THE IRRADIATION OF HUMAN VOLUNTEER SUBJECTS IN RESEARCH

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The uses of radiation in diagnostic radiology and nuclear medicine are justified by the benefits that are expected to accrue to the persons being examined. But in medical research it is sometimes necessary to obtain data from normal healthy individuals. These subjects do not themselves gain any physical benefit from such research.

CONSTRAINTS

Because of the possible detrimental effects of radiation, besides its ALARA concept, the ICRP recommends[1] that in the case of pure medical research:

(a) the irradiation of persons should be undertaken only by properly qualified and trained persons,
(b) the irradiation should have the consent of the institution,
(c) such consent should be based on advice of an appropriate expert committee and be subject to local and national regulations,
(d) the volunteer subjects should fully exercise their free will,
(e) the estimated irradiation risks should be explained to subjects,
(f) the magnitude of the detriment to the volunteers should be authorised for each research program.

The ICRP states that the higher the dose the more rigorous should be the selection of true volunteers and their capability of understanding the risk. In the case of children and other persons incapable of giving their true consent, experimental irradiation should be undertaken only if the expected dose-equivalent is of the order of one-tenth of the limit applicable to members of the general public[1]. In Australia the NHMRC has recommended the following principles[2]:

(g) annual doses should not exceed those for members of the public,
(h) the actual doses delivered should be the lowest practical,
(i) adequate precautions should be taken against overdosage,
(j) only true volunteers should participate,
(k) an expert committee of the institution should evaluate a comprehensive safety assessment for each proposed irradiation.

In 1967 the World Health Organisation made recommendations for the control of experimental radiation. The WHO Report[3], which appeared subsequent to the investigations discussed below, provides guidelines rather than prescriptions for making decisions in specific cases. It suggests four categories into which projects can be classified depending upon the amount of total body or weighted single-organ radiation dose to be received by a subject. Category 1 contains projects which produce an annual total body dose of less than 50 mrem; i.e. within variations of natural background and hence of negligible risk[3].

Two examples of the irradiation of human volunteer subjects in research are described below.

EXAMPLE 1

As part of a study of artificial hip joints, information is needed as to the extent of shortening of the femur, in vivo, when the normal load of the body weight is applied. This information can be deduced by superimposing two diagnostic radiographs of the femur, the first radiograph obtained when a subject bears his weight on one leg only, and the second when the subject bears no weight on that leg (i.e. it is suspended). The proposed x-ray plant settings are: 68 kV, 100 mA, 0.12 sec, 1.83 m FFD, 2 mm Al filtration.

For dosimetry purposes, ideally, measurements of absorbed doses could be made in a phantom, but an estimate can be made as follows[4]. From the literature typical measurements of exposure made at a distance of 1.68 m (corresponding to the anterior surface of the leg) under similar plant conditions to the above, yield an average exposure value of 5.2 μC/kg (20 mR) per film. Neglecting attenuation within the leg, the absorbed doses at 70 kV in bone (97 Gy.kg/C=2.5 rad/R) and in soft tissue (bone marrow and gonads; 35 Gy.kg/C=0.9 rad/R), yield dose equivalents of 500 μSv (50 mrem) in bone and 180 μSv (18 mrem) in bone marrow and gonad tissue. These values are considerably less than the respective annual maximum permissible doses[5] of 3,000 mrem and 500 mrem for volunteers by factors of 60 and 27 respectively. As the smaller number is the more restrictive, up to 27 films could be obtained from a single volunteer. The dose is minimised by requiring only two films per volunteer, totalling 7% of the annual maximum permissible dose-equivalent. In current ICRP terms[1], the Effective Dose Equivalent ($\Sigma w_T H_T$) for gonads + red bone marrow + bone surface is 30 mrem, placing this project in WHO category 1.

An expert committee was established to evaluate the safety of the proposed project. After consideration the committee gave its approval to the project, subject to the following conditions.

1. Only the least number of volunteers needed should participate.
2. All volunteers must be at least 21 years of age (now 18 years).
3. The investigation be restricted to male subjects and a gonad shield be used for all x-ray exposures.
4. Each volunteer must sign a Form of Consent after having read the NHMRC Statement on Human Experimentation[6] and a description of the proposed project. Subjects must have the opportunity of asking any questions and of reading the project safety assessment.

EXAMPLE 2

To improve dialysis treatment of renal failure, basic information is needed as to the rates of movement of various blood solutes between different compartments in the body[7]. The measurements can be performed by injecting into patients undergoing regular dialysis treatment, a known quantity of radioactively labelled solute, and subsequently analysing the activity contained in sequential blood samples.

