Radiation in MRC supported research in the 1950s and 1960s

Report of a Committee of Inquiry

Committee members

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RADIATION IN MRC SUPPORTED RESEARCH IN THE 1950s AND 1960s

1. INTRODUCTION

1.1 On 6 July 1995, a television documentary entitled 'Deadly Experiments' was broadcast on Channel 4 as part of the 'True Stories' series. The programme, produced by Twenty-Twenty Television, featured a number of research projects conducted between 1950 and 1970 in which either measurements were made of the amount of radiation absorbed by, or radioactive substances were administered to, human subjects in the UK and USA.

1.2 The level of public concern generated by the broadcast and the implication of unethical practices in the conduct of some of the research sponsored by the MRC, has acted as the trigger for the MRC to establish this independent Committee of Inquiry. Its remit has been to clarify the facts surrounding the research and to examine issues of acceptability and consent in the context of the scientific and ethical standards of the period in which the research was carried out. The full terms of reference of the Committee and details of Membership follow on from this introduction. Though established by the MRC, and indeed chaired by a current Council member, this Committee has operated independently and has been free to pursue those issues and avenues of enquiry which it deemed to be of relevance to its terms of reference.

1.3 The Committee has restricted its investigation to MRC-funded research conducted in the UK. Research carried out in the United States of America was considered to be outside the remit of this Committee. A Presidential Advisory Committee on Human Radiation Experiments has recently reported in relation to events across the Atlantic and interested individuals may wish to refer to the final report of that Committee for further information in relation to research carried out in the USA[1].

1.4 The following studies featured in the programme were funded by the MRC. References for the appropriate scientific publications are contained at Annex 3:

The study measuring levels of Strontium 90 uptake, in which samples of bone were taken at autopsy (the programme featured a case in North Wales where the femora were removed from a deceased infant).

The work carried out at University College London and reported in 1952 and 1958, in which radioiodine was administered to women in order to measure thyroid function throughout the menstrual cycle and in pregnancy.

The work carried out at the Hammersmith Hospital, London, in 1953, in which radioactive sodium was used to measure maternal placental blood flow in normal and hypertensive women.

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1 **Final report of the Advisory Committee on Human Radiation Experiments** (Govt. stock no. 061-000-00-848-9) New York: Oxford University Press 1996

The studies at Aberdeen Maternity Hospital, which investigated iodine metabolism and maternal thyroid function during pregnancy, and the development of the human fetal thyroid.

The Coventry study in which women from the Asian community were asked to consume specially prepared chapattis in order to measure levels of iron absorption, with a view to investigating the problem of anaemia.

1.5 The Committee considered that the concerns raised in the programme as a whole fell into a number of broad categories:

accepted practice in relation to obtaining consent and informed consent;

the participation of pregnant women in research;

the recruitment of research subjects from an ethnic minority or non-English speaking community;

the inclusion of children in research (whether living or deceased, *in* or *ex-utero*);

the use of radioactive material for therapeutic and non-therapeutic purposes.

A final issue which presented itself related to the inclusion of the mentally ill as research subjects, though the studies featured in the programme were conducted exclusively in the USA. This 'category' of studies gives particular concern in that it included research subjects who may have been unable to give informed consent by reason of their disability. The programme makers themselves expressed particular concern about this type of study in a meeting with the Committee Chairman. Accordingly, the Committee has given additional consideration to two studies carried out at the former MRC Neuropsychiatric Unit in order to explore the issues raised.

1.6 The programme also included references to other studies (e.g. whole-body irradiation carried out at the Churchill Hospital Oxford and work in Liverpool in 1953). These studies were not MRC funded and detailed consideration has therefore not been given to them. In the former case, as it has been confirmed that the radiation was administered for the treatment of cancer, there is no question of this having been an 'experiment'.

1.7 The specific purpose of this Committee has been to address concerns raised in relation to the studies featured in the programme. However, this report also considers a number of broader issues identified, using the MRC-sponsored research as case studies. These include consideration of how much information needs to be disclosed to research subjects in order to obtain valid consent? Should practice alter when participants in a study are from a community that is broadly non-English speaking? Finally, this report sets out briefly the current debate surrounding the use of radioactive material generally.

1.8 The Committee would like to extend its thanks to all those individuals – participants in the research, scientists and researchers – who gave freely of their time, experiences and expertise. The Committee would like to record its particular thanks to Karen Williams, who acted as its Secretary throughout, despite a change in her role at the MRC, and who provided sound advice and excellent drafting, as well as an even temper and great patience. This report would not have been possible without her considerable efforts and insight.

THE MEMBERS OF THE COMMITTEE OF INQUIRY

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2. COMMITTEE MEMBERSHIP

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TERMS OF REFERENCE

- To establish, as far as possible, the facts concerning the MRC sponsored experiments criticised in the television programme
- To establish whether the experiments were designed to address health questions and were acceptable in the context of the time at which they were carried out
- To establish whether procedures with regard to the obtaining of consent were reasonable in the context of the time at which the experiments were carried out
- To establish whether the techniques used were reasonable in the context of the time at which the experiments were carried out
- To consider whether any modification of present-day procedures for the obtaining of consent is necessary
- To consider other issues which may emerge from discussion
- To report to the Medical Research Council and to make the report public

3. BACKGROUND

3.1 The Committee has sought to address its terms of reference from a number of different angles.

3.2 Given the fact that the research was conducted anything up to 40 years ago, it was vital to determine the legal and societal context of the period. The Committee accordingly consulted Dr Richard Nicholson (editor, Bulletin of Medical Ethics) who provided valuable background information. This information has been drawn upon in the historical background to the discussion of the specific research studies.

3.3 The years that have passed since the research was conducted has restricted the number of research scientists and study participants with whom it was possible to speak. Some have left the country, others have died, some are untraceable. It was also recognised that the passage of time might also have had an effect on personal recollections. However, it was considered vital to speak with those who were still available - Dr Keith E Halnan, Professor Peter Elwood, Mrs Grace Brown, Mrs Loretta Tennant and Mrs Kathleen Morrison. All these people have shared their recollections freely and openly and have given an invaluable insight into the research.

3.4 It was not possible to contact some important people. The Committee regrets that it did not have an opportunity to speak with either the health visitor who was used to translate in Coventry or the daughter of one of the original research subjects in Coventry. A British Library literature search did not yield detailed information on the types of burial and bereavement practices which were prevalent in North Wales in the late 1950s, though the Committee has been able to speak with two individuals concerning established practices at the time. It was not possible to speak with the researchers who led the Aberdeen studies – Dr Aboul-Khair has left the country and the other principal researchers are now dead. We are however, grateful to Dr Hytten who collaborated on some of their studies, and who provided the Committee with such advice as he could.

3.5 The Committee took evidence in a number of forms - some witnesses gave evidence in person, others gave specific advice in writing. The Committee also commissioned evidence where it felt it was appropriate e.g. from Dr Nicholson, Professor Alex Elliott and Professor Nicholas Wald.

3.6 In relation to each of the studies, the Committee has sought to establish whether the study was ethical by reference to a number of questions:

- What was the study trying to establish/achieve? What was its scientific value/validity?
- What was the potential benefit of the study - and to whom? Specifically, in this case, was radioactive material used for therapeutic benefit or were healthy volunteers exposed to test the effect of human exposure to these materials? If the study was non-therapeutic, was it intended that wider society or future patients would benefit from the acquisition of greater knowledge ?

- What were the risks of the study ? Was the dose of radioactive material likely to have been harmful ? Did any other components of the research protocol cause concern? In retrospect, was there any long term harm to participants – either physical or psychological ?
- Consent. Was it sought ? Were participants able to consent – especially in the case of infants, ethnic minorities and the mentally ill? Was consent fully informed? What information was given in terms of the nature of the study, possible discomfort, risk and the right to refuse or withdraw from the study?

3.7 This report gives consideration to the specific MRC research featured, with reference to the criteria above. Consideration is given to what was normal and accepted practice at the time the research was conducted, and the formal guidelines (if any) that existed at the time. The wider issues arising from the programme are also discussed.

4. HISTORICAL CONTEXT

4.1 Before considering the individual studies featured in the programme, it was important to understand the historical and legal background against which the research took place. The results of the research featured were reported (at their most recent) more than 28 years ago. Researchers during the period did not work within the standards or context that would be the case today. Society itself was more paternalistic by nature and it was uncommon for people to question the motives or methods of those in positions of authority.

4.2 This chapter considers:

- how thinking on research involving human subjects developed over the period;
- the guidance available on radiation in medicine;
- the guidance available on the use of radiation in research at the time.

General research guidelines

4.3 Firstly, consideration must be given to the nature of general guidelines for the conduct of research on human subjects, and to what extent they were followed. Research involving radioisotopes was not the only work being carried out during the period under investigation. What was the general prevailing context in which research was conducted at the time?

4.4 The Nuremberg Code[2] has been in existence since 1947. However, it can be argued that recent literature on the Code[3] has given an exaggerated impression of its influence in regulating the conduct of medical research in the first two decades following the Second World War. It appears that medical researchers, if they thought about the Code at all, may have regarded it as something of an ideal, rather than practical guidance. It is referred to infrequently in the contemporary medical literature, both in the UK and USA. Paul Beeson, Professor of Medicine at Yale (and formerly Nuffield Professor of Clinical Medicine at Oxford) and a doyen of American medical researchers, wrote in 1964[4]:

"I think we must read the Nuremberg Code in reference to the conditions under which it was written. This is a wonderful document to say why the war crimes were atrocities, but it is not a very good guide to clinical investigation which is done with high motives."

2 **The Nuremberg Code, 1947** Reprinted in Dictionary of Medical Ethics (2nd edn) Darton, Longman & Todd, London 1981

3 R J Lifton. **The Nazi Doctors: A study of the psychology of evil.** Macmillan, London. 1986

4 P B Beeson et al. Panel discussion: **Moral issues in clinical research.** Yale Journal of Biology and Medicine (1964) 36, 455-76

4.5 There is suggestive evidence in Maurice Pappworth's book[5] that doctors and researchers in the UK did not appreciate that the Nuremberg Code applied to conventional medical research, linking it instead only to the war crimes trial of the same name. He described hundreds of experiments – all published – carried out in the first 20 years after the war that were to varying degrees unethical, unkind and dangerous. Few can have been performed in accordance with the Code, not only because of the high levels of risk often involved, but also because the obtaining of consent was rarely mentioned.

4.6 Whatever the reasons, the Nuremberg Code did not appear to have figured in the minds of researchers. In 1964, however, the World Medical Association drew up the Declaration of Helsinki[6], which included a series of principles which were directed at research on human subjects. These principles include the requirement to obtain consent.

4.7 The MRC issued its own guidance on the use of human participants in medical research in its report for 1962-63, guidelines which now seem to have been ahead of their time. For research not of direct benefit to an individual, the MRC statement says "In investigations of this type it is therefore always necessary to ensure that the true consent of the subject is explicitly obtained". In respect of children it says "In the strict view of the law, parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may carry some risk of harm". The MRC statement differs from the Nuremberg Code and the Declaration of Helsinki, both of which lay down more specific guidance on the need to balance likely benefits against risk. The original 1964 version of the Declaration of Helsinki, for instance, included the following in its basic principles (both of which have remained essentially unaltered in subsequent revisions to the Declaration):

"3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others."

4.8 It is difficult to pinpoint precisely when the changes in attitude to medical research began, so that today research without consent is regarded as unacceptable, as is research with a poor risk-benefit balance. The passing of the US National Research Act in 1974, with strengthening of the FDA requirements for consent, undoubtedly helped in the USA. In the UK, the establishment of research ethics committees from the late 1960s onwards has unarguably affected the context in which research is conducted. The almost universal acceptance of the 1975 (and now the 1989) version of the Declaration of Helsinki must also have played a part, as have the various guidelines issued by Royal Colleges in the United Kingdom, and the establishment of the Local Research Ethics Committee framework.

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5 M H Pappworth. **Human guinea pigs.** Routledge and Kegan Paul, London, 1967

6 World Medical Association. **Declaration of Helsinki: Recommendations guiding doctors in clinical research, 1964.** Reprinted in **Dictionary of Medical Ethics.** Darton, Longman & Todd, London 1977

The use of radiation in medicine

4.9 Although the rapid development of nuclear physics during the Second World War was largely geared to the development of atomic weapons, the potential which the discipline offered to industry, medicine, and research very rapidly became apparent during this period. With the end of hostilities, know-how which had been reserved for the wartime effort was applied to a wide range of uses.

4.10 Awareness of the potential risks developed in parallel. The issue of radiation protection during the early post-war years appears to have focused on the risks to industrial workers, doctors, and scientists , whose work involved regular exposure to man-made ionising radiation, with the effects on patients of single or occasional exposure very little considered. This was the rationale behind the setting up of the MRC's Radiobiological Research Unit, at Harwell, in 1947[7]. Contemporary knowledge about the possible dangers of radiobiological exposure was summarised through the publication, around 1948, on an Introductory Manual on the Control of Health Hazards from Radioactive Materials. This was prepared for the MRC by the Atomic Energy Research Establishment at Harwell.

4.11 The first step towards controlling the use of radiation in medicine in the UK was the passing of the Radioactive Substances Act in 1948, which provided for the licensing of medical and dental practitioners who used ionising radiation. However, this provision could not be put into effect until there was a code of practice, compliance with which would be linked to the granting of a licence. Such a Code of Practice for the Protection of Persons Exposed to Ionising Radiation was produced by the Ministry of Health in 1957 and applied to those administering radiation; no mention was made of the protection of patients.

4.12 The MRC's Report to Parliament for 1948-50 discussed the health and research issues raised by wartime advances in nuclear physics. It highlighted the importance of ensuring patient safety in experimental radiotherapy, and explained the principles which the MRC followed in controlling the use of the limited supplies of radioisotopes then available. The Report carried an article on biological aspects of atomic physics which – whilst not a guideline as such – included a passage about the importance of ensuring patient safety in experimental radiotherapy; the report states that:

"great caution must be exercise when giving [radioactive isotopes] in therapeutic doses to patients of either sex in the reproductive period of life or to any patients with an expectation of life exceeding five years. These principles have so far guided the Council's [Radioactive Isotope] Panel in allocating radioactive isotopes for clinical use"[8].

However, the Report did not discuss risk in radioisotope tracer studies.

7 **Report of the Medical Research Council for the years 1945-48**, HMSO, 28, 97-8

8 **Report of the Medical Research Council for the years 1948-50**, HMSO, 27

4.13 The International Commission on Radiological Protection first considered protection for patients in 1955. That year, a sub-committee on protection against X-rays advised that given 'the increasing use of radiation for diagnostic and therapeutic purposes, it appears appropriate to give some guidance regarding the protection of patients"[9]. The Sub-Committee noted that, in some countries, some patients were receiving a total dose from X-ray diagnosis in excess of the total dose of those who were exposed to radiation as a result of their occupation.

4.14 The MRC Committee on the Hazards to Man of Nuclear and Allied Radiation was set up in 1955 to report on the medical aspects of nuclear radiation – this in response to a request from the then Prime Minister, as a consequence of public concern over the effects of nuclear weapons testing. In the event, the Committee dealt with the wider problem of the hazards which might arise from all forms of nuclear and allied radiation. The Committee's first report was published in 1956[10]. It found that medical and dental radiology contributed the greatest proportion of all the man-made sources of radiation to which man was exposed. The report eventually took the form of a White Paper, presented to Parliament later that year. At the same time, evidence was building up of elevated death rates from leukaemia among radiologists, among atom bomb survivors, and among those given radiotherapy for ankylosing spondylitis[11]. Partly in response to this, the Minister of Health and the Secretary of State for Scotland set up a committee at the end of 1956, chaired by Lord Adrian, to examine "Radiological hazards to patients". This Committee produced three reports over the next 10 years and, in the course of its inquiry, surveyed the numbers and types of X-ray examinations carried out during one week in all Britain's hospitals, chest clinics, dental surgeries and other institutions.

4.15 The first, interim, report of the Adrian Committee[12] was produced quickly to try to allay public fears about mass chest radiography, fears which had been aroused by the increase in radioactive fallout caused by atmospheric nuclear testing. The report concluded that mass radiography, at the (then) rate of nearly 5,000,000 examinations each year, would cause about 20 more cases of leukaemia than expected (out of a total of about 2,500). However, since in 1957 mass radiography had detected 17,835 cases of pulmonary tuberculosis, 9,400 cases of pneumoconiosis, 2,362 cases of lung cancer and 12,000 cardiac abnormalities, the Adrian Committee regarded that the slightly raised risk of leukaemia was outweighed by the benefits.

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9 **Recommendations of the International Commission on Radiological Protection**, British Journal of Radiology (1955), Supplement No. 6.

