroscopy. The left kidney was then located using B-mode ultra-sound and finally the in-vivo measurement was made with the patient lying supine for just over half an hour.

The results showed that the mean cadmium level in the hypertensive group (3.3 ± 2.3 mg) was not significantly different from that in the control group (4.4 ± 2.7 mg) (16). However, since the hypertensive patients had been receiving therapy the treatment might have removed cadmium originally bound in the kidney. Unfortunately, only spot samples of urine were available for cadmium analysis, so it was not possible to state whether the hypertensive group had a higher 24h excretion of cadmium than the controls. Nevertheless, by assuming a total body burden equal to three times the renal burden and a urinary excretion rate of 1.3 l/day for normotensives and 1.6 l/day for hypertensives under treatment (17), it was calculated that the mean biological half-life of cadmium in the body was 17.4 ± 13.0 y in the control group and only 10.9 ± 7.7 y in the hypertensives (18). The control value is very close to the 15.7 years reported by Ellis (19) but there are no data on this parameter in treated hypertensives.

The results also showed no significant correlation between either blood, urine, or renal cadmium, but the smokers had significantly ($p < 0.05$) higher blood cadmium levels than the non-smokers and their renal cadmium contents were also elevated (20). The increase in cadmium content of the kidney in smokers is approximately 0.04mg per pack-year (no. of packs/day x years smoked).

Finally, in terms of the residues of environmental contamination in the Lower Swansea Valley, it is of interest to note that the mean cadmium levels observed in both groups are comparable with data published by other workers for non occupationally-exposed individuals (18).

2.2.2. Occupational exposure. In addition to the hypertension study, the Cd burdens in several other persons have also been measured. These included two occupationally-exposed workers (at a Zn-smelter and a Ni-Cd battery plant), one of whom was found to have a very high concentration of 400 ppm in the kidney cortex and only a moderately elevated level of 8 ppm in the liver (21). Blood (28.3 µg/l) and urine (14.4 µg/g creatinine) cadmium were both elevated, but there was no evidence of renal dysfunction. This case report, taken together with other recent occupational studies, suggests that the onset of dysfunction is not simply related to the level of cadmium in the kidney.

2.3. Calcium and iron

2.3.1. Spinal calcium. A feasibility study was performed to investigate the potential usefulness of the present ^{252}Cf irradiation facility for spinal calcium measurements using the ^{48}Ca (n, γ) ^{49}Ca reaction (15). A set of rectangular collimator inserts were constructed to permit the selective

irradiation of a 20cm length of lumbar spine in the supine patient. Preliminary results indicated that the sensitivity of the technique using a new 200 μg source and two 15.2 x 15.2 cm NaI (Tl) detectors would be 2000 counts in the ^{49}Ca photopeak for a 25 min. irradiation, 30 sec cooling period, 15 min count and a skin dose of 50 mSv (5 rem). Although the combined activation-counting response was found to be very non-uniform with depth, the technique may be potentially suitable for serial measurements, provided that care is taken in accurately reproducing the patient's position on each occasion.

2.3.2. Liver iron. The possibilities for measuring liver iron by the neutron inelastic scattering reaction $^{56}Fe\ (n,n'\gamma)\ ^{56}Fe$ were also examined (15). This reaction yields a 0.847 MeV 'prompt' gamma ray with a cross-section of 1.14 barns at 3 MeV. With very minor modifications to the present irradiation facility, i.e. increasing the collimator diameter and detector-skin distance to 10 and 6cm respectively, it is possible to detect (2 SD's of the background) 1.6 g of iron in a 1.1 l liver phantom for a skin dose of 8 mSv (800 mrem). Although this is too insensitive to detect normal liver iron burdens, the apparatus could be used to assess the efficacy of treatment in persons with abnormally high levels of iron.

3. BERYLLIUM - PROJECT GINA

In 1979 a second research proposal to examine the feasibility of measuring beryllium *in-vivo* was funded by the Welsh Scheme. Project GINA (Gamma-ray Induced Neutron Activation) aims to exploit the uniquely low (γ,n) threshold energy (1.67 MeV) in beryllium by irradiating the subject with photons of energy between 1.67 and 2.2 MeV (the photonuclear threshold in deuterium) and detecting the neutron and photon products of the reaction.

Some preliminary experiments were carried out by Ettinger et al at Brookhaven National Laboratory in 1979/80 (22). These results showed that with a large array of BF_3 detectors, it should be possible to detect 3.4 mg of beryllium in the lungs for a dose of 2.5 rads. With further technical innovations it was suggested that the detection limit might be reduced to about 1 mg.