Each subject will receive two intravenous injections of ^{14}C-labelled urea and two of ^{14}C-labelled creatinine. Each injection will contain 2.4 MBq (65 μCi) activity of ^{14}C-labelled solute dissolved in 15 ml of sterilised saline. At least two weeks will elapse between consecutive injections. Both solutes are expected to be distributed in a total volume of about 30 litres. The amount of labelled urea or creatinine remaining after two weeks would be about 3.7 kBq (0.1 μCi). The project envisages the participation of four stabilised chronic haemodialysis patients of either sex, aged between 20 and 40 years and having a life expectancy ranging from 5 to 10 years.

Adopting an average beta energy value of 0.052 Mev, and assuming that the absorber is infinitely large with respect to the range of radiation, then the initial absorbed dose-rate from a single injection is given by:

$$\frac{2.4 \times 10^{6}\,s^{-1} \times 0.052\ \text{Mev} \times 1.6 \times 10^{-13}\ \text{J.(Mev)}^{-1}}{30\ \text{kg}}$$

$$= 0.67\ \text{nGy.s}^{-1}\ (0.24\ \text{mrad.h}^{-1})$$

Hence with unit quality factor, the initial dose-equivalent rate, D_o, is 0.24 mrem.h^{-1} (0.67 nSv.s^{-1}). The decrease in activity due to radioactive decay in a year is negligible. Thus using the above biological elimination data the effective decay constant λ is given by:

$$\frac{3.7\ \text{kBq}}{2.4\ \text{MBq}} = \exp(-\lambda t) = \exp(-\lambda x 2 \times 168\ \text{h})$$

$$\text{Hence } \lambda = 0.0193\ \text{h}^{-1}$$

The annual dose-equivalent, D, is obtained by substituting these values into the equation for cumulative dose.

$$D = \frac{D_o}{\lambda}\left[1-\exp(-\lambda T)\right] = \frac{0.24\ \text{mrem h}^{-1}}{0.0193\ \text{h}^{-1}}\left[1-\exp(-0.0193\ \text{h}^{-1} \times 8736\ \text{h})\right]$$

$$= 12.4\ \text{mrem (124 μSv)}$$

The total annual dose-equivalent from four such doses is 50 mrem. This value is only 10% of the whole-body annual maximum permissible dose-equivalent.

As in Example 1 an expert committee gave its approval subject to previous conditions 1,2,4 and the following:

5. Each subject should be exposed to the minimum number of tests.
6. Supervision is necessary to prevent overdosage.

The Committee also considered the dependence of dose on the rate of elimination of the active solute; responsibilities resulting from multi-institutional participation; the free expression of consent and the lodging of signed consent forms.

Subsequently the Committee approved an extension to the project to include 2.4 MBq (65 μCi) of ^{14}C-sucrose and 5.5 MBq (150 μCi) of ^{3}H-vitamin B12. Using the above method, and allowing for double injection and different volumes of body fluid it was found that the ^{14}C-sucrose would deliver an annual dose-equivalent of 50 mrem (500 μSv). The ^{3}H-vitamin B12 has a different energy and different effective decay constant which will produce an annual dose-equivalent of 37 mrem (370 μSv)[4]. This project, which was in WHO Category 1, has since been completed[7]. In current ICRP terms[1], the annual dose-equivalent of 12.4 mrem is 10% of the dose-equivalent limit.

Because of rapid excretion, the committed dose-equivalent is also 12.4 mrem.

GENERALISED USE OF HUMAN SUBJECTS

In experimental procedures that involve the use of human volunteer subjects, there is a need to protect the rights and welfare of the subjects, and to safeguard the interests of the institution and the investigator. Generally, it is not easy to satisfy the separate ideal criteria of the three interested parties. Minimum requirements are listed in two authoritative documents[6,8].

At the University of New South Wales a set of rules governing experimental procedures of any type involving human subjects has been adopted[9]. The rules have been subject to lengthy consideration within the University. They provide for a committee to advise the Vice-Chancellor on all applications to undertake human subject research, and they make provision for certain exclusions.

Some difficulties which have been encountered include the wording of the consent form which, if to fully satisfy lawyers, would deter most potential subjects. To obtain "informed" consent, an investigator must give a full and frank disclosure of the proposed procedures and of all the risks entailed; this sometimes can defeat the purpose of the research. Insurance policies are usually effected to cover liability for possible claims resulting from negligence. In human subject research the claims could result from intentional acts. With greater community awareness of the need for social responsibility in science, the Committee will have challenging situations to consider.

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