10 Medical Research Council, **The hazards to man of nuclear and allied radiations**. HMSO, London, 1956

11 Medical Research Council, **Annual Report for 1955-56**; MRC Special Report Series 295 (1957) **Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis** (Court-Brown and Doll)

12 Ministry of Health, Department of Health for Scotland. **Radiological hazards to patients. Interim report of the committee** (chairman: Lord Adrian) HMSO, London, 1959

4.16 The second report[13] gave much fuller details of the one week survey, from which it was computed that the average dose of radiation received by Britons was 19.4 milliroentgens per person per annum. Diagnostic radiology accounted for 14.2 milliroentgens, and radiotherapy for 5.2 milliroentgens. The Committee made many recommendations, some of them specific to various X-ray techniques and equipment, and some of them more general. The general recommendations were:

"a) There should be clear-cut clinical indications before any X-ray examination is undertaken, and it should be ascertained whether there has been any previous radiological examination which would make further examination unnecessary. For this purpose the case sheet should have a section labelled "previous X-rays".

b) To reduce unnecessary examination, arrangements should be made for the ready availability of previous films and for the routine transfer of films from one hospital to another.

c) All requests for examinations should state precisely the clinical indications and the information required.

d) There should be consultation between clinician and radiologist before extensive or repeated radiological examinations of young individuals are undertaken. It must be realised that radiological exposure is just as much the responsibility of the clinician as of the radiologist.

e) To reduce the necessity for repeat investigation, strict attention should be paid to adequate preparation of the patient before abdominal investigation.

f) Special precautions should be adopted in the radiography of pregnant women. Only essential examinations should be carried out during pregnancy and particular care should be taken to avoid irradiation of the foetus whenever possible. In all women of child-bearing age the clinician requesting the examination should never overlook the possibility of early pregnancy.

g) Any previous history of radiotherapy should be ascertained before a new course of treatment is undertaken. Permanent records of all radiotherapy should be maintained and be readily available for transfer from one hospital to another.

h) Consideration should always be given to alternative methods of treatment before radiotherapy for non-malignant conditions is undertaken."

4.17 The last of the above recommendations draws attention to a feature of medicine in the 1940s and 1950s, that many conditions other than cancers were treated with radiation (for instance, a wide range of skin conditions, and fungal infections such as ringworm). Radiotherapy was also used in ankylosing spondylitis, various arthritic conditions and even in deafness. The average gonadal dose of radiation ranged from less than 100 mrad to over 150 rad in women irradiated for "arthritic and rheumatic conditions" (including sciatica) – the latter dose might have been enough to sterilise some women. While the Adrian Committee recommended that external radiotherapy no longer be used in ten of the 46 conditions in which its use was recorded, it recognised

13 Ministry of Health, Department of Health for Scotland. **Radiological hazards to patients. Second report of the committee** (chairman: Lord Adrian) HMSO, London, 1960

a limited application in the remaining conditions, though today it would not be considered appropriate to use radiotherapy in these conditions.

4.18 The Committee's final report[14] concentrated on the somatic effects of radiation, producing from extensive calculations the estimate that the "diagnostic use of X-rays in 1957 produced on average a bone marrow dose of some 32 mrads per person per annum". It concluded:

"These findings support the conclusions and recommendations given in our Second Report. They reveal no necessity for major restrictions in radiological work. The number and type of examinations must be dictated by the needs of the patient. The implementation of the recommendations of our Second Report will materially reduce dose to the bone marrow as well as to the gonads."

4.19 A Committee that included some key figures in medical research at the time – Austin Bradford Hill, Thomas Holmes Sellars and Brian Windeyer, as well as the chairman, Lord Adrian – concluded that it was safe and sensible to continue using ionising radiation at doses and for some diagnostic reasons which would not be the case today (because alternative methods have since been introduced).

4.20 A second report to the Medical Research Council in 1960 on the Hazards to Man of Nuclear and Allied Radiations[15] endorsed the views of the Adrian Committee.

Radiation and research

4.21 From 1945 onwards, medical researchers, and research organisations such as MRC, became increasing involved in assessing the risks to health from the wider use of radiation (see above), and preparing advice for government. At the same time, the wider availability of radioisotopes, and new research methods, meant that radioactive tracers became a standard tool in biomedical research, and research using radiation in imaging, and in radiotherapy, also widened.

4.22 In 1945, the MRC set up its Committee on Medical and Biological Applications of Nuclear Physics, the first of nine committees which operated at various stages during the 1940s, 50s and 60s, to consider basic research into biological effects of radiation, research into health risks, emerging evidence on risks and protection, and research into new clinical applications of radiation. The work of two subcommittees during this period – the Isotope Advisory Panel (4.23), and the Working Party on Doses for Volunteers and Patients (4.26) – is relevant to this inquiry into research practices.

[14] Ministry of Health, Department of Health for Scotland. **Radiological hazards to patients. Final report of the committee** (chairman: Lord Adrian) HMSO, London, 1966

[15] Medical Research Council. **The hazards to man of nuclear and allied radiations. A second report to the Medical Research Council.** HMSO, London, 1960

4.23 In 1948, the Committee on Medical and Biological Applications of Nuclear Physics MRC set up the Advisory Panel on the Allocation of Radioactive Isotopes for Clinical Use (often referred to simply as 'Isotope Advisory Panel'). Its original function was to advise on the nation-wide 'rationing' of such isotopes. which were then in short supply. Subsequently, however, its main role became to authorise the allocation of radioisotopes, for any research or clinical use in the UK. Most, if not all, of the studies using isotope tracers conducted in the 1950s and 1960s in this report would have been approved by this Panel: certainly, those in Aberdeen were. Records of the Panel's assessment are not available, but from other documents is it clear that the assessment took account of the details of the dosage, the method of administration to patients and volunteers and the safety measures to safeguard the health of the relevant scientists and laboratory technicians[16]. Users were also asked "to notify the Advisory Panel of any untoward or unexpected effects observed in the course of the work with radioactive isotopes". However, guidelines also made it clear that in MRC's view, the ultimate responsibility for any harm caused rested with those conducting the research[17].

4.24 In the USA, the initial controls on the use of radioisotopes in research were similar. The supply of material was, initially, controlled by government, and requests for radioisotopes for research in humans were granted only after the potential risk had been considered. However, it is impossible to establish how effectively these central controls were implemented, and there is no evidence that risk assessments were undertaken for research using external radiation (e.g. x-rays).

4.25 In both countries, there do not appear to have been any widely used guidelines for research groups themselves. A 1953 paper from Marshall Brucer[18] (one of the leading specialists in radioisotopes at the time) is perhaps representative of he period. The paper discussed the advantages of using guidelines for the effective use of radiation in research, without any suggestion of the need for precautions. A sample of research studies in which radiation was used published before the mid-1950s is likely to show no mention of consent having been obtained (even for studies of no possible benefit to research subjects) and no indication of follow-up studies conducted to explore possible long-term effects of radiation exposure.

4.26 By the late 1960s, there appears to have been greater concern about the need to set standards in research. In 1969, John Stanbury[19], in his presidential address to the American Thyroid Association, proposed guidelines for the use of radioisotopes in research. In the same year, MRC's Committee on Protection against Ionising Radiation (PIRC) asked their Working Party on Doses for Volunteers and Patients to draw up guidelines on doses for volunteers and patients. They defined three dose bands – those which would be unacceptable under any circumstances, those which

16 See MRC file FD7/616 – document reference MRC 57/97, 'Radioactive isotopes for clinical use' (1957)

17 **Research Grants** MRC Pamphlet 1967 edition, paragraph 19

18 M Brucer, **Encouraging and Discouraging Research with Therapeutic Radioisotopes.** Journal of the Kentucky Medical Association (1953) 51, 243-7

19 J B Stanbury, **On the use of radioisotopes in human experimentation.** Journal of Nuclear Medicine (1970) 11, 586-91

presented some risk and could be accepted if true consent was obtained, and those which entailed negligible risk (e.g. whole body dose of <100mrem (1mSv)) for which consent was not considered necessary at that time. These draft proposals were successively re-worked over the following few years, but, in the event, they were never published: in 1973, the MRC's Council finally decided that defining levels of "negligible" risk was not desirable[20]. Nevertheless, this work gives us a useful indication of how experts in the field viewed the risks involved, towards the end of the period covered by this inquiry (see 5.6.9).

4.27 However, even these steps seem to have been ahead of their time – as late as 1978 an editorial[21] in the American Journal of Roentgenology on the ethics of human experimentation made no mention of any guidelines for research involving radiation, nor did it draw attention to any specific difficulties with the use of radiation in research. Three major works on the ethics of research on human beings published in the US in the 1960s[22], 1970s[23], or 1980s[24] also failed to make substantial mention of research involving radiation. Beecher[25] and Pappworth[26] both mention isolated examples of research involving radiation, which they considered unethical, none of which appear to have received much attention.

4.28 The earliest widely published British guidelines on the irradiation of human subjects for medical research appear to be those of the British Institute of Radiology in 1975. From 1978, the administration of radioactive substances to patients or volunteers was legally regulated, and a new body, the Administration of Radioactive Substances Advisory Committee (ARSAC) was established to advice Health Ministers on applications for clinical or research use of radioactive substances. In 1988, the National Radiological Protection Board issued new guidance notes[27] for protection against ionising radiation which included a section on medical research. They categorised research projects according to the level of effective dose equivalent, and advised on the categories of radiation exposure for the different groups of potential research subjects. No specific guidance on the conduct of research involving radiation in human subjects was therefore available to British researchers until after all the research featured in this particular television programme was concluded.

20 Minutes of the Council meeting of 15 November 1973

21 WH McAlister. Guest Editorial, **Human experimentation regulations and ethics.** *American Journal of Roentgenology* (1978) 130, 1200-01

22 P A Freund (ed.) **Experimentation with human subjects.** George Allen and Unwin, London, 1972. (First appeared as a special issue of **Daedalus, 1969**)

23 J Katz. **Experimentation with human beings.** Russell Sage Foundation, New York, 1972.

24 R J Levine. **Ethics and regulation of human research.** Urban and Schwarzenberg, Baltimore, 1981.

25 H K Beecher. **Ethics and clinical research.** New England Journal of Medicine (1966) 274, 1354-60

26 M H Pappworth. **Human guinea pigs.** Routledge and Kegan Paul, London, 1967

27 National Radiological Protection Board et al. **Guidance notes for the protection of persons against ionising radiation arising from medical and dental use.** HMSO, London, 1988.

Conclusions

4.29 No specific guidelines on the conduct of research using ionising radiation on human beings were generally available to researchers in the United Kingdom until 1975 – some five years after the publication of the results of the latest study featured in the programme. Nevertheless, scientific knowledge of the potential health effects developed steadily over the period, and awareness of the risks grew.

4.30 Throughout the period, the MRC's Isotope Advisory Panel provided some central advice on, and control of, the use of radioisotopes in research and medicine – though not on other uses of radiation.

4.31 The ethos surrounding research involving patients and volunteers was also developing slowly at this time. Awareness of the 1947 Nuremberg Code appears to have been limited, and it was not until the early or mid 1960s that widely recognised and accepted ethical guidelines for research (addressing consent, the balance of risk and benefit, and other issues) emerged.

5. THE MRC RESEARCH FEATURED IN THE PROGRAMME

5.1 As well as entering into a discussion on particular concerns raised by the programme, this report first seeks to establish a clear factual background on the purpose and methods of each of the particular studies featured.

5.2 Monitoring Strontium-90 in bone and tissue

5.2.1 **Purpose and Background to Study:** Significant Governmental and public concern in the mid 1950's over the problem of radioactive fallout resulting from the atmospheric testing of nuclear weapons led to the Government announcing plans to monitor this new form of environmental contamination. The UK Atomic Energy Authority (UKAEA) established a programme to monitor levels of Strontium-90 in human bone in the UK in 1955. Following increasing levels of public concern, the Government established a standing committee set up under the auspices of the MRC and Agriculture Research Council – the Joint Committee on the Monitoring of Radioactivity from Fallout. The Committee had a specific remit to monitor the effects of the products of nuclear fission, not only in bone and other tissues, but also in air and rainwater, and assumed responsibility for the UKAEA studies from 1957. Monitoring was extended to the human diet in 1958.

5.2.2 Monitoring of Strontium-90 in human bone was discontinued in 1970; monitoring of levels in the human diet continued and results are now published by the National Radiological Protection Board.

5.2.3 **Method:** Pathologists were requested to supply samples of fresh bone obtained at routine autopsy. Until 1966, the femur was the standard sample obtained – this was switched to vertebrae for the final few years of the study. The sample was then reduced to ash and the level of Strontium-90 measured. This measurement was then corrected to take account of the level of naturally occurring strontium-90 in human bone. In addition to the level of Strontium-90, a record was also kept of the type of sample, the date of death, age at death and the county in which the individual was resident at time of death. Samples were taken throughout the UK. It does not appear that consent for the removal of samples was sought.

5.2.4 **Risk from radiation:** individuals were not subjected to any radiation exposure as a result of the study.

5.2.5 **Results:** Results demonstrated that levels of Strontium-90 recorded peaked in 1964 following the extensive testing of nuclear weapons carried out by the USA and USSR in 1961-62. The data produced by the study contributed to an accurate assessment of the effect of widespread nuclear testing, which in turn ultimately informed the debate about a world-wide ban on atmospheric nuclear testing.

5.2.6 **Discussion:** The mothers featured from North Wales 'participated' in the only piece of MRC funded research included in the television programme which did not involve radioactive material being administered to human subjects. As such, there is no issue

of 'risk from radiation' to be considered. However, the subsequent disclosure by the documentary of details about inclusion in the study has nevertheless resulted in emotional distress to the individuals involved. It was apparent from the programme (and confirmed by Grace Brown when the Committee met with her) that parental consent was not sought before the bone samples were taken at autopsy. Indeed, until researchers from Twenty-Twenty Television contacted them, neither of the women featured had any knowledge of what had occurred.

5.2.7 Mrs Brown confirmed that she and her husband had consented to a post-mortem being carried out on their son in order to establish the cause of his sudden death. Though consenting to the procedure itself caused some distress, they agreed that if knowledge could be gained that might possibly save another child's life, the death of their own child would not have been wholly in vain. Consent was at no stage sought for the removal of bones. Once the post-mortem had been conducted, Mrs Brown did not request to see her son again. Therefore, the issue of access did not arise. This is different from the other case featured in the programme, where Jean Pritchard expressed a wish to dress her daughter in her christening robe prior to burial. Access to the body was denied, presumably with a view to preventing the additional distress of discovering that the femora had been removed.

5.2.8 The Committee has tried to establish what would have been normal practice during the period in relation to a deceased infant. Whether it would have been usual at the time for a mother to ask to see the body of her child might well have depended on the particular area of the country – it certainly seems to be the case that it would have been common in Wales at that time for the family to wish to have, and to be allowed, access to the body. We have been advised by a retired nurse who worked in Anglesey for 30 years that it was customary for relatives to see the body before burial. However, in other parts of the country, access to the body might have been a rare occurrence. Given the generally paternalistic nature of both medicine and wider society during the period, a doctor may not have offered access to the body, for fear of causing further distress. Under the provisions of the 1961 Human Tissue Act, there is no legal 'ownership' of a cadaver; the act instead focuses on the concept of a person in lawful possession. However, regardless of the legal position, the Committee believes that the moral issues are the real concern in this case. One needs only to look to organ transplantation for a contemporary parallel – it would be unthinkable for a doctor today to remove organs at autopsy without seeking the prior consent of relatives, regardless of the provisions of the Human Tissue Act.

5.2.9 Regardless of the ethics of removing tissues at autopsy without consent, a wide range of tissues were often removed during the period for research purposes, without the consent of relatives. However, the boundaries between the requirements of an autopsy to establish the cause of death and those for extending the range of knowledge and understanding of disease are blurred. Such examinations might or might not be regarded as research, depending on whether a hypothesis was being tested. It is not denied that the purposes of research may require tissue samples to be taken at post-mortem. However, in the absence of explicit information to the contrary, relatives (both then and now) agreeing to the performance of a post-mortem do so primarily to

discover the cause of death, and most will have some (albeit limited) knowledge of what the procedure entails. Despite this, there is nevertheless an expectation that the body will be returned to them without unnecessary mutilation and it is this expectation which may be violated when samples are taken without consent. Given the prevailing context of research at the time this study was carried out, the practice adopted in this study is perhaps, in retrospect, hardly surprising. However, this should not detract from the fact that it is unacceptable to deny access to any mother who wished to hold, dress or otherwise touch her child, or indeed to remove tissues which might prevent her from doing so (other than what might be required to establish the cause of death) without parental consent.

5.2.10 As is the case with the other studies, contemporary practice differs from that of the 1950s. Today, Research Ethics Committees (RECs) ask that the consent of relatives is obtained prior to post-mortem for the use of a body for research purposes, and in some cases have asked that the body is returned in as 'normal' a condition as possible (e.g. by specifically requiring that a removed bone is replaced with an artificial substitute) as a pre-condition of the study going ahead.

5.3 Iodine uptake by the thyroid during menstrual cycle and pregnancy using I^{131}

5.3.1 **Investigators:** E Pochin, University College London (published 1952)[28]

5.3.2 **Purpose and Background to Study:** The purpose of this study is not explicitly detailed in the scientific publication. However, the paper indicates that the study aimed to gain knowledge of the changes in the thyroid gland during the menstrual cycle and during pregnancy by measuring the rate of uptake of iodine.