Experimental work in Swansea is continuing with BF_3 counters and an ^{124}Sb source, but in the near future it is hoped to obtain a pulsed bremsstrahlung spectrum from the University's 2 MV Van de Graaff accelerator. By counting only in the beam-off period it is hoped to detect slowed neutrons and secondary capture gamma rays above a much-reduced background.

Unfortunately, for a variety of reasons, a research student (again financed by an SRC CASE Studentship) was not appointed until the end of 1980. Consequently, this work has not progressed as quickly as one would have wished.

4. CADMIUM - PROJECT TOSCA

Project TOSCA (Toxicity and Occupational Studies on CAdmium) has recently become the third research proposal to be funded by the Welsh Scheme. This project is a direct result of the findings in the two occupationally-exposed workers previously discussed (21). These were that kidney dysfunction may not be simply dependent upon the amount of Cd stored in the renal cortex but might be related to an increase in plasma Cd-metallothionein, which in turn may be dependent upon the hepatic content of the complex.

The proposal is to measure the kidney and liver cadmium levels in a local group of exposed workers and to relate these values to biochemical and physiological indices of renal function such as proteinuria, B_2-microglobulinuria and glomerular filtration rate. After the initial baseline studies, all subjects will be followed-up at 6-monthly intervals for repeat biochemical investigations. It is intended to repeat the in-vivo measurements only every 2 years, or whenever signs of renal dysfunction first occur. In this way it is hoped to obtain a complete picture of the changes in all relevant parameters over a period of time and thereby be in a position to better define the critical indices of cadmium nephrotoxicity.

5. FUTURE PLANS

In the short term it is intended to take advantage of the funding for Project TOSCA to measure the kidney cadmium burdens in a group of newly-diagnosed hypertensive patients. These will be retrospectively matched, where possible, with the existing groups of treated hypertensive and control subjects to determine the effect of anti-hypertensive therapy on the cadmium content of the kidney.

In the medium term, new accommodation is being built for the hospital department of Medical Physics, which will contain purpose-built rooms for partial-body IVNAA and a shadow-shield whole-body counter. An improved activation instrument will be built using Poly-Cast and Poly-Pb/B shielding from Reactor Experiments Inc., and containing a tapered collimator to take advantage of the compact source dimensions of ^{252}Cf. It is hoped to design a multipurpose instrument suitable for kidney and liver cadmium and spinal calcium. By employing a scanning geometry, it should be possible also to measure total-body nitrogen and hydrogen as described by Vartsky et al (23). Although using a ^{252}Cf source, recent data (13) suggest that the uniformity of activation should be only slightly inferior to that obtained from ^{238}Pu,Be neutrons.

Within the University Physics Department, work will be

centred on the 2MV Van de Graaff accelerator. At present, this accelerates electrons only, but a conversion to positive ion mode could provide a pulsed D-D neutron source of energy suitable for the measurement of silicon and other elements by neutron inelastic scattering reactions (22).

Substantial funding is currently being sought for these and other (e.g XRF analysis) in-vivo body composition studies in Swansea.

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Addendum to the Paper on "The Development of in-vivo Body Composition Studies at Swansea" by W.D.Morgan

Since 1981, substantial progress has been made both in the completion of existing work and in the funding of the new projects described in section 5.

Firstly, it is pleasing to record that Project GINA (section 3 above) reached a satisfactory conclusion with the acceptance of a Ph.D. thesis by P.A. Ali entitled "An Evaluation of Methods for the In-Vivo Detection of Beryllium." This work suggested that by using a filtered source of ^{124}Sb for bilateral irradiation of the chest, and an array of twenty BF_3 counters, a detection limit of 0.56 mg of beryllium per lung can be achieved for a skin dose of 50 mGy. A full description of these experiments has been submitted for publication (24).

The cadmium work (Project TOSCA) is continuing, but as this is a longitudinal study over 5 years of a group of Cd-exposed workers no results are yet available for publication.

In 1982, the Swansea In-Vivo Analysis Research Group (SIVARG) was awarded three Project Grants by the Medical Research Council. These provided support for additional staff, namely a Senior Research Assistant (Dr. A. Kacperek), a Research Assistant (Mr. S.J.S. Ryde), a part-time Medical Assistant (Dr. S. Cobbold) and additional technical staff, as well as funding for essential new equipment.

The first of these projects - a new ^{252}Cf-based system for the in-vivo determination of Cd,Ca and N - is well underway, and a system description is included elsewhere in this report. In addition to measuring nitrogen by prompt-gamma analysis, it is now expected that total body calcium also may be measured by the prompt technique (25). A particular feature of the new system is the fully automated pneumatic source transfer mechanism which will enable selenium to be measured by cyclic activation analysis (26).

The second grant was awarded for the development of a system to measure silicon and other elements by the neutron inelastic scattering technique. Work is in progress to convert the University Van de Graaff accelerator to provide a pulsed beam of 5 MeV neutrons, and when this is completed a series of phantom experiments will be undertaken using a specially-designed fast counting system.