5.3.3 **Method:** Radioiodine (Iodine^{131}) was given intravenously to each of five female and five male participants once a week for four successive weeks. Counting rates using a Geiger counter were measured from subjects' necks and thighs 2 hours after each dose was administered. Counting rates were taken immediately before the administration of each dose for control purposes. The thyroid uptake from each dose was estimated by the ratio between the rise in counting rate taken simultaneously at the neck and thigh (the 'neck-thigh ratio' method developed by Pochin and utilised again in the Halnan study below). After completion of the tests, the female participants notified the research team of the dates on which their monthly period had started whilst the study was being conducted; male subjects were used as a control group to record variations in thyroid activity which were not of menstrual origin. A further series of tests was conducted in which 57 women were given single or double tests at different stages in their menstrual cycles. The method was as described above. In a third series of tests, similar data was collected (using the same method) in relation to five subjects during pregnancy and within a few weeks of delivery. The neck:thigh ratio was measured 4 hours after the administration of oral radioiodine and recorded at 12, 24 and 36 weeks gestation and 7 weeks after delivery.

[28] Full publication details for this and the following studies can be found at Annex 3

5.3.4 **Risk from radiation:** The risks of this study would have been restricted to the long-term effects of radioiodine on the thyroid gland of the mother and that of the fetus. The Iodine^{131} used in this study had a half-life of around 8 days. This study administered relatively high doses, with an estimated risk of induction of fatal cancer (assuming a linear hypothesis) of some 8.4 in 10,000. A detailed analysis of the dosage used is contained at Annex 4.

5.3.5 **Results:** The first two series of tests demonstrated that the thyroid uptake of iodine did not appear to be affected by the menstrual cycle. The third set of data demonstrated that the neck:thigh ratio appeared to increase slightly during pregnancy; of greater significance was the drop in the ratio after delivery, relative to the value during pregnancy. However, the sample size (five patients) was too small to enable any firm conclusions to be drawn from this finding. The study was not for the direct benefit of participants and there is no recorded evidence that the consent of the participants was sought.

5.3.6 **Discussion:** When the study was reported, little was known about thyroid function during pregnancy and whether thyroid function varied during the menstrual cycle. The availability of radioiodine (I^{131}) provided for the first time a simple, minimally invasive means of measuring thyroid function. Furthermore, these measurements could be taken without discomfort to the patient (other than of the injection required). This newly-available approach was introduced in the early 1950s into general clinical practice for the diagnosis of thyroid disease and its interpretation required knowledge of the normal range of results in different conditions (including pregnancy and throughout the menstrual cycle). There was evidence from the frequent development of goitre that the thyroid gland behaved differently during pregnancy, but it was unclear as to whether this was due to normal physiological changes or was evidence of disease. This work was subsequently taken forward by the work conducted by Dr Keith E Halnan at UCL and the group at the Aberdeen Maternity Hospital (see below).

5.3.7 As has already been stated, there is no evidence as to whether informed consent was obtained from the participants involved, though it might be assumed that at least some information was disclosed from the fact that all of the participants had to 'consent' to the intravenous injection which the study required. This study involved the second highest doses of all the studies which the Committee has considered (see Annex 4), though even this posed only a negligible risk. The study delivered no personal therapeutic benefit to the participants involved, though benefit would derive to others from the improved knowledge about thyroid function in pregnancy and the normal range of test results. Given the (albeit negligible) risk posed by the radioactive iodine and the lack of personal benefit to study participants, concerns would today be expressed if such a study was conducted without fully informed consent. However, it was not practice at the time this study was conducted to require investigators to present details about the risks or benefits of studies and request and record their formal consent.

5.4 Iodine uptake by the thyroid in pregnancy, using I^{132}

5.4.1 **Investigator:** Dr Keith E Halnan, University College London (published 1958)

5.4.2 **Purpose and Background to Study:** Prior to the introduction of radioiodine, the only reliable method of measuring thyroid function was to measure the human metabolic rate at rest. This was a cumbersome and lengthy process involving an overnight stay in hospital, with a number of measurements taken while the subject remained resting.

5.4.3 Diagnosing thyroid dysfunction during pregnancy is important as thyrotoxicosis (an overactive thyroid) is a condition potentially dangerous to both mother and child. At the time there were no reliable biochemical methods of monitoring thyroid function; the advent of radioiodine allowed these important measurements to be taken quickly and with none of the previous inconvenience to the patient. If it proved to be an effective method of monitoring thyroid function, it was planned to develop the method into a test for routine clinical use.

5.4.4 **Method:** Study volunteers were recruited from the University College Hospital antenatal clinic with 2-4 volunteers recruited in successive weeks until a total of 25 women was reached. All women had the purpose and nature of the study explained to them orally. A dose of Iodine^{132} was given to participants orally one or two hours after breakfast. Two hours later the neck and thigh activities were simultaneously measured (the neck-thigh ratio method developed previously by Pochin). Measurements were taken at 12, 24 and 36 weeks gestation and 1 and 6 weeks post-partum.

5.4.5 **Risk from radiation:** Iodine^{132} was utilised for the study as its half life of 2.3 hours is considerably shorter than the Iodine^{131} used in the Pochin Study (with a half-life of 8 days). The risks to the patient were correspondingly reduced. Professor Elliott has concluded that the risk from the dose used in this study incurred a maximum risk of induction of fatal cancer (assuming a linear hypothesis) of 6 in 1,000,000. Further details are contained in Annex 4.

5.4.6 **Results:** This was primarily a non-therapeutic study, for which consent was sought prior to inclusion in the study. The results of the study produced valuable data about the function of the thyroid during pregnancy, showing a clear difference in the uptake of radioiodine in the thyroid of pregnant women. As has been mentioned above, the test was designed for diagnostic use in routine clinical practice. However the lengthy process involved in preparing Iodine^{132}, coupled with the advent of biochemical methods of taking such measurements a few years after the study was conducted, resulted in the test being little used in practice.

5.4.7 **Discussion:** The research conducted by Dr Halnan was to gain information about thyroid function during and after pregnancy and would not have benefited the participants directly. However, as a result of the study, there would have been a benefit to any patient who was suspected to be suffering from thyroid dysfunction (in that the condition, once discovered, could have been treated). The study appears to have been conducted to scientific and ethical standards judged to be high even today, with a clear purpose aimed at improving diagnostic methods for a potentially serious condition.

As with so many of the other studies, we were unable to trace any of the study participants who were recruited into the Halnan study, though we were able to speak with Dr Halnan himself. The paper publishing the research is exceptional in that it contains an explicit reference to the obtaining of consent from the study participants. Dr Halnan confirmed that he supplied as much information as possible to study participants, including a reference to the fact that the study involved the administration of 'a tiny dose' of radioactive material. Women were expressly given the opportunity to refuse to participate; many did agree to be included in the study, including the wives of some doctors. Explanations given prior to the study were accordingly modified to take into account the different levels of knowledge possessed by the study participants and Dr Halnan offered women the opportunity to discuss the matter with their husbands before making a final decision on participation. As was common, both then and now, the research team also took the test themselves. The explicit reference to the obtaining of consent, coupled with the level of information given to the participants by Dr Halnan, appears to have been well in advance of the standards at the time.

5.4.8 No follow up studies were conducted, partly because Dr Halnan himself moved to Manchester shortly after the research was conducted, and also because he considered the risk from the radioactive material to have been minimal (the dose was no larger than the routine diagnostic dose used during the period for measuring thyroid function). Dr Halnan informed the Committee that, at the time of conducting his study, Pochin had already researched the records of over 20,000 patients world-wide who had received radioiodine for thyrotoxicosis at far higher doses than were administered in Halnan's study. Pochin had found no evidence to support the view that the level of radiation used led to an increased incidence of cancer or leukaemia.

5.5 Changes in thyroid function during pregnancy, using I^{132}

5.5.1 **Investigators:** S A Aboul-Khair, J Crooks, A C Turnbull, F E Hytten, Aberdeen (published 1964)

5.5.2 **Purpose and Background to Study:** At the time this research was conducted, a number of other pieces of research had already been published about thyroid function during pregnancy. The results of these studies presented an incomplete picture of thyroid function and, indeed, studies sometimes contradicted one another. As a result, the physiological changes which occurred in thyroid function during pregnancy were not clearly understood. As has already been stated above, thyroid dysfunction during pregnancy was a condition which presented a risk to both mother and child. Before a decision could be taken as to whether a particular patient was at risk, it was first necessary to establish the normal rate of thyroid activity in pregnancy (for comparative purposes). This study therefore aimed to resolve the contradictory evidence on thyroid function by taking measurements of iodine uptake and the renal handling of iodine during pregnancy

5.5.3 **Method:** Fifteen pregnant women were studied as outpatients before the 12th week and during the 16th, 24th, 32nd and 36th week of pregnancy. Four women were additionally studied during the 39th week. Thirteen of the original subjects were additionally studied in the 2nd, 6th and 12th week post-partum. Post-partum, subjects were

divided into two groups – 7 women who chose to breast-feed, and 6 who chose to feed their babies artificially. The latter group were given stilboestrol 3 times daily in the first 6 days following delivery to suppress milk production.

5.5.4 Thirteen non-pregnant subjects constituted a control group.

5.5.5 Iodine metabolism was studied using Iodine^{132}, administered intravenously. Between 1 and 2½ hours after administration, measurements were taken of the rate of clearance of the radioactive iodine by the thyroid gland. Measurements were also taken of the renal clearance of iodine.

5.5.6 **Risk from Radiation:** The greatest risk from exposure to the radioactive material in this study (assuming a linear hypothesis) applied to the mothers and fetuses, with a risk of fatal cancer of 3.7 and 5.3 in 100,000 respectively. The control group had much lower exposure, and a risk of around 3 in 1,000,000.

5.5.7 **Results:** The study concluded that the renal clearance of iodine increased early in pregnancy, remained high throughout and returned to normal levels within 6 weeks post partum. There was an associated fall in the level of iodine concentration in the plasma during the same period. The findings of the study did not support the prevailing hypothesis (proposed by other research) to explain the high incidence of goitre during pregnancy. However, the evidence which emerged did support the alternative hypothesis that pregnancy resulted in an iodine deficiency, which began early in pregnancy and continued throughout. To compensate for this, it appeared that the thyroid gland increased in size and cleared more plasma of iodine in order to produce the same amount of thyroid hormone as for a non-pregnant female.

5.5.8 **Discussion:** In relation to this study, the Committee was fortunate to meet with Kathleen Morrison and Loretta Tennant, former study participants, who supplied a clear and open account of their recollections. It is clear that some information was provided to them by the Research Unit at Aberdeen Maternity Hospital. However, given that neither woman was initially aware that radioactive material was being used or that testing would continue after the birth of their children, this information was obviously not as comprehensive as it could have been. We understand that, at the time, the clinical investigators themselves did not always have a deep understanding of the risks from different uses of radioactivity, and would have relied on the advice of physicists. Whatever was said to participants in research would probably have been quite vague, reflecting the investigators' own knowledge. In this case, neither participant recalled receiving information about possible discomfort or risk and, as was normal practice at the time, neither was asked to give written consent to participation in the study (though both would have given it at the time if asked). Neither had been told what the results of the study were, or supplied with a copy of the scientific paper published as a result.

5.5.9 This study appears to have been conducted in line with the prevailing research practice at the time and, from the information available, it did not expose the participants to a significant level of risk (but see also 5.6 and Chapter 6 below). Consent was sought, but information was not given about the level of possible risk from the radioactive material administered. In Mrs Morrison's case, this failure has led to her

being concerned about the possible effects of the study throughout the 30 years since it was conducted – an issue which will be returned to below. Mrs Morrison informed the Committee that her mind would have been set at rest if a systematic check up or follow-up study had been carried out on participants to confirm that no undesirable side effects had developed. It is accepted by the Committee that it is unrealistic to expect follow-up studies to be conducted for all research and that these are only conducted if there are reasons for suspecting possible long-term effects. However, this should not detract from the fact that reassurance and information should be available to study participants or their GPs should they require it.

5.5.10 Concern was expressed in the "Deadly Experiments" TV documentary that the study led to an increased incidence of thyroid cancer in Aberdeen. Data published in the Cancer Incidence in Five Continents series indicate that, in international terms, Scotland's ranking for thyroid cancer was unremarkable during the period 1978 to 1987 (see Annex 8, Table 1). However, data published in Cancer Registration Statistics Scotland 1981-1990 (CRSS) show that standardised registration ratios for thyroid cancer are elevated for both men and women in the Grampian region when compared with the ratios for Scotland during the period 1981-1990 (also at Annex 8, Table 2). The lower 95% confidence interval for thyroid cancer in females in the Grampian region is well above 100, implying an elevated rate that is statistically significant. The lower 95% confidence interval of 99 (below 100) for males increases its likelihood of having arisen by chance. Unpublished data supplied by the Scottish Cancer Registry also show that the world age standardised rates for thyroid cancer for males and females were higher for Grampian compared with Scotland as a whole for each of four consecutive five-year periods spanning 1975 – 1994 (Annex 8, Table 3).

5.5.11 The elevated standardised registration ratios for thyroid cancer in the Grampian region should be interpreted with caution. Relatively rare diseases can be subject to substantial fluctuations in incidence simply through the play of chance. The relatively small numbers of cases of thyroid cancer are reflected by wide confidence intervals.

5.5.12 It is also possible for some apparently statistically significant results to arise by chance. The CRSS contains, in effect, multiple tests of significance – each cancer site has standardised registration ratios and 95% confidence intervals calculated for 15 Health Boards and separately for males and females. On the other hand, the incidence of thyroid cancer in Grampian does appear to have been consistently elevated over time. Another general explanation for the observed excess may be ascertainment bias – consistently better reporting of cases of cancer in one part of the country resulting in that part of the country appearing to have a higher incidence of cancer. However, other cancers might also be expected to be more common in the Grampian region if ascertainment bias had occurred, but this does not appear to be the case.

5.5.13 Two additional important limitations of the data lead us to conclude that the apparently elevated incidence of thyroid cancer in Grampian cannot be explained at present, or necessarily be attributed to the exposure of some individuals to radioiodine in the 1960s. Firstly, the place of residence at the time of diagnosis may well differ from the place of residence at the time of the relevant exposure. The number of females living in Grampian who were diagnosed as suffering from thyroid cancer during the period

1975 to 1994 and were also exposed to radioiodine during the research carried out in the 1960s is unknown. Secondly, the incidence of thyroid cancer in both males and females in Grampian may be higher than in other parts of Scotland for other unknown reasons.

5.5.14 No follow up took place of study participants and it is recognised that these findings cause concern to them and to their offspring. However, a number of population studies have contributed to a better understanding of the association between radiation exposure and thyroid cancer. The studies employed different methodologies and populations from many countries (survivors of the atomic bombings in Japan and patients treated with radiotherapy for skin disorders, for example) exposed to a wide range of doses. All have demonstrated significantly increased risks of thyroid cancer following radiation exposure during childhood, but external exposure during adulthood and internal exposure to therapeutic or diagnostic doses of I^{131} have not been linked convincingly to thyroid cancer[29].

5.5.15 Despite the reassurance which studies of radiation exposure may offer, the results may not be directly applicable to the study participants in Aberdeen, and it is unsatisfactory for them to remain uninformed about the presumably negligible but nevertheless unquantified risks which they may have faced. In view of this, the feasibility of a further study to examine the possible association between the apparent excess incidence of thyroid cancer in Grampian women and exposure to radioiodine in the 1960s should be explored. The obvious way to investigate this further would be to conduct an analytical epidemiological study. However, if study records no longer exist, it would be impossible to conduct an unbiased retrospective cohort study or to overcome problems of recall bias in a case control study. In suggesting a further study, it is recognised that there may be considerable practical difficulties. These may make it difficult, if not impossible, to conduct a study which can conclusively prove or disprove any relationship between participation in the original study and the incidence of thyroid cancer.

5.6 Structural and functional development of the human fetal thyroid, using I^{131}

5.6.1 **Investigators:** S A Aboul-Khair, T J Buchanan, J Crooks, A C Turnbull (published 1966)

5.6.2 **Purpose and background to Study:** The use of radioiodine in clinical and experimental medicine had become well established in the 1960s. Studies of thyroid function during pregnancy had been carried out in preceding years using the short-lived isotope I^{132}. Although the doses used in these earlier studies were described by the investigators as being within permissible limits in terms of irradiation to the fetal thyroid and gonads, it was the opinion of the authors of this study that this view was based on inadequate data primarily because the biological half-life of iodine in the fetal glands was unknown at the time of the previous studies (the calculation of the risk to the fetus for these earlier studies was based on an estimate of the biological half-life).

[29] Ron E. **Thyroid Cancer.** In Schottenfeld D, Fraumeni J F (editors) Cancer Epidemiology and Prevention. 2nd Ed. Oxford university press 1996. p1005

5.6.3 As the determination of the actual biological half-life of iodine had in fact proved to be an overestimate, this study aimed to investigate how the fetal thyroid gland developed its capacity to trap iodine and to obtain more accurate estimates of irradiation doses to the fetal thyroid and gonads following the administration of radioisotopes of iodine – either by accident or intention - to pregnant women.

5.6.4 **Method:** The study was carried out in 37 women with normal pregnancies in whom therapeutic termination was performed on medical or psychiatric grounds. 29 pregnant women had a hysterotomy after an injection of I^{131}. Their period of gestation ranged from 13 to 23 weeks. Levels of radioactivity were measured in the fetal thyroid gland as well as the rest of the fetus, amniotic fluid and maternal plasma. In 2 women having a hysterotomy at 8 and 9 weeks of pregnancy, the fetal thyroid gland could not be identified and levels of radioiodine administered to the mothers were measured in the fetus. In the remaining women, no radioiodine was administered prior to termination, but fetal thyroid glands were obtained for histological examination. We understand that the normal practice would have been to flush remaining radioiodine out of the body after the hysterotomy: this would have significantly reduced womenís exposure, but regrettably, the published account does not specify whether or not this was done.

5.6.5 **Risk from Radiation:** This study, using the long-lived I^{131} isotope, involved the highest exposures of any of the studies. If radioiodine was not flushed out at the end of the study, the risk of inducing a fatal cancer ranged from 12.7 in 10,000 for those receiving the very highest doses, to 6.3 in 10,000. .

5.6.6 **Results:** The growth and the capacity of the fetal thyroid gland to concentrate radioiodine increased as gestation progressed, whilst the estimated biological half-life of radioiodine was much shorter than that of the adult up to the 19th week of gestation.

5.6.7 **Discussion:** The data obtained were used to calculate irradiation doses to the fetal thyroid and gonads produced by isotopes of iodine entering the maternal circulation.

5.6.8 This study demonstrated that the earlier estimate of iodine absorbtion by the human fetus was in fact an over-estimate. This work therefore consolidated previous knowledge on the issue and gave a better understanding of the risks posed to the human fetus in using radioiodine. Contemporary observers might question whether it was ethical to conduct both this and the earlier research when it was unclear of the risk to which participants were being exposed in the study. However, human physiology was being extensively studied throughout the period during which these studies were conducted and many investigations were carried out aimed at increasing the general pool of scientific and clinical knowledge. Despite the fact that the precise biological half-life of iodine was unknown at the time, the studies were carried out within the accepted parameters of the period in terms of risk to the participants.

5.6.9 The doses of radiation involved in the study were, for some participants, many times higher than diagnostic x-ray of the period. However, the 1969 MRC Working Party (see 4.26) considered that non-therapeutic studies involving exposures of up to 5rems (equivalent to 50mSv for many types of radiation) could be acceptable if true consent

was given. The highest doses in this study were around 25mSv: while one might question, with hindsight, whether this level of exposure was justified by the knowledge gained, it would not have been considered unacceptable at the time.

5.7 Placental blood flow, pre-eclampsia, and hypertension, using Sodium[24]

5.7.1 **Investigators:** J C McClure Browne and N Veall, Hammersmith Hospital, London (published 1953)

5.7.2 **Purpose and Background to Study:** At the time this study was conducted, knowledge about human placental blood flow was incomplete, largely due to the difficulties of studying the placenta *in vivo*. A serious complication of some pregnancies is raised blood pressure and circulatory changes (eclampsia or pre-eclampsia) which may result in the death of the fetus and/or mother. When this study was carried out, eclampsia was thought to be caused by a reduction in the blood supply to the placenta, with a consequential rise in the blood pressure of the mother (almost as if the mother's blood pressure increased in order to restore the blood flow to the fetus). However, this theory remained untestable until the advent of radioisotope tracers allowed placental blood flow to be estimated by measuring the rate at which such an isotope was cleared from within the placenta.

5.7.3 **Method:** Women who were 38 weeks pregnant or over were admitted to hospital for participation in the study; it was a precondition of entry to the study that the placenta was found to be situated partly or wholly on the anterior uterine wall (located using a radioactive sodium method). Three days elapsed in order to allow the residual radioactivity from this initial investigation to drop, during which time subjects' blood pressure was taken twice daily and a mean level calculated. A needle was inserted into the chorio-decidual space (the blood-filled space between the placenta and wall of the uterus) and a small amount of saline, containing 10 microcuries of radioactive sodium, was injected. The needle was immediately withdrawn and a Geiger counter tube was placed over the site of the injection and a record taken of the rate of decrease in the level of radiation (as an indirect measure of blood flow). A record of the weight of the placenta was taken at the time of delivery.

5.7.4 **Risk from radiation:** Detailed figures are contained in Annex 4; Professor Elliott has concluded that the risk posed by the dose used in the study had a 'worst-case' risk of induction of fatal cancer (assuming a linear hypothesis) of 6.5 in 1,000,000.

5.7.5 **Results:** The study determined the relative rates of maternal blood flow in the placentae of normal, pre-eclamptic and chronically-hypertensive women. Placental blood flow was found to be reduced to about one third in pregnant women who developed a raised blood pressure (pre-eclampsia). However a similar reduction was observed in pregnant patients with chronic high blood pressure, which suggested that the cause of the low placental blood flow lay outside of the placenta. However, this did not exclude the possibility of a further rise due to low placental blood flow. The study therefore contributed valuable new information about placental blood-flow and further informed scientific debate about the causes and effects of pre-eclampsia and hypertension in pregnancy.

5.7.6 **Discussion:** Understanding of the mechanism of the production of raised blood pressure in pregnancy is needed if rational measures to prevent and/or treat it are to be developed. While the results of this non-therapeutic study did not deliver any direct benefit to either the mothers or children involved, the results had the potential to deliver great benefit to others.

5.7.7 To satisfy the ethical requirements of contemporary research, such a study would today require that the risks of the study were very small and greatly outweighed by the potential benefits – preferably to the patients themselves, or otherwise to others through increased medical knowledge. It would also be a requirement that the patients understood the nature of the research and its risks and freely gave their consent. However, in the 1950s, researchers and clinicians tended to make these judgements on behalf of their patients. Even if the nature of the research was explained to patients and their consent sought, this was unlikely to have been recorded in the scientific publication.

5.7.8 Professor Elliott has again largely reassured the Committee in relation to the risk posed by the dose of radiation administered – this was not an excessive risk when compared with a diagnostic dose used at around that period. As is common with research literature of the period, no information is supplied concerning the obtaining of informed consent from the participants. Nor has the Committee been able to speak with either of the researchers or participants involved. The research was reported in 1953 (i.e. 44 years ago) and it is probable that many individuals concerned with the study have now died.

5.7.9 A factor which caused the Committee concern relates to the method used to introduce radioactive sodium into the placenta, and in particular the specific piece of injection apparatus developed in the study (a picture of which is reproduced in the scientific paper). The Committee has accordingly consulted Professor Philip Steer (Obstetrics and Gynaecology at the Charing Cross and Westminster Medical School) who has advised that the procedure used in this study differs little in reality from Chorionic Villus Sampling (CVS) – a contemporary procedure in which a needle is inserted into the placenta itself in order to withdraw a small sample. Professor Steer is satisfied that the technique would not have posed an unacceptable risk and both he and Professor Wald have agreed that, as the procedure was carried out at 38 weeks gestation, the child could have been delivered immediately by caesarean section if there had been any complications. However, there must remain some concern that a procedure of no benefit to the subject (and for which no consent was recorded) may have resulted in a caesarean section – a procedure which carries a known risk to mother and child. It is also considered that the existence of this significant additional procedure (i.e. the needling of the placenta) required that consent be obtained from the participants.

5.8 Studies of brain metabolism which included mentally ill patients, using Sodium24 and Sulphur35

5.8.1 As has already been mentioned above, this 'type' of study raises particular issues in relation to obtaining consent, as participants may not be capable of giving consent by virtue of their mental condition. The Committee has looked briefly at two studies

carried out at an MRC unit in the early 1960s (see Annex 3 for full details of the appropriate scientific publications).

5.8.2 **Principal Investigators:** (a) A J Coppen and D M Shaw (published 1963), and (b) D Kemali, M K Gaitonde and A J Coppen, MRC Neuropsychiatric Research Unit, Surrey (published 1963)

5.8.3 **Purpose and background of studies:** Both of these studies were aimed at investigating metabolic processes in patients suffering from either schizophrenia or a depressive illness – processes about which little had previously been known.

In the first case, a study was made of the distribution of sodium between cells and the extracellular space. In the second, an investigation was made into the blood-cerebrospinal fluid barrier in patients with mental disorders.

5.8.4 **Method:** In both studies, a radioactive isotope was administered to patients (either orally or intravenously) with samples subsequently taken of blood and urine (in the first case) and blood and cerebrospinal fluid (in the second study) for measurement purposes. Full details of the methods used in each case are detailed in the appropriate scientific papers and are not reproduced here.

5.8.5 **Risk from Radiation:** The effective doses in both studies were similar. Assuming a linear hypothesis, there was a 'worst-case' risk of induction of fatal cancer ranged between 6.3 in 10,000 and 7.8 in 10,000. Detailed calculations are in Annex 4. As with the other research discussed, the advent of radioisotopes enabled the metabolic processes at work in patients with these conditions to be studied in vivo for the first time.

5.8.6 **Results:** The first study established that levels of residual sodium (including intracellular and some bone sodium) was very significantly increased in patients suffering from depression. This suggested that the metabolism of depressed patients differed from normal subjects in this respect. The second study established the rate of transfer of methionine sulphone from blood to lumbar cerebrospinal fluid in man. Both studies contributed valuable information about the metabolic and biochemical processes at work in patients with depressive illness and schizophrenia, thus leading to a greater understanding of the causes of these conditions. The Committee understands from Dr Coppen that the research findings enabled the MRC unit to pioneer new types of long-term treatment for severely depressed patients.

5.8.7 **Discussion:** As with the other studies above, it must be concluded that none of the participants in either of these studies would have received direct personal benefit from their participation, though the knowledge obtained would have contributed to the understanding (and presumably the ultimate treatment) of the condition from which they were suffering. The risk of harm posed by exposure to the radioactive isotope was again negligible.

5.8.8 The major issue to be addressed, therefore, is once again that of consent. As with the other studies examined from around this period, no mention is made in the scientific publications as to whether consent was sought from the participants, or whether the purpose, nature and risks of their participation was explained to them. Dr Coppen has, however, informed the Committee that oral consent was always sought from

participants and that no patient was included in the study who was incapable of giving this consent. It was explained to participants that the study would involve the administration of a radioactive material and that the Radiological Protection Unit and Belmont Hospital had approved the use of this material. It must be remembered that standards in relation to the obtaining of patient consent were not generally as rigorous as is the case today (certainly now, written consent is insisted upon as the norm). At the time these studies were conducted even those participants who were fully capable of giving informed consent were often not supplied with full details in relation to the study. The schizophrenic or depressed patients were not in reality treated any differently from other study participants of the period.

5.8.9 The second study involved participants undergoing a lumbar puncture in order to remove a sample of cerebrospinal fluid for analysis. The Committee's concerns in relation to this procedure are similar to those discussed above under the McClure Browne and Veall study in that participants were required to undergo a procedure (involving discomfort) with which a known risk was associated for no direct benefit to themselves. As in the Hammersmith study, the existence of this additional procedure required that consent be obtained from the participants concerned.

5.9 Anaemia and iron in the Indian diet ("Chapatti Study"), using Iron^{55} and Iron^{59}

5.9.1 **Principal Investigator:** Dr P Elwood, MRC Epidemiology Unit (South Wales) (published 1970)

5.9.2 **Purpose and background of study:** At the time the study was conducted, Dr Elwood was a member of the World Health Organisation (WHO) Panel on Anaemia. The Panel was particularly interested in a previous piece of Dr Elwood's work in which iron had been baked into bread and consumed by volunteers, whose level of iron absorption was then measured. At the time, anaemia was a particular problem in the Third World and the panel accordingly encouraged Dr Elwood to conduct a similar study using non-fermented wheat products to mimic a third world diet. Such a study would enable an assessment to be made of the level of iron absorbed from an Indian diet. If it became apparent that low iron absorption was resulting in widespread anaemia, this could then be corrected through dietary supplementation.

5.9.3 A radioisotope was added as a 'marker' to the iron enabling measurements of iron absorption to be made far more accurately that would be the case if any other technique was used. This technique also reduced the time period required for the study, as conclusions could be reached over a period of weeks, rather than years. The study protocol was discussed with a number of scientists and was submitted to the MRC Radioactive Isotope Panel before the study commenced; no queries or concerns were raised about the methodology.

5.9.4 **Method:** Koga II wheat was grown specifically for the project by the Agriculture Research Council, and radioactive iron was added to it at the time of earing. The wheat was milled into white and wholemeal flour and a radioactive iron salt was added to the latter. An equal number of chapattis was then prepared from each type of flour under

the supervision of an Indian housewife. Once cooked, each chapatti was weighed, labelled, and frozen until eaten. Twenty-one Asian women, whose diet was closely similar to that of residents in the Punjab, were invited to participate in the study. A member of the research team (frequently Dr Elwood himself) visited each participant to explain the nature of the study. As the study population did not speak English, a local health visitor acted as interpreter; a member of the participant's family was also often utilised in this role.

5.9.5 Each woman was supplied with one chapatti on each of four consecutive mornings and asked to consume it as part of her normal diet. All four chapattis were made from either white or wholemeal flour; women were randomly allocated to one of the two groups. All women were visited a few hours after each chapatti was delivered to ensure it had been consumed in its entirety and to record the time of consumption. Seventeen days after the last chapatti had been eaten, women were taken in small groups by a member of the research team to a laboratory at Harwell in order to measure the level of iron retention.

5.9.6 **Risk from Radiation:** Professor Alex Elliott has estimated (see Annex 4) that the risk posed by the dose used in the study had a 'worst-case' risk of induction of fatal cancer (assuming a linear hypothesis) of approximately 35 in 1,000,000. The Harwell Laboratories were utilised as, at the time, they possessed the only equipment in the UK capable of making accurate measurements of the extremely low levels of radiation used in the study. Dr Elwood informed the Committee that it was unlikely that the laboratories would have been mentioned to the patients by name; however, it is doubtful whether the name would been recognised by the study participants at the time.

5.9.7 **Results:** The purpose of the study was to examine whether the problem of anaemia in the Asian population could be addressed by adding an iron supplement to food (in this case, flour). Thus, healthy volunteers participated in a study from which they personally would have received no immediate benefit, though the benefit to others (particularly overseas) was potentially great

5.9.8 **Discussion:** Following the broadcast of the television programme, and the subsequent publicity generated, there was a high level of public concern in relation to this study, which resulted in Coventry Health Authority carrying out their own investigation (included at Annex 5). Their report was fully endorsed at a public meeting of the Health Authority on 19 September 1995 and is fully endorsed by this Committee. The study was carried out for medical purposes and there is no question of there having been any link with the military. It was also established early on that the risk from the radioactive iron was very small – therefore the main issue to be examined in relation to this study centred on the obtaining of informed consent from the Asian women concerned.

5.9.9 Both this Committee and Coventry Health Authority were hampered in that none of the original research subjects came forward, despite numerous avenues being pursued. Nor were we able to locate the health visitor who was used as interpreter for the study. It is the Committee's understanding that the interpreter used by the research

team may not have been totally effective in communicating information to the study participants. As many of the visits were conducted outside school hours, participants' children were often asked by the research team to interpret instead. The relevant languages and dialects from the Indian sub-continent were likely not to have had the necessary technical terms in their vocabularies, and it is possible that a word did not exist for 'radiation' in any of them. The language and vocabulary barrier must have acted against the effective communication of factual information to the study participants. It must also be remembered that this was a close-knit community. Though pure conjecture, it is possible to assume that some information was exchanged between study participants and their families. Some women may also have sought information from Dr Shah (the local General Practitioner who served a large part of the Asian community at the time). Dr Shah died some years ago and it is therefore impossible to determine what information he may have passed to the research participants. A combination of these factors makes it difficult to ascertain what degree of information was actually possessed by the participants; it is possible that, despite the best intentions of the research team, full details of the study were not grasped by the women involved.

5.9.10 Against this, it is apparent that Dr Elwood took his responsibilities in relation to informing the women very seriously – he did not delegate the task of obtaining consent to anyone outside the research team, and frequently visited participants personally. He was conscious of the difference between a therapeutic and non-therapeutic study and took pains to ensure that all participants were aware that they were not receiving treatment for their anaemia (or any other pre-existing condition). All available evidence supports the view that a serious attempt was made to inform study participants effectively. Nor is there any evidence that the study was conducted in secret; Dr Elwood supplied the Committee with correspondence between himself and research participants and their families, which points to the study having been conducted openly. This view is supported by the fact that the study results were discussed after their publication by an informal research committee, which met at the local medical school to discuss research issues.

5.9.11 Overall, Dr Elwood is seen to be a researcher of the highest integrity who did not 'cut corners' in conducting his research. Indeed, this appears to have been a 'model' study in which research practice exceeded the prevailing standards of the period. Dr Elwood reacted quickly and positively to the approach both from this Committee and Coventry Health Authority, and answered all questions fully and openly. However, both society and research practice have changed markedly in the years since this study was conducted. Should such a study be proposed today, the study protocol would have to be passed by a research ethics committee, written consent would be required from study participants, and the services of a professional interpreter would be insisted on as a condition of carrying out the study. Coventry Research Ethics Committee have issued guidelines to ensure that study participants whose first language is not English properly understand the nature of any research, prior to giving written consent.

5.9.12 Though this was a non-therapeutic study, the overall purpose of the research was directly relevant to the health issues affecting the Asian community at the time. The study population was not identified in order to take advantage of their limited under-

standing of English; rather, it was because they consisted of the very societal group affected by the medical condition under investigation. It would have been inappropriate for a researcher to think that the problem of anaemia in the Asian population could be adequately researched by using white research subjects, consuming an 'English' diet.