Finally, the third grant has enabled the Group to become active in the field of in-vivo X-ray fluorescence analysis. Measurements of lead can now be made using apparatus similar to that described by other workers; but the main objective of our research is to measure platinum in the kidneys of patients who are undergoing cis-platinum chemotherapy. Initial phantom studies are shortly to be published (27) and the first patient measurements are scheduled for this summer.

W. D. Morgan
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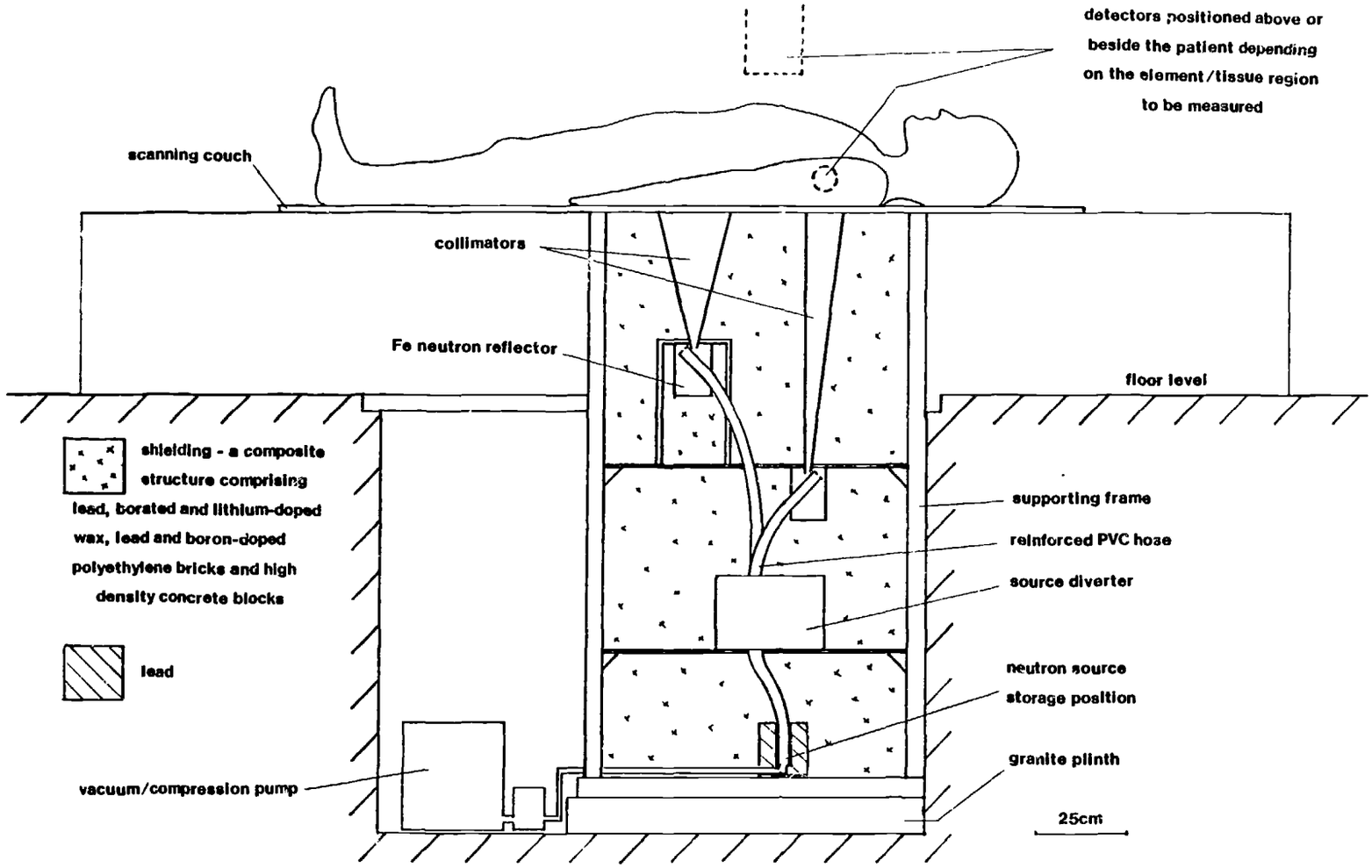
detectors positioned above or beside the patient depending on the element/tissue region to be measured
scanning couch
collimators
Fe neutron reflector
floor level
shielding - a composite structure comprising lead, borated and lithium-doped wax, lead and boron-doped polyethylene bricks and high density concrete blocks
lead
supporting frame
reinforced PVC hose
source diverter
neutron source storage position
granite plinth
vacuum/compression pump
25cm