5.9.13 The needs of ethnic minority research subjects generally are now better recognised, and accordingly treated more sensitively, than in the past. The level of information required to obtain informed consent from any non-English speaking study population must be the same as for an indigenous population, i.e. all key facts concerning the study, and the risks associated with it, should be effectively communicated. However, care needs to be taken in relation to the actual communication of those facts – both in terms of possible vocabulary limitations and the ways in which some languages are actually written. Given the difficulties in ensuring truly informed consent in this situation, the Committee briefly considered whether non-English speaking subjects should ever be asked to participate in research. However, it was recognised that it is equally important to ensure that the research needs of ethnic minorities are not neglected because of perceived difficulties in including them as study participants. Indeed, in the USA in 1995, the Food and Drug Administration (FDA) proposed that all research protocols should ensure an equitable study population in terms of gender and ethnic split where this was appropriate[30]. The US National Institutes of Health[31] and the Centers for Disease Control and Prevention[32] have policies for equitable recruitment into research studies.

30 Federal Register Vol 60 no 174, Friday Sept 8 1995, Proposed Rules

31 Federal Register Vol 60 no 179, Friday Sept 15 1995, Notices

32 Federal Register Vol 59 Monday March 28 1994, Notices

6. RADIATION AND RISKS

6.1 The risks presented by the use of radioactive tracers in these studies, and the perception of these risks by participants and others, are central to the concerns raised by the documentary. It is for this reason that the Committee has presented estimates of the risk of fatal cancers in its discussion of each study in the preceding pages. The scientific terms and concepts used are explained in Annexes 6 and 7, and dose and risk calculations are shown in Annex 4.

Uncertainty in estimating risk

6.2 The Committee was told there is a current scientific debate on the risks associated with low levels of natural or artificial radiation[33]. The debate is an important one: concern about the risks associated with medical use of radiation in diagnosis or treatment leads some people to refuse potentially beneficial treatments, and the lack of knowledge of the risks makes it difficult for doctors to advise their patients, and for individuals to weigh up the risks properly. The Committee has not attempted to come to any conclusions on what is a highly contested issue, which is unlikely to be resolved satisfactorily in the near future without more research. However, the following paragraphs provide a brief summary of the arguments.

6.3 Current risk estimates and radiation protection guidelines are based mainly on epidemiological studies of health effects in humans, and in particular on the populations exposed to radiation in Hiroshima and Nagasaki, as a result of subsequent nuclear weapons tests, in medical treatments, or in the workplace. There have also been studies of the populations of regions with high natural background radiation. This research is far from straightforward, and a range of confounding factors have to be taken into account. The effects of radiation vary with the type and dose rate, but it can be difficult to establish the actual doses received many years previously. Many elements of an individual's medical condition, environment, and lifestyle can affect life expectancy and risk of cancer, and it can be difficult to establish that differences in health between those exposed to radiation and those not exposed (or the lack of differences) are not due to these influences. Also, and especially for relatively low doses, the estimates of risk are based on rare occurrences in relatively small groups of people, and the margin of error is high. As a result, estimates are derived mainly by extrapolating from the incidence of illness in those who received high doses – mainly atom bomb survivors – and by applying a dose rate reduction factor and assuming that the dose-effect relationship is linear (i.e. the linear hypothesis implies that one-tenth of the dose means one-tenth of the risk)[34].

6.4 Some recent research suggests that this approach over-estimates the risk from very low doses of radiation, such as those in most of the research in this inquiry. The evidence comes from both biological studies (on cultured cells or animals) and epidemiological studies:

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33 See, for example, Science, September & November 1994; Lancet, 15 October 1994; New Scientist, 2 December 1995

34 For a review of the problems involved in estimating risk, see the 1990 report of the US National Research Council's Committee on Biological Effects of Ionising Radiations: "Health effects of exposure to low levels of ionising radiation" (National Academy Press)

- cells have mechanisms for removing the free radicals produced by radiation, and for repairing damage to DNA. There are also mechanisms which cause damaged cells to apoptose (destroy themselves) or to be destroyed by the immune system, and basic research is still revelaing new mechanisms by which cells respond to damage. Some experiments suggest that the mechanism for removing free radicals, at least, can be stimulated by radiation, so that subsequent exposure cause less damage[35]. Some extremely rare genetic defects can cause loss of DNA repair mechanisms, and people affected have a greater susceptibility to radiation damage.
- some epidemiological studies show no measurable effects of low-level radiation. For instance, in a study of 70,000 US shipyard workers[36] those whose work exposed them to artificial radiation (often less than 5mSv) had fewer cancers than other workers.

6.5 This evidence leads some to propose that risk at low doses may be very much lower than assumed, and that there is a "safe threshold" – of perhaps several tens of mSv – below which the damage from radiation exposure additional to the natural background can be contained by the body, but above which these mechanisms are overwhelmed. A 1994 report from the United Nations' UNSCEAR committee[37] cautiously stated that the statistical limitations of the current evidence, no conclusions could be drawn about the dose response relationship below 200mGy.

6.6 Others, however, do not accept the evidence or the theory. The damage to DNA from radiation is usually more severe than that caused in other ways, and the normal repair mechanisms may not be relevant, although damaged DNA which escapes repair also usually triggers cells to apoptose. Understanding of the basic cellular processes involved in radiation damage is still limited, and it is not possible to be clear about the role of other repair mechanisms. At the same time, basic research is still revealing new routes by which radiation can damage the genome, and the implications of these effects are not yet clear.

6.7 There are also epidemiological studies of low dose exposure which contradict studies such as those of shipyard workers, and support the estimates produced by extrapolating from higher doses. A recent study of 96,000 workers in the nuclear industry, most of whom were exposed to less than 50mSv, produced estimates of risk of leukaemia only slightly below those produced by extrapolation from high-dose studies of atomic bomb survivors[38].

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35 See for example: Holm-Elkraim et al., Int. J. radiation biol. 1990; 58: 97-100, and Feinendegen et al., Stem Cells 1995; 13 (Suppl.1) 7-20.

36 Cameron J., Health Physics Society Newsletter 20:9 (1992). An earlier study of shipyard workers was reported in Rinsky et al., Lancet (1981) p231.

37 Sources and effects of ionising radiation, UNSCEAR 1994. (Annex B: Adaptive responses to radiation in cells and organisms). New York, 1994.

38 "Direct estimates of cancer mortality due to low doses of ionising radiation: an international study" – a report of a study group of the International Agency for Research on Cancer. Lancet (1994) 344, p1039

6.8 Finally, some have suggested[39] that atomic bomb survivors may not be representative of the whole population, and argued that in theory, this could mean that risks at low doses are underestimated. This remains speculative at present, though it is generally accepted that it is inappropriate to extrapolate from data obtained only at high doses, down to doses close to zero, in the absence of data at the lower level.

The Committee's approach to risk

6.9 Throughout its work, the Committee has adhered to the assumptions in the 1991 report of the International Commission on Radiation Protection, which are based mainly on linear extrapolation from higher doses. While some might argue that this over-estimates the risk, and others that it underestimates, we have chosen to adhere to the most widely accepted scientific model for estimating risk. In any case, for those studies involving the highest doses, i.e. the work in London and Aberdeen using I^{132} and I^{131}, the dose to thyroid tissue was likely to be above the threshold of a linear hypothesis.

6.10 Even with these cautious assumptions, the risk posed to those participating in the studies was extremely small: Annex 8 gives examples of comparable risks in other areas. In most cases the level of exposure was less than would have been involved in a chest X-ray at the time (0.5 to 5mSv). The exposures in the study by Pochin in London, and one of the studies in Aberdeen, were three to five times higher (12.5-25mSv). Nevertheless, the exposure involved was smaller than some current diagnostic procedures, and the risks were low. In 1969, some years after the last of these studies, the opinion of the MRC Working Party (see 4.26) was that doses up to 5 rem (equivalent to 50mSv) could be acceptable in non-therapeutic volunteer studies with valid consent. It would appear, therefore, doses of 12.5-25mSv would not have been seen as unacceptable at the time, although they would certainly have been towards the upper end of the acceptable range.

6.11 Overall, the Committee has concluded that there is no evidence that the radiation used in any of the studies has harmed study participants, or that the research methods were inconsistent with contemporary standards.

Exposure during pregnancy

6.12 Of particular relevance to some of the work featured in the programme (and discussed above) is the issue of the effect on the fetus of radiation administered to an expectant mother. Work published by Dr Alice Stewart[40] (who gave evidence to the Committee) in the mid-1950s first suggested an association between X-rays administered during the early and middle stages of pregnancy and a slightly increased risk to the child of leukaemia, compared to those children whose mothers were not so exposed.

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39 "A-bomb radiation and evidence of late effects other than cancer" Stewart A M, Kneale G M. Health Phys. (1990) 58, p729

40 First mentioned in a preliminary report – A M Stewart, J Webb, D Giles and D Hewitt **'Malignant diseases in children and diagnostic irradiation *in utero*'** Lancet 1956 p447. Followed up by A M Stewart, J Webb and D Hewitt **'A survey of childhood malignancies'** BMJ 1958 1495-1508

6.13 In view of the potential harm to the fetus, it has been questioned why radioactive material continued to be administered to expectant mothers for research purposes in the few years immediately following the publication of Dr Stewart's work. Although X-rays were still used for medical purposes up to the advent of ultrasound, their use in non-therapeutic research is more difficult to justify.

6.14 This is a point which the Committee discussed at some depth with Professor Nicholas Wald, who gave evidence as an independent scientist. He recalled that Dr Stewart had published new findings which had been regarded as fairly radical at the time. Those applying science base their decisions on an established consensus of opinion, and seldom respond to new ideas with abrupt change: rather, Dr Stewart's work would have prompted others to conduct research seeking to replicate or disprove her findings. Professor Wald was not of the opinion that there had been any attempt to 'cover-up' Dr Stewart's findings, but that they had been regarded initially with scepticism. As further work was published supporting Dr Stewart's hypothesis, the consensus view held by the scientific community in general would have gradually altered, with a resultant change in research and clinical practice. This is a process that would have taken some years. It would be wrong to state that it would have been considered unacceptable to use radioactivity in research involving pregnant women (e.g. that of Dr Halnan) carried out in the years immediately after the publication of Dr Stewart's work; but it would be reasonable to expect increasing caution with the subsequent passage of time, and certainly by the time the studies in Aberdeen were carried out in the mid-1960s.

7. CONCLUSIONS

7.1 This inquiry was established as a result of the broadcast of the 'True Stories' television documentary, which described work conducted in both the UK and USA. The Committee has looked solely into that work featured in the documentary which was sponsored by the MRC and carried out in the UK. The documentary brought to the public's attention that research had been conducted in the 1950s and 1960s using radioactive isotopes and raised a number of specific questions about the research featured, which this Committee has sought to address.

7.2 This Committee also considered that there were further issues meriting consideration which had not been specifically addressed in the documentary, e.g. that of follow up studies. The Committee has welcomed this valuable opportunity to look at some of these general concerns and at policies relating to the treatment of research participants, which have been underlying issues throughout the last few decades. These issues have also been the focus of debate for a number of professional bodies over the years, who have issued their own guidelines to doctors and researchers.

Were any of the studies conducted to obtain information of military significance?

7.3 The Committee has found no evidence to support the implication that any of the research examined was conducted for military purposes. The closest any of the research came to this was the investigation of the public health consequences of atmospheric nuclear testing. It should also be made clear that all the UK research was subsequently published in an appropriate scientific publication – a fact which clearly contradicts any implication that this was research conducted in secret for sinister purposes.

Was any of the research unethical?

7.4 The nature of the research examined in the course of this inquiry varied considerably, from the observation of the effects of nuclear fallout on the population, to the study of the benefit of iron added to the diet of women from particular communities, where anaemia was a common problem. The Committee did not find that the nature of the research itself was unethical in any regard. However, there were concerns over questions of consent, understanding in the light of giving consent, and the degree to which risk was explained to the participants or even taken into account by researchers.

7.5 It is accepted that research teams may not have supplied as much information as would today be the case. If information was withheld from participants or their families (e.g. as in the study monitoring strontium levels in bone), it is more likely that this resulted from the paternalistic nature of research and medicine during the period (and the wish not to add further to the distress of the bereaved) than for any more questionable reason. However, it is clear that the standards prevalent in research during the period were generally adhered to, although the actions of the individuals carrying out the research, in one case, did not meet the standards of the time (7.9).

7.6 It was also the case that doctors during the period routinely made judgements about the risk-benefit ratio of both research and therapeutic interventions without express reference to the individuals involved. Again, this was in line with the paternalistic nature of science (and indeed wider society) at the time. The prevailing context in which research and medicine is conducted has undergone a radical change in the intervening years and such decisions are today routinely taken in conjunction with patients/study participants. In contemporary society, it would not be considered acceptable to ask individuals to participate in a research study (particularly if it is a non-therapeutic study), unless the research team were able to explain the full nature of the risk to which that individual was being exposed. However, at the time some of these studies were conducted, such information about risk was simply not available – indeed, the research was aimed at obtaining precisely that type of information.

7.7 Even where explanations were given to study participants, such as in the case of the specially baked chappatis to study the effects of iron in the Asian diet, and the study was conducted with a clear goal, we believe that it would not be considered acceptable to conduct such research nowadays without proper interpretation, and written material in the participants' own languages being made available. Nor is it believed that it would be acceptable to carry out research on pregnant women of the kind examined, without clearer guidelines as to the effect of the radioactivity, however little, on the fetuses or women involved. There is no question in the Committee's mind that the subsequent changes that have occurred both in research practice/regulation and in wider society would have resulted in most of the studies featured being conducted differently if they were undertaken in the 1990s.

7.8 That having been said, on the whole the MRC-sponsored studies looked at were conducted with ethical standards ahead of their time. There is clear evidence in Coventry (Professor Elwood) and in London (Dr Keith E Halnan) that information was given and consent sought, even though the level of understanding may have been limited and the implications of risk were probably not considered as fully as they might be today.

Did any of the researchers (or their agents) act unethically?

7.9 On the whole, the Committee is satisfied that the research teams acted ethically and up to the standards of the period. The case featured in North Wales, however, merits further comment. This was the only study that the Committee understands to have caused distress at the actual time it was carried out.

7.10 The removal of the samples at autopsy was consistent with the prevailing practice of the period. If a sample had been removed without consent (whether to determine the cause of death or for research purposes), this would not have been considered unethical at the time.

7.11 What is considered unacceptable by today's standards (and perhaps even those of the 1950s) was that the removal of femora resulted in a mother being unable to see her child's body before burial. This should not have happened and would not be considered acceptable in contemporary research. What the Committee considers to be unacceptable by any standards was that the removal of femora led to doctors deciding that a mother should be denied access to her child's body – a decision which, in hindsight, was high-handed.

Were any patients put at risk of harm – either in the long or short term?

7.12 Following advice from Professor Elliott and Dr Sobnack, the Committee is satisfied that the risk of harm from radiation to the participants was negligible in most of the studies. In the Aberdeen study involving high doses of I^{131}, the risk was still very small, but was nonetheless, for some participants, close to the upper limit of what was, so far as we can tell, considered ethical and acceptable in non-therapeutic research around that time (see 4.26).

7.13 The Committee has, however, expressed some concern over short-term risks from some of the procedures used – particularly the insertion of a needle into a human placenta (at the Hammersmith Hospital) and the performance of a lumbar puncture (at the MRC Neuropsychiatric Unit). In the former case, any complications could have resulted in a caesarean section, a procedure carrying a known risk to mother and child. A lumbar puncture also subjects a study participant to known risk in addition to possible pain or discomfort. In both cases, there was no direct therapeutic benefit to the individual participants concerned.

7.14 It has also become apparent that some individuals have suffered long-term psychological harm as a result of their participation (e.g. in the case of Mrs Morrison, who has harboured concerns about her participation in the study throughout the 30 years that have elapsed). The broadcast of the programme itself has also engendered concern in some former participants (e.g. in the case of Mrs Tennant, who has since become concerned about possible long-term effects). However, it must be recognised that, in other instances, individuals may have been glad that the programme has brought certain facts and issues out into the open. Mrs Brown in particular made it clear to the Committee that she preferred to know what had happened all those years ago, despite the distress caused, rather than continuing in ignorance.

7.15 The Committee accepts that the programme has acted as a valuable trigger to the examination of both specific and more wide-ranging concerns about the research featured. However, it nevertheless made some misleading connections between research conducted in the USA and UK, which has caused unnecessary anxiety amongst the general public.

Records of/information for research participants and follow-up studies

7.16 It has become apparent during the course of conducting this inquiry that it is necessary to ensure that information is available to former study participants, should they require it in future years. This could take the form of a note in their GP records to indicate their participation in the study, or an accessible full list of participants for all studies involving human participants, enabling their GP to check their participation. Concern was particularly expressed in Coventry that no reference to the study could be found in any of the participants' GP notes. However unfortunate this omission, the Committee has concluded that it cannot be regarded as exceptional for the period. The absence of a reference in GP notes (as was the case in Coventry) or of a definitive list of participants makes it very difficult to offer reassurance to subjects who are subsequently concerned about their participation in a study. It also renders it difficult to conduct follow-up studies (or indeed for Committees to conduct inquiries such as these) in cases where there is possible cause for concern. It is doubly important that

information can be obtained where the principal researcher is a foreign national, who may return to his native country in the future. Even today, detailed records of research participants are still not kept for many research studies.

7.17 It is appreciated that this requirement raises issues of where and how such records should be kept, as well as more practical problems (in terms of storage space if paper records are to be kept, data protection issues if records are to be computerised). The place where the research was conducted must form a natural focus for queries from concerned individuals or their GPs. It is therefore important that records are either kept at the actual institution itself, or the institution is able to direct individuals onwards effectively. A further option would be to keep such records on a national computer database. Such a scheme relies on the introduction of a unique NHS number for every individual and future advances in information technology would undoubtedly further facilitate such a database. This is an issue which merits serious consideration. It was apparent from the Committee's meeting with Kathleen Morrison that her participation in the study had been a cause of anxiety throughout the 30 years that have since elapsed. The presence of some records – even limited – surrounding the study might have enabled her GP to put her mind at rest.

Information for study participants

7.18 It was also found that research subjects would regard it as helpful to know the results of the study, something which does not always happen at present, and which is now recommended most strongly. As participants have given their time and may have experienced some discomfort or been exposed to some risk as a consequence of the study, it is the minimum of courtesy to inform them of the outcome of the study and thank them for their participation. The latter often does not happen, except in a line on some information sheets, rather than (perhaps more appropriately) after the study has been concluded. In some cases, it is believed that a follow-up, checking on whether there have been any long-term side effects, and giving reassurance about the study, would also be helpful. This emerged particularly strongly from the Aberdeen studies, but may also be the case in many others. We recommend that the MRC give this matter urgent consideration and that the Council flags up the question of information and follow-up for research subjects in the wider research community.

Contemporary research and the role of Local Research Ethics Committees

7.19 Nowadays, any research involving human subjects is required to be scrutinised by a research ethics committee (REC). These committees consist of clinicians, nurses and lay-people (i.e. non-clinicians) and their role is to advise on the ethical acceptability of each research project put before them. If such research as was featured in the programme were to be carried out today, one would expect a detailed explanation, plus an assessment of risk, to be considered by the REC before participants were asked to join, and clear guidelines as to whether this was 'therapeutic' research (in other words possibility of benefit to the individuals themselves) or 'non-therapeutic' research (where there was no direct benefit to participants). It would also be clear whether participants were healthy volunteers, who volunteered as a result of an

advertisement to take part, or patients who were recruited through health service contacts. This status is often muddled outside of RECs, and the nature of participants' rights ill understood, if accepted at all. The advice given by RECs includes ensuring that research subjects are exposed to no greater risk of harm or discomfort than that to which they would otherwise be exposed as ordinary patients, or in ordinary life if they are healthy volunteers, and that a person's consent is sought and recorded as a matter of course before he/she is enrolled as a participant in any project.

7.20 The REC would now require fully detailed written information sheets, with evidence of understanding by participants; the Committee would expect the removal of tissues for research purposes at autopsy to be carried out only with the consent of next of kin; the Committee would expect people who participated in research to understand the purpose and nature of the research, and to agree that it was something worth studying, and would expect researchers to be very clear about letting patients' GPs know that they had been entered into a study.

7.21 The rigour which most RECs employ in reviewing research means that the public can be reassured that it is unlikely that unethical research is conducted within the National Health Service. However, at the time the research discussed in the television programme was carried out, these RECs did not exist; hence there could have been no independent review of the research project's ethical acceptability in the way that there would be today.

7.22 Everyone in society benefits from good research. It matters that research can continue to be conducted, including research that uses human participants. However, there is no justification for such research to be conducted to the detriment of human participants, nor for research to be conducted without their knowledge and agreement. The risk of harm, however slight, is a risk that the individual particiant has to choose to bear – and in non-therapeutic research the risk is borne in the knowledge that it will not benefit their current illness. Participants must be exposed to no more than minimal risk and their informed agreement to participate in the research should be obtained as a matter of course. It should also be made clear that they are free to refuse to participate, or to withdraw from the study at any time.

7.23 The lesson of this inquiry is that there is a need to recognise that, despite the efforts of scientists, individuals may continue to harbour concerns about the research in which they participate and that further mechanisms should be introduced to ensure these concerns are addressed, particularly in the longer term. The Committee has found little evidence of unethical practice in the light of the time in which the research was carried out. However, the Committee did find an attitude amongst some researchers that regarded research participants as dispensable, who did not need to be informed, thanked or kept in touch in any way. This may still be as true in the 1990s as it was in the 1950s and 1960s, and it is this concern which the Committee would like to voice not only to the MRC in particular, but to the wider research community in general, for it is believed that participants do not feel truly involved in the research in which they participate. Instead, even now, participants may feel that their concerns are of little import in the light of the wider benefit in terms of scientific knowledge.

8. RECOMMENDATIONS

8.1 The Committee fully endorses the current MRC Code of Practice in relation to informed consent (and other codes of practice currently in use) and recommends that these codes continue to be kept under active review in the light of the evidence presented in this report and any future developments.

8.2 It should be the responsibility of a central body to ensure that researchers are fully aware of the importance of ensuring that everyone involved in a research project (however peripherally) are made aware of current codes of practice in relation to consent and that these are adhered to.

8.3 (a) Information concerning participation in research, plus details of the study protocol, should be easily accessible to study participants and/or their GPs. Such records should be available on a long-term basis.

(b) Researchers should feed back study results to participants as a matter of routine and participants should be offered a copy of the scientific publication in which the study is reported.

(c) Researchers should be aware that study participants may retain continuing concerns about the consequences of their participation in a study, no matter how diligently a research team has sought to explain the risks and implications to them. A long-term contact point/source of information for participants and/or their GPs is therefore vital.

(d) Until such time as central NHS records are kept, it is the responsibility of researchers to ensure that a note is kept in a patient's GP notes, specifically detailing that they have participated in a research study. This should apply for both therapeutic and non-therapeutic research.

8.4 Grampian Health Board should, if feasible, conduct further epidemiological analysis of the prevalence of thyroid cancer in the region. Although the risks from the research studies examined in this report were extremely small, further epidemiological work could be extremely valuable in reassuring those who took part in the research, and the wider public, that their concerns will beaddressed .

8.5 The National Radiological Protection Board (NRPB) and other radiation regulatory authorities should continue to re-evaluate the risk to humans from low-level radiation, with a view to establishing whether or not there is a level at which exposure to radiation may be considered effectively 'harmless'.

8.6 We recommend that the MRC itself, along with other research and patient bodies, considers the development of a strategy for an ongoing exchange of views between researchers and study participants on such subjects as:

- risk;
- the extent to which individual participants should be kept informed about the progress of the study;

- follow-up and access to information about other studies;
- real advances made in medicine as a result of research.

The Committee did not give consideration to whether this should take the form of occasional conferences, a regular publication, or simply an umbrella body of interested parties to discuss these issues – this must be decided by the parties involved. The Committee's experience in hearing evidence during this inquiry has convinced it that a regular exchange of views between scientists and the lay community about the value of research, its progress, about patients, healthy volunteers and the concerns of the general public is essential. Such an exchange would serve to educate both researchers and study participants and allay concerns held by the general public in relation to research. Such a dialogue would be in addition to the regular work on the ethical conduct of research already conducted by bodies such as the Royal College of Physicians and the Committee most strongly recommends action on this issue.

ANNEX 1 – LIST OF WITNESSES

Dr D Brewster	Director, Scottish Cancer Registry, Edinburgh
Mrs G Brown	Mother from North Wales (in connection with the monitoring of Strontium 90 levels in bone and tissue)
Prof. Sir Cyril Chantler	Dean, United Medical and Dental Schools of Guy's and St Thomas' Hospitals
Dr A Coppen	former researcher at the MRC Neuropsychiatric Unit, who investigated the metabolic changes at work in patients suffering from schizophrenia or depressive illness.
Prof. A Elliott	Department of Clinical Physics, University of Glasgow
Dr D Evered	former Second Secretary, Medical Research Council
Prof. P Elwood	Principal investigator from the Coventry study measuring the uptake of iron from chapattis
Dr Keith E Halnan	Principal investigator from the UCL study on the radioactive uptake of the human thyroid in pregnancy.
Mr C Howgrave-Graham	Chief Executive, Coventry Health Authority
Dr K MacRae	Statistician (asked to analyse the increased risk of cancer from participation in one of the studies)
Mrs K Morrison	Study participant, Aberdeen
Dr R Nicholson	Editor, Bulletin of Medical Ethics
Dr J G Paterson	Director of Public Health, Grampian Health Board, Aberdeen
Prof. P J Steer	Department of Obstetrics & Gynaecology, Charing Cross & Westminster Medical School

Dr A M Stewart	Department of Public Health & Epidemiology, University of Birmingham
Mrs L Tennant	Study participant, Aberdeen
Prof. N J Wald	Department of Environmental Medicine, Medical College of St Bartholomew's Hospital, London
Dr F Hytten	Clinician at Aberdeen Maternity Hospital in the 1960s: involved in some of the research

ANNEX 2 – KEY DATES IN THE HISTORY OF THE REGULATION OF MEDICAL AND RESEARCH USES OF RADIATION IN THE UK

Below is a brief summary of the information discussed in depth in the section on historical context (chapter 4). The MRC work featured in the programme has also been included so that the reader may view the work in the light of the prevailing research climate of the time.

1947	**Nuremberg Code**
1948	**Radioactive Substances Act** passed in UK (licensing of medical and dental practitioners using ionising radiation – but not brought into effect till introduction of 1957 Code of Practice)
1952	Results of Pochin research at UCL published
1953	Results of McClure-Browne and Veall work at Hammersmith published
1955	***International Commission on* Radiological Protection** – first consideration of protection for patients
1955	Monitoring of UK levels of Strontium-90 in human bone started by UKAEA
1956	MRC report published on 'The Hazards to Man of Nuclear and Allied Radiation'
1956	Preliminary results by Stewart published in relation to diagnostic irradiation in utero and malignant diseases in children. Followed up by a further paper in 1958
1956	***Adrian Committee*** *established to establish radiological* hazards to patients
1957	Ministry of Health published Code of Practice for Protection of Persons Exposed to Ionising Radiation (thus enabling the provisions of the Radioactive Substances Act to be implemented)
1957	Establishment of Joint Committee on Monitoring of Radioactivity from Fallout - MRC involvement commenced in monitoring of Strontium-90 levels

1958	Results of Halnan work at UCL published
1959	**1st report of Adrian Committee** published concluding the risk of leukaemia from mass chest radiography was acceptable, given the diagnostic merits of the procedure
1960	**2nd report of Adrian Committee** – use of external radiography discontinued in 10 of 46 conditions following publication
1962-63	Research carried out in Aberdeen
1963	Results of work at MRC Neuropsychiatric Unit published
1963	MRC published general guidelines on use of Human Participants in research
1964	Declaration of Helsinki
1966	**Final report of Adrian Committee**
1970	Establishment of first Research Ethics Committees
1970	**John Stanbury Address** in USA suggesting guidelines for the use of radioisotopes in research
1970	Results of Elwood research in Coventry published
1970	Monitoring of Strontium-90 levels in UK discontinued
1975	**British Institute of Radiology** – earliest British Guidelines on irradiation of human subjects for medical research
1978	Medicines (Administration of Radioactive Substances) Regulations 1978 and Medicines (Radioactive Substances) Order introduce legal controls on administration of radioactive subtsances. ARSAC established.
1988	**NRPB Guidelines** in UK

ANNEX 3 – LIST OF SCIENTIFIC PUBLICATIONS

Below is a list of relevant publications from the MRC-funded research featured in the programme, and which has been discussed in this report. This does not claim to be a comprehensive reading list - rather it is intended as a starting point for those who wish to learn more about specific research projects, or the results that arose from a particular piece of work.

Monitoring of Strontium 90 in bone and tissue

Assay of Strontium-90 in Human Bone in the United Kingdom	Published by HMSO	MRC Monitoring Report Series 1-19
The Uptake and Turnover of ^{90}Sr in the Human Skeleton	Phys. Med. Biol. 1984 Vol 29 No. 9 1045-1061	D G Papworth and J Vennart

University College London

The Iodine Uptake of the Human Thyroid throughout the Menstrual Cycle and in pregnancy	Clin.Sci 1952	E E Pochin
The Radioiodine Uptake of the Human Thyroid in Pregnancy	Clin. Sci 1958; Vol 17, 281-289	Dr Keith E Halnan

Hammersmith Hospital, London

The Maternal Placental Blood Flow in Normotensive and Hypertensive Women	Journal of O&G of the British Empire, April 1953. Vol 60, No 2 p 141-147	J C McClure-Browne and N Veall

Aberdeen

The Physiological Changes in Thyroid Function during Pregnancy	Clin Sci 1964;27, 195-207	S A Aboul-Khair, J Crooks, A C Turnbull, F E Hytten
Structural and Functional Development of the Human Fetal Thyroid	Clin Sci 1966, 31, 415-424	S A Aboul-Khair, T J Buchanan, J Crooks, A C Turnbull

MRC Neuropsychiatric Unit

Mineral Metabolism in Melancholia	BMJ 7 Dec. 1963: 1439-1444	A J Coppen and D M Shaw
The Transfer of ^{35}S-methionine-sulphone across the blood-cerebrospinal fluid barrier	J Neuro Neurosurg Psychiat. 1963: 26, 220 - 222	D Kemali, M K Gaitonde and A J Coppen

Coventry

Absorption of Iron from Chapatti made from Wheat Flour	American Journal of Clinical Nutrition, Vol 23 No 10, October 1970 pp1267-1271	P C Elwood, I T Benjamin, J D Eakins, D A Brown, P C de Kock and J U Shah

ANNEX 4 – ANALYSIS OF RADIATION DOSES USED IN STUDIES

Based on analyses by :

Professor A Elliott, Dept. of Clinical Physics, University of Glasgow

Dr Ravin Sobnack, Dept. of Nuclear Medicine, St Bartholomew's Hospital

Introduction

The studies are:

1) The iodine uptake of the human thyroid throughout the menstrual cycle and in pregnancy (Pochin: *Clin. Sci. 1952*)

2) The radioiodine uptake of the human thyroid in pregnancy (Halnan: *Clin. Sci. 1958*)

3) Thyroid physiology and iodine metabolism in pregnancy (Aboul-Khair: (a) *Clin. Sci 1964*, (b) *Clin. Sci 1966*)

4) The maternal placental blood flow in normotensive and hypertensive women (McClure-Browne and Veall: *Journal of O&G of the British Empire 1953*)

5) Transport across the blood / CSF barrier in health and mentally ill people (Coppen: (a) *J. Neurol. Neurosurg. Psychiat. 1960*, (b) *J. Neurol. Neuorsurg. Psychiat. 1963*)

6) Iron uptake (Elwood: American *J. Clin. Nutr. 1970*)

The numbers of study participants are in Appendix 1, with radiation dose estimates in Appendix 2.

Pregnancy

Studies 1-3 were concerned with the administration of radioactive iodine, which is taken up by the thyroid gland. In pregnancy, it is known to cross the placenta and be taken up by the fetal thyroid; it will thus irradiate the fetus directly. This will be in addition to the radiation dose received by the fetus from the radioactivity circulating in the mother's body. Fetal uptake of iodine is assumed to be zero before the 14th week of gestation, rising to some 5% of the amount administered to the mother by week 36. There are two consequences of fetal irradiation – a slightly increased risk of cancer and a slight potential for mental retardation. If the babies were breast-fed, there would be a transfer of radioiodine in the mother's milk at the time of the post-partum studies.

In study 4, radioactive sodium was injected into the placental pool, a proportion of which crosses the placental barrier into the fetal circulation. Once again, there will be direct and indirect irradiation of the fetus.

In the case of non-pregnant patients, we need to consider the risk of cancer induction to the subject while, in the case of pregnant patients, we need to consider the risks to both mother and fetus.

Experimental design and doses

Study 1 utilised 10 normal controls, each of whom were studied 4 times with 260kBq of iodine-131 being administered on each occasion. Assuming a thyroid update of 25%, the total effective dose equivalent (EDE) received was 13.5mSv. For the sterility/obesity patients, who were studied twice, the EDE was 6.8mSv. In the case of the 5 pregnant patients, the maternal EDE was 16.7mSv from the four tests. The fetal radiation dose arose from indirect contribution only at week 12, with both direct and indirect contributions at weeks 24a and 36; a worst-case assumption that all mothers were breast feeding gives an additional contribution from the post-partum test. The total EDE was less than 4.2mSv.

Study 2 used iodine-132, with a shorter half-life in order to minimise the radiation dose. The normals received an EDE of 0.05mSv, while the hypo- and hyper-thyroid patients received 0.04 and 0.12mSv respectively. In the main pregnancy study, the maternal EDE was 0.34mSv and the fetal EDE was 0.1mSv. The corresponding figures for the T3 and thyrotropic hormone trials were 0.46/0.23mSv and 0.39/0/18sMv respectively. The control EDEs were 0.32 and 0.26mSv.

Iodine-132 was used also in Study 3(a), where the EDE to the controls, sporadic goitre and thyrotoxic patients were 0.06, 0.1 and 0.2mSv respectively. The worst case (most studied)EDEs in the pregnancy study were 0.74mSv to the other and 0.3mSv to the fetus.

Study 3(b) used Iodine 131, and involved the highest effective doses of any of these studies, reaching 25mSv for those receiving 40uCi of Iodine 131. Doses ranged from 40 to 20uCi, but the paper does not record how many of the participants received the highest dose.

In all of the above experiments, the radiation dose to the thyroid itself will have been much higher. For instance, in paper 1, the maternal thyroid radiation dose would have been some 150mSv, the fetal thyroid dose being some 300-350mSv. In papers 2 and 3, the worst cases would have been 3mSv and 6-7mSv.

In Study 4, the administration of the sodium-24 led to a maternal EDE of 0.13mSv and a fetal EDE of 0.2mSv. The risk for severe mental retardation is assumed at 30 IQ points per Sv to the fetal brain, with a threshold of 100mSv calculated, no effect would be expected.

Study 5(a) used Sodium 24, and, in some participants, Tritium, with an EDE of 1.56mSv for those receiving both. Study 5(b) used a methionine compound containing Sulphur 35, giving and EDE of 1.3mSv.

The doses in Study 6 proved particularly difficult to estimate, but the doses involved were clearly among the lowest of any study. The highest possible doses would have been around 0.59mSv.

Doses and cancer risk

From ICRP 60, assuming a linear model, the risk estimate for fatal cancer is 5.0×10^{-5} per mSv for adults. The corresponding figure for irradiation in utero is thought to be some 2-3 times higher; the worst-case factor of 3 has been used below.

The risks for induction of fatal cancer from each of the experiments are thus less than;

Study 1 –	normals	6.8×10^{-4}
	patients	3.4×10^{-4}
	mothers	8.4×10^{-4}
	fetus	6.3×10^{-4}
Study 2 –	normals	2.5×12^{-6}
	hypothyroid	2.0×10^{-6}
	hyperthyroid	6.0×10^{-6}
	mothers	1.7×10^{-5}
	fetus	1.5×10^{-5}
	T3 controls	1.6×10^{-5}
	T3 mothers	2.3×10^{-5}
	T3 fetus	3.5×10^{-5}
	hormone controls	1.3×10^{-5}
	hormone mothers	2.0×10^{-5}
	hormone fetus	2.7×10^{-5}
Study 3(a) –	controls	3.0×10^{-6}
	sporadic goitre	5.0×10^{-6}
	thyrotoxic	1.0×10^{-5}
	mothers	3.7×10^{-5}
	fetus	5.3×10^{-5}
Study 3(b) –	highest dose	12.7×10^{-4}
	lowest dose	6.3×10^{-4}
Study 4 –	mothers	6.5×10^{-6}
	fetus	3.0×10^{-5}
Study 5(a) –	general dose	6.3×10^{-5}
	16 highest doses	7.8×10^{-5}
Study 5 (b) –	general dose	6.5×10^{-5}
Study 6 –	worst case	3.0×10^{-5}

For comparison, the EDE from a chest X-ray in, say 1960, would have been about 0.5-5mSv (corresponding risk between 2.5-25 x 10^{-5}). By 1969, at the time of Study 6, the EDE would have been in the range 0.1 – 5mSv, depending on the equipment used. As can be clearly seen, the risks from experiments 2, 3(a), 4, and 6 are well within this range.

Experiments 1 and 3(b) fall above this level, although the radiation doses involved are less than would be received following a radionuclide heart scan today. They should be compared also with the natural background radiation level of 2-2.5mSv per year for the UK and the current permissible limit for members of the public of 5mSv per year (to be reduced to 1mSv per year).

References

1. International Commission on Radiological Protection, Publication 53, Oxford, Pergammon Press, 1987.

2. International Commission on Radiological Protection, Publication 60, Oxford, Pergammon Press, 1991.

3. Medical Internal Radiation Dose Committee, Dose estimate report no 5, JNM 16, 857-860, 1975.

APPENDIX 1: STUDY PARTICIPANTS

1. The iodine uptake of the human thyroid throughout the menstrual cycle and in pregnancy

i) Menstrual cycle studies
- 5 male volunteers, studied 4 times
- 5 female volunteers, studied 4 times
- 57 patients, obesity/sterility
  - of these, 23 retested
  - (i.e. 23 studied twice, 34 studied once)

ii) Pregnancy study
- 5 patients, ages not given, tested during pregnancy
  - 4 patients studied 5 times
  - 1 patient studied 4 times

2. The radioiodine uptake of the human thyroid in pregnancy

i) Routine tests
- 44 patients with no thyroid disease
- 27 volunteers
- 11 hypothyroid patients
- 29 hyperthyroid patients

ii) Pregnancy study
- 25 patients, ages not given, studied during pregnancy
  - 16 patients studied 5 times
  - 3 patients studied 4 times
  - 1 patient studied 3 times
  - 1 patient studied twice
  - 2 patients studied once

iii) T3 study
- 2 pregnant patients, studied 6 times
- 4 volunteers, studied 6 times

iv) Thyrotropic hormone study
- 3 pregnant patients, studied 5 times
- 3 volunteers, studied 5 times

3. Studies of thyroid physiology and iodine metabolism in pregnancy

(a) 1964 paper on changes in function during pregnancy

i) Sporadic goitre studies;
33 patients, aged 17-63, studied once

ii) Thyrotoxicosis studies;
11 patients, aged 27-53, studied once

iii) Controls for above;
18 volunteers, similar age distribution, studied once

iv) Pregnancy study;
15 patients, ages not given, studied during pregnancy
1 dropped from study, investigations unknown
of the remaining 14, 1 patient studied 4 times
9 patients studied 5 times
4 patients studied 6 times

13 latter patients studied 3 times post-partum

v) Controls for above;
13 volunteers, similar age distribution, studied once

For these groups, the thyroid uptake values at 2.5h post-administration were:

i) mean thyroid uptake 40%
ii) mean thyroid uptake 78%
iii) mean thyroid uptake 22%
iv) mean thyroid uptake during pregnancy 31.5% (29.8-34.5)
at 2w/k post partum 27.5%
at 6/12w/k post partum 22%
v) mean thyroid uptake 21.5%

(b) 1966 paper on development of the fetal thyroid

i) 29 patients undergoing termination of pregnancy, given 20-40uCi of I131

ii) 2 patients undergoing termination of pregnancy, given 20uCi of I131

iii) 6 controls

The remaining radioiodine may have been flushed out once the experimental measurements were complete. This was normal practice at the time, but is not specifically mentioned in the paper. Our calculations are based on the worst case: i.e. they assume that it was not done.

4. The maternal placental blood flow in normotensive and hypertensive women

Study population

274 placental localisations (carried out as routine and so not considered here)
25 blood flow studies

5. Transport across the blood/CSF barrier in healthy and mentally ill people

(a) 1960 paper on studies using sodium 24

i) 12 controls

ii) 41 patients who were, or had been, treated for depression
16 of these received 18.5 MBq tritium in addition to the sodium 24

iii) 19 schizophrenic patients

(b) 1963 paper on studies using sulphur 35

i) 13 patients

6. Anaemia and iron in the Indian diet ("Chapatti Study")

21 female volunteers of Indian origin living in the Coventry area

APPENDIX 2 – ADMINISTERED ACTIVITIES AND DOSES

(N.B. the number of times the study participants were given the dose is in Appendix 1, above)

1. 7uCi (260kBq) of iodine-131, physical half-life 8 days
2. 6uCi (220kBq) of iodine-132, physical half-life 2.3 hours
3(a) 4-7uCi (150-260kBq) of iodine-132, physical half-life 2.3 hours
3(b) 20-40 uCi (260kBq) of iodine-131, physical half-life 8 days
4. 10uCi (370kBq) of sodium-24, physical half-life 15 hours.
5(a) 100UCi (3.7MBq) of sodium-24, physical half-life 15 hours
5(b) 30uCi (1.11MBq) sulphur-35, physical half-life, 87 days
6. estimated 20uCi of iron-55 and 2uCi of iron-59, physical half-lives 2.7 years and 44 days, respectively

Study 1: Iodine 131 dosimetry

Activity administered to subjects = 7uCi = 260kBq

Assume normal uptake of 25%, uptake during pregnancy 35%

i) Radiation dose to 10 normals (EDE)
= 13mSv/MBq administered
= 4 x 0.26 x 13mSv
= 13.5mSv

ii) Radiation dose to 57 patients (EDE)
= 13mSv/MBq administered
= 0.26 x 13mSv
= 3.4mSv
(6.8mSv for those retested)

iii) Radiation doses to pregnant patients (EDE)
= 17mSv/MBq administered
= 3 x 0.26 x 17mSv
= 13.3mSv
plus post-partum test = 13mSv/MBq administered
= 0.26 x 13mSv
= 3.4mSv
Total EDE = 16.7mSv

iv) Radiation dose to fetus (EDE)
Indirect from mother = 0.05mSv/MBq administered
= 3 x 0.26 x 0.05mSv
= 0.04mSv
Direct = 200mSv/MBq absorbed
= 200 x 0.26 x 0.04 x 2mSv
= 4.16mSv
Total EDE = 4.2mSv

Study 2: Iodine-132 dosimetry

Activity administered to subjects = 6uCi = 220kBq

Assume normal uptake of 25%, uptake during pregnancy 35%

i) Radiation dose to 71 normals (EDE)
= 0.24mSv/MBq administered
= 0.24 x 0.22mSv
= 0.05mSv

ii) Radiation dose to 11 hypothyroid patients (EDE)
= 0.20mSv/MBq administered
= 0.20 x 0.22mSv
= 0.04mSv

iii) Radiation dose to 29 hyperthyroid patients (EDE)
= 0.55mSv/MBq administered
= 0.55 x 0.22mSv
= 0.12mSv

iv) Radiation dose to pregnant patients (EDE)
= 0.35mSv/MBq administered
= 3 x 0.35 x 0.22mSv
= 0.23mSv
plus post-partum studies = 2 x 0.24 x 0.22mSv
= 0.11mSv
Total EDE = 0.34mSv

v) Radiation dose to fetus (EDE)
Indirect from mother = 0.04mSv/MBq administered
= 3 x 0.04 x 0.22mSv
= 0.03mSv
Direct = 4mSv/MBq absorbed
= 2 x 4 x 0.22 x 0.04mSv
= 0.07mSv
Total EDE = 0.1mSv

vi) Radiation dose to T3 controls (EDE)
= 0.24mSv/MBq administered
= 6 x 0.24 x 0.22mSv
= 0.32mSv

vii) Radiation dose to pregnant T3 patients (EDE)
= 0.35mSv/MBq administered
= 6 x 0.35 x 0.22mSv
= 0.46mSv

viii) Radiation dose to T3 fetus (EDE)

Indirect from mother	= 0.04mSv/MBq administered
	= 6 x 0.04 x 0.22mSv
	= 0.05mSv
Direct	= 4mSv/MBq absorbed
	= 5 x 4 x 0.22 x 0.04mSv
	= 0.18mSv
Total EDE	= 0.23mSv

ix) Radiation dose to thyrotropic hormone controls (EDE)

= 0.24mSv/MBq administered
= 5 x 0.24 x 0.22mSv
= 0.26mSv

x) Radiation dose to pregnant thyrotropic hormone patients (EDE)

= 0.35mSv/MBq administered
= 5 x 0.35 x 0.22mSv
= 0.39mSv

xi) Radiation dose to thyrotropic hormone fetus (EDE)

Indirect from mother	= 0.04mSv/MBq administered
	= 5 x 0.04 x 0.22mSv
	= 0.04mSv
Direct	= 4mSv/MBq absorbed
	= 4 x 4 x 0.22 x 0.04mSv
	= 0.14mSv
Total EDE	= 0.18mSv

Study 3 (a) : Iodine-132 dosimetry

Activity administered to subjects = 7uCi = 260kBq (maximum)

Assume normal uptake of 25%, uptake during pregnancy 35%

i) Radiation dose to 18 controls (EDE)
= 0.24mSv/MBq administered
= 0.24 x 0.26mSv
= 0.06mSv

ii) Radiation dose to 33 sporadic goitre patients (EDE)
= 0.40mSv/MBq administered
= 0.4 x 0.26mSv
= 0.1mSv

iii) Radiation dose to 11 thyrotoxic patients (EDE)
= 0.75mSv/MBq administered
= 0.75 x 0.26mSv
= 0.2mSv

iv) Radiation dose to pregnant patients (worst case EDE)
= 0.35mSv/MBq administered
= 6 x 0.35 x 0.26mSv
= 0.55mSv

plus post-partum studies = 3 x 0.24 x 0.26mSv
= 0.19mSv

Total EDE = 0.74mSv

v) Radiation dose to fetus (worst case EDE)

Indirect from mother = 0.04mSv/MBq administered
= 6 x 0.04 x 0.26mSv
= 0.06mSv

Direct = 4mSv?MBq absorbed
= 5 x 4 x 0.26 x 0.04mSv
= 0.21mSv

From breast milk = 2mSv/MBq ingested
= 3 x 2 x 0.26 x 0.05mSv
= 0.08mSv

Total EDE = 0.35mSv

Study 3 (b) : Iodine-131 dosimetry

Activity administered to subjects = 20 - 40uCi = 745 -1490kBq

Assume uptake during pregnancy 35% (see Study 1 above)

Radiation dose to patients (worst case EDE)
= 17mSv/MBq administered
= 25mSv

For the lowest dose of 20uCi the EDE would be 12.5mSv, and the six controls received no dose.

Study 4: Na-24 dosimetry

Activity administered to mother = 10uCi = 370kBq

Activity transferred to fetus = 1uCi = 37kBq

i) Radiation dose to mother (EDE)
= 0.34mSv/MBq administered
= 0.34 x 0.37mSv
= 0.13mSv

ii) Radiation dose to fetus (EDE)

Indirect from mother	= 0.29mSv/MBq administered
	= 0.29 x 0.37mSv
	= 0.11mSv
From absorbed activity	= 2.5mSv/MBq absorbed
	= 2.5 x 0.037mSv
	= 0.09mSv
Total EDE	= 0.2mSv

Study 5(a): Na 24 and H 3 dosimetry

Activity administered to all participants = 100uCi Na 24 = 3.7MBq

Radiation dose (EDE)	= 0.34 mSv/MBq administered
	= 1.26 mSv
Additional tritium dose (16 patients)	= 18.5MBq
EDE	= 0.016 mSv/MBq administered
	= 0.30 mSv

Total EDE for the 16 patients receiving both = 1.56mSv

Study 5(b): Sulphur dosimetry

EDE	= 1.17mSv/MBq administered
	= 1.17 x 1.11mSv
	= 1.3 mSv

Study 6 : Iron dosimetry

The data in the paper by Elwood et al. in the American Journal of Clinical Nutrition state that each woman involved ate 4 chapatti with random allocation to white or wholemeal. Since the wholemeal contained more radioiron, the worst case would be if all four were of this variety. Dr Elwood's letter of 22/12/69 to Dr. Thomas indicates that the contents of each chapatti were:

wholemeal	: 5uCi of Fe-55 and 0.5uCi of Fe-59
white	: 2uCi of Fe-55 and 0.25uCi of Fe-59

The same letter states that the above values were measured on 24/09/69 and a telephone conversation with Dr. Elwood indicated that this was prior to administration. The values will thus be an overestimate of that actually administered. Assume that the total ingested activities were:

Fe-55 : 20uCi = 740kBq
Fe-59 : 2uCi = 74kBq

It may be that these values relate to the flour used, since there is a large discrepancy between the weights cited and the text of the Am. J. Clin.Nut. paper; no other information is available from MRC's own records. The values assumed are therefore fairly certain not to be underestimates. From ICRP53, the effective dose equivalent (EDE) for adults assuming normal biodistribution is:

Fe-55 : 059mSv/MBq
Fe-59 : 2.00mSv/MBq

Thus the total EDE from the study would be:

$$(0.59 \times 0.74) + (2.0 \times 0.074) = 0.44 + 0.148 = 0.59\text{mSv}$$

ANNEX 5 – REPORT OF INQUIRY INTO 'CHAPATTI STUDY' IN COVENTRY, CONDUCTED BY COVENTRY HEALTH

REPORT TO: **Coventry Health, 19th September 1995**

FROM: **Chris Howgrave-Graham, Chief Executive**

TITLE: **MRC Chapatti Study, 1969**

1.0 Introduction

1.1 On the evening of 6th July 1995, Channel 4 showed a documentary in the "True Stories" series entitled "Deadly Experiments". Along with many "experiments" allegedly linked to the nuclear industry, it told the story of an MRC funded trial in which "radioactive chapattis" were allegedly fed to Coventry women. A Coventry woman, Pritam Kaur, who was involved in the "experiment" was interviewed. There was subsequently extensive coverage in the Coventry Evening Telegraph, Central News and BBC Midlands Today.

1.2 Immediately after this, Coventry Health publicised the availability of our free helpline (0800 137799) for any Coventry resident with concerns about the study. Two calls were received but neither were from people involved in the study. Concern was however expressed about the study from Bob Ainsworth MP (Coventry North East) and Hardev Singh Bahia (Chairman of Coventry Racial Equality Council.

1.3 We were able quickly to discover that the study in question had been carried out under the supervision of Dr (now Professor) Peter Elwood of the MRC in Cardiff, and he readily accepted an invitation to meet with myself, Dr Keith Williams, Mr Ainsworth and Mr Singh Bahia the following Monday morning. At this meeting, many points were discussed and clarified. Investigations continued, and a public meeting was held at the Indian Community Centre on the following Thursday evening.

1.4 From initial discussions, it became clear that the research concerned the problems of absorption of iron from chapatti flour by Asian women which was evaluated by labelling chapattis with radioactive isotopes of iron. The study was subsequently published in the American Journal of Clinical Nutrition (Appendix A).

1.5 Three main areas of concern were raised with us:-

a) Was the research carred out by Professor Elwood linked with other nuclear research as was possibly suggested by the Channel 4 programme?

b) Was people's health put at risk?

c) Was proper informed consent obtained?

2.0 Purpose of the research

2.1 On question 1, we obtained categorical assurance from Professor Elwood that the research was carried out on medical grounds as part of a long term research interest of

his in nutrition and iron deficiency. Professor Elwood has supplied details of all his research in this area and he holds an eminent post as Director of the Medical Research Council Epidemiology Unit in Cardiff. He has never been involved in any research of a military nature, and stated that the only reason why women involved in the study were taken to Harwell was because that was then the only place which had equipment sensitive enough to measure suchi a low dose of radiation.

3.0 Potential risk to health

3.1 On the second question concerning the dose of radiation used, we have contacted Professor A T Elliott of the Department of Clinical Physics and Bio-Engineering in Glasgow for an independent assessment of the risk involved (Appendix B). Taking an absolutely "worst case view" (the actual doses may have been very much less), the total amount of radioactivity absorbed would have been in the order of 0.59 mSv. We naturally absorb radiation in our daily lives. This amount equates to about an additional 3 months of natural background radiation and is of the same order of magnitude as a single chest X-ray taken at that time. (A similar X-ray taken today would have a much lower dose approximately 0.02 mSv). The risk of cancer from such a dose is approximately I in 28,571. This would be considered very low.

3.2 One of the participants recalls having more than the 4 chapattis involved in the study. Her recollection is of having 2 chapattis, tvice a week for four veeks. Professor Etwood maintains that this could not have been the case. Had it been, the "worst case" assessment in paragraph 3.1 would need to be multiplied by four.

3.3 Professor Elwood and other researchers involved themselves took the same dose of radioactive iron as the participants.

3.4 One of the questions raised has been how long a period of time would need to pass before the radiation level to which the participants were exposed would retum to background levels. Most of the chapattis would be passed through the body in a matter of days and the amount of iron absorbed would have varied depending on what was eaten or drunk with the chapattis. Of the relatively small percentage absorbed it would take some 60 days for iron 59 and 700 days for iron 55 to reach the stage where less than 1% of the original amount of iron absorbed in the body remained. One could regard these as the extreme times for the body content to effectively return to background.

4.0 Consent

4.1 By far the most difficult question to answer some 26 years after the study is that of informed consent. Nowadays any such study would have to be passed by the Coventry Research and Ethical Committee, a written explanation would have to be given to each participant and consent would have to be obtained in writing.

4.2 In 1969 these arrangements did not apply. There was a local research committee, but this was purely informal and did not have the role of the present committee. It was simply a forum to discuss research issues and the chapatti study was referred to in one of the meetings. The committee had no role in ensuring consent was obtained.

4.3 At that time it was common practice to obtain only verbal consent. Professor Elwood has stated that he visited all the women at home to explain the purpose and nature of the experiment and to seek consent. He has also stated that a family neighbour was present plus a local health authority Asian health visitor who spoke an appropriate language. It was explained that small amounts of radiation would be used.

4.4 Professor Elwood indicated that the MRC would have had details of correspondence and he has been able to produce correspondence with members of some of the participants' families and vith one of the local health staff involved. These indicate that the purpose of the study and the fact that small amounts of radiation would be used was openly referred to.

4.5 Unfortunately the MRC no longer has the list of participants in the study, so we have only been able to hear from the small number who have come forward as a result of the Channel 4 programme and subsequent publicity. At the public meeting it was stated that two of the participants who had come forward had no recollection of giving informed consent. The patients involved were all on the list of one G.P.,.Dr. Shah, who died several years ago. Two of these have given the Director of Public Health permission to look in their G.P.'s case notes to see if the study is recorded therein. No record could be found in either case. We would have expected at least a reference to the fact that they had been invited and agreed to participate in the study.

5.0 Conclusions and recommendations

5.1 With reference to the three areas of concern referred to in paragraph 1.5, the Director of Public Health and I have concluded;

- On the basis of all the evidence supplied to us it is clear that the research carried out by Professor Elwood was purely health related and part of a wide range of work carried out by him looking into nutrition and iron deficiency.
- Although it is impossible to say there are no risks in uch a study, the health risks were very low. We understand approval was received from the MRC Isotope panel.
- Although there are different recollections between some of the participants and Professor Elwood and not all the MRC records were available, Professor Elwood has produced several pieces of correspondence which endorse what he has said he did and establish
- clearly that the study was openly conducted, with clear reference to the fact that small amounts of radiation would be used.

5.2 It is worth re-emphasising to people the current arrangements for obtaining research approval in Coventry and elsewhere. These are covered in paragraph 4.1, the key points being that consent has to be informed and in writing. We would also now have more formal arrangements to ensure proper interpreters were used when needed.

5.3 G.P.s are expected to keep proper notes of consultations and we would also expect them to keep a record of their patients' involvement in research when they have put forward a patient as a participant.

5.4 With regard to the MRC research I am writing to the MRC to clarify how long they would expect the various records of research studies to be retained so that this aspect is clear for all concemed.

5.5 The investigations we have carried out together with Mr. Bahia,Chairman of the Coventry Racial Equality Council and Mr. Bob Ainsworth M.P. have identified that the Channel 4 Progranune "Deadly Experiments" has caused considerable unnecessary concem to the Asian people in Coventry and potentially undermined their confidence in the National Health Service. Our investigations have also indicated that the research carried out by the makers of the programme was seriously lacking. Had they had the courtesy to contact Professor Elwood as we did they would quickly have established that their portrayal of events was seriously misleading. We would expect more professional standards of investigation and checking by all those involved. We will be taking these matters up formally with all those concerned and the appropriate complaints bodies.

5.6 Mr. Bahia, Mr. Ainsworth and I will be issuing a joint press release and holding a press conference.

5.7 The DHA and FHSA are asked to receive this report which publicly concludes the investigations we have carried out in response to the very understandable concerns of the Asian people in Coventry.

Chris Howgrave-Graham
Chief Executive, Coventry Health

ANNEX 6 – DEFINITIONS

RADIOACTIVE MATERIAL

Radioactivity

The decay of unstable atomic nuclei through the emission of ionising radiation. The resulting nucleus may itself be unstable, and undergo further radioactive decay. The most common types are **alpha radiation** (made up of helium nuclei), **beta radiation** (made up of electrons), and **gamma** and **x-rays**, consisting of photons. In medicine, gamma and x-rays are used for diagnosis, and beta radiation is used in therapy. Alpha radiation is not used in conventional medicine.

Units of Radioactivity

The **becquerel (Bq)** is a measure of radioactivity equal to one atomic disintegration per second. The curie (Ci) is a formerly used measure based on the radioactivity of 1 gram of radium, equal to 3.7 x 1010 Bq

Half-life

Half life is a measure of the rate of exponential decay of the radioactivity of a radioactive isotope. The **half life** is the time taken for the activity to be reduced by one half, that is for one half of the atoms present to disintegrate.

EXPOSURE TO RADIATION

Units of Radiation

The basic unit of radiation exposure is the roentgen, which is a measure of the degree to which the exposure would ionize air. The currently accepted unit of radiation absorbed dose is the **gray (Gy)** which is a measure of the energy absorbed from radiation, per unit mass.

Biological effects

The different types of radiation vary in the scale of their biological effects for a given amount of energy absorbed by tissue. A **Sievert (Sv)** is an estimated unit, used for radiation protection purposes, of biological equivalent dose. It is obtained by multiplying the absorbed dose by a factor reflecting the relative ability of that type of radiation to cause damage.

Effective dose

The dose to the various organs of the body from natural or man-made radiation varies according to the circumstances. **"Effective Dose Equivalent" (EDE)** is an estimate of the equivalent dose for the whole person, to allow comparisons between different types of exposure. EDE is based on weightings for each organ, and for the type of radiation.

In this report, dose is usually expressed as Effective Dose Equivalent, in milliSieverts.

Natural background radiation

The largest source of exposure to radiation is natural background radiation, produced by the decay of minute amounts of naturally occuring radioactive material in our environment, food, and bodies, and from cosmic rays. The annual exposure varies between districts: the effective dose equivalent per year is about 2 mSv in London and 10 mSv in Aberdeen.

RESEARCH AND TREATMENT

Therapeutic Research

Research in which the researcher intends to benefit the research participant as well as to obtain generalisable knowledge. An example would be studying the effectiveness of a new treatment in patients.

Non-therapeutic research

Research in which the researcher does not aim to benefit the research participant directly. Examples would be studying ill people to establish the basic cause of the illness, or testing new treatments in healthy volunteers.

ANNEX 7 – RELATIVE RISKS

General Risks

A risk of death of 1 in a million is caused by:

- Smoking 1½ cigarettes in a lifetime
- 0.1 millisieverts of absorbed radiation dose *(1982 estimate: current estimates are lower, at 0.02 millisieverts)*

[Brill 1982]

A man aged 42 has a 1 in a million chance of dying (from any cause) simply by living for 1 day. A man aged 60 incurs the same risk of death by living for 20 minutes.

Average lifespan shortening associated with varying conditions

• Heart disease shortens life	2100 days
• Accidents in the home	95 days
• Accidents at work	74 days
• National background radiation	8 days
• Medical X-rays	6 days
• Nuclear Medicine	4 hours

All figures assume a linear hypothesis.

Pregnancy risks

- 3% of children are born with clinically significant congenital malformations[41]
- Minor and major malformations together amount to 14% of births[42]
- The risk of a congenital abnormality due to radiation of the foetus from 0.5 mSv is 1 in 100,000 (assuming a linear hypothesis)
- The natural risk of childhood cancer is around 1 in 1300. Assuming a linear hypothesis, a doubling of this risk would occur with 25 mGy (for example from pelvic X-ray computed tomography) (Hart, 1994)

The Ionising Radiation Regulations 1985 states that the dose limits for the abdomen of a woman of reproductive capacity from occupational exposure "shall be (less than) 13 mSv in any consecutive 3 month interval" and for the abdomen of a pregnant woman "shall be (less than) 10 mSv during the declared term of pregnancy".

The Administration of Radioactive Substances Advisory Committee (1993) recommended that the dose to the fetus should not exceed 0.5mSv.

41 Moore KL and Persaud TVN **'The Developing Human, Clinically Orientated Embryology'** 5th ed. WH Saunders Co. Philidelphia 1993

42 Martine Vrijheid and Araceli Busby. London School of Hygiene and Tropical Medicine

Equivalent effective doses from current X ray and Nuclear medicine investigations

Investigation	*Effective dose, mSv*
Chest X ray	0.04
Kidney nuclear medicine study	0.7
Annual Natural Background	2.0
Lumbar spine X ray	2.2
Bone scan	3.5
Barium meal	4.6
Kidney X ray	4.6
Cardiac scan	6.8
Chest X ray CT	8.3
Barium enema	8.7

(Source: Mountford and Nunan, 1995)

References and further reading:

Ionising Radiation Regulations (1985) Health and Safety No 133 HMSO London 1987 p.36

Low Level Radiation Effects: A Fact Book (1982 and update 1985) Ed A B Brill. The Society of Nuclear Medicine, New York

Notes for Guidance on the Administration of Radioactive Substances for the Purposes of Diagnosis, Treatment and Research (1993) Department of Health and Social Security, London

Absorbed Radiation in Patients: A Memorandum for the Ethical Committee (1991) Britton KE, Gilday DL (reproduced in Clinical Nuclear Medicine 2nd Edition Maisey MN, Britton KE, Gildey DL, Chapman and Hall Medical, London 620-623)

Radiation Risk and Ethical Consent. Mountford PJ, Nunan TO. Nuclear Medicine Communications 1995; 16: 1-3

Diagnostic Medical Exposures to Ionising Radiation During Pregnancy. Hart GC. Nuclear Medicine Communications 1994; 15: 403-404.

ANNEX 8 – DATA ON THE INCIDENCE OF THYROID CANCER IN SCOTLAND

See following Tables 1, 2 and 3

TABLE 1

CANCER OF THE THYROID (ICD-9 193)

World age standardised incidence rates (per 100,000) for selected European countries

Males	1973-77	1978-82	1983-87	Females	1973-77	1978-82	1983-87
Italy (Varese)	2.3	1.9	2.0	Finland	3.9	5.2	5.8
Switzerland (Vaud)	1.2	1.8	1.8	Norway	4.4	5.1	5.1
Germany (Saarland)	1.1	1.6	1.8	Italy (Varese)	5.1	3.7	4.9
Finland	1.6	1.6	1.8	Switzerland (Vaud)	4.7	4.0	4.3
Sweden	1.5	1.6	1.6	Sweden	3.8	4.3	3.8
Norway	1.5	1.7	1.6	Germany	2.7	3.7	3.6
France (Bas-Rhin)	1.2	1.0	1.5	France (Bas-Rhin)	2.6	2.8	2.9
Spain (Zaragoza)	1.2	0.5	1.1	Scotland	-	1.9	2.0
Denmark	0.9	0.9	1.0	Denmark	1.4	1.9	2.0
Scotland	-	0.6	0.9	Spain (Zaragoza)	5.4	1.7	1.9
England & Wales	-	0.6	0.7	Netherlands (Eindhoven)	-	1.9	1.9
Netherlands (Eindhoven)	-	1.0	0.7	England & Wales	-	1.5	1.5

(1) Muir CS, Waterhouse, J, Mack T, Powell J, Whelan S (editors). *Cancer Incidence in Five Continents, Volume V.* IARC Scientific Publication No. 88. Lyon: International Agency for Research on Cancer, 1987. [covers the period of incidence 1978-1982)

(2) Parkin DM Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J (editors). *Cancer incidence in Five Continents, Volume VI.* IARC Scientific Publication No. 120. Lyon: International Agency for Research on Cancer, 1992. [covers the period of incidence 1983-1987]

TABLE 2

CANCER OF THE THYROID

Numbers of registrations, standardised registration ratios (SRRs) and 95% confidence intervals (95% CI) by health board of residence. 1981-90

	Males			Females		
	Regs	SRR	95% C1	Regs	SRR	95% C1
Argyll & Clyde	14	63	37 - 106	49	79	60 - 105
Ayrshire & Arran	19	99	63 - 155	38	72	52 - 99
Borders	4	69	26 - 184	22	139	91 - 211
Dumfries & Galloway	5	61	25 - 147	14	65	39 - 110
Fife	22	124	82 - 189	45	94	70 - 126
Forth Valley	20	144	93 - 224	41	110	81 - 150
Grampian	35	138	99 - 193	105	154	127 - 186
Greater Glasgow	31	64	45 - 90	126	90	76 - 107
Highland	10	97	52 - 181	34	125	89 - 174
Lanarkshire	23	86	57 - 129	61	84	65 - 107
Lothian	41	109	80 - 148	124	116	97 - 138
Orkney	1	91	13 - 648	3	108	35 - 336
Shetland	2	169	42 - 677	8	265	133 - 530
Tayside	27	129	88 - 188	45	77	57 - 102
Western Isles	6	336	151 - 748	7	152	73 - 320

Sharp L, Black RJ, Hamkess EF, Finlayson AR, Muir CS. *Cancer Regisiration Statistics Scotland 1981-1990. P102*

TABLE 3

Number of registrations of Thyroid Cancer (ICD-9 193) in Scotland and Grampian Health Board by sex, age group and 5 year diagnosis periods; 1975-1994 with crude and World age standardised

Scotland — **Males**

Age group	1975-79	1980-84	1985-89	1990-94
0 - 14	0	1	0	0
15 - 34	17	17	19	20
35 - 44	6	13	22	22
45 - 54	16	20	22	21
55 - 64	16	21	28	25
65 - 74	28	35	21	41
75 +	15	11	19	16
All ages	98	118	131	145
Crude Rate	0.78	0.95	1.06	1.17
WASR	0.63	0.76	0.84	0.88

Grampian Health Board — **Males**

Age group	1975-79	1980-84	1985-89	1990-94
0 - 14	0	0	0	0
15 - 34	3	6	3	2
35 - 44	0	3	3	5
45 - 54	2	1	3	3
55 - 64	0	4	2	3
65 - 74	3	5	1	4
75 +	6	3	3	1
All ages	14	22	15	18
Crude Rate	1.26	1.85	1.21	1.40
WASR	0.86	1.51	0.96	1.09

Scotland — **Females**

Age group	1975-79	1980-84	1985-89	1990-94
0 – 14	2	2	2	3
15 – 34	50	66	70	95
35 – 44	47	50	51	59
45 – 54	44	43	59	57
55 – 64	53	52	57	50
65 – 74	82	60	65	56
75 +	101	90	76	58
All ages	379	363	380	378
Crude Rate	2.82	2.72	2.88	2.86
WASR	1.93	1.91	2.07	2.15

Grampian Health Board — **Females**

Age group	1975-79	1980-84	1985-89	1990-94
0 – 14	0	2	1	0
15 – 34	4	5	17	10
35 – 44	6	8	13	7
45 – 54	7	6	10	8
55 – 64	4	8	8	5
65 – 74	4	6	4	3
75 +	13	10	7	11
All ages	38	45	60	44
Crude Rate	3.20	3.60	4.67	3.33
WASR	2.16	2.72	3.88	2.38

Source: unpublished data, Scottish Cancer Registry