The Use of Radioisotopes in Human Experiments : Comments in Response to Recent Media Articles

by

R.E.Boyd
Australian Nuclear Science and Technology Organisation
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Abstract:

Recent newspaper articles question the propriety and ethical foundation of early experimental programs in which radioisotopes were administered to human subjects.

This paper describes the relevant activities of Ansto's predecessor, the Australian Atomic Energy Commission(AAEC), and provides an historical background to these and subsequent events.

Print Media References to Experiments on Humans and Any Involvement of Ansto's Predecessor, the AAEC.

Reference is made to articles which appeared in the Melbourne and Sydney dailies on the 31 March 1994.

Ansto's predecessor, the Australian Atomic Energy Commission(AAEC), was linked to some of the issues raised in these articles through its association with the Commonwealth X-ray and Radium Laboratory (CXRL, an agency of the Commonwealth Department of Health and the precursor of the Australian Radiation Laboratory), but was not involved in either the selection or approval of any of the experimental programs that are the focus of the newspaper articles. It is also true to state that no member of the staff of either Ansto or the AAEC has ever administered a radioisotope to a human subject for the purposes of diagnosis, therapy, medical research or for any other reason.

In the period under review in the newspaper articles, most of the radioisotopes employed in medical and medical research applications were imported from overseas(USA, UK, Canada, France, Holland and Israel).For example, in the twelve months ending 30 June 1962, some 987 shipments including 37 different radioisotopes and a large number of labelled compounds were procured by CXRL. Of these only 47 shipments including 5 different radioisotopes were supplied by the AAEC. However in the course of the next decade this situation changed dramatically until more than 95% of shipments originated from Lucas Heights(see later description of events 1960 - 1970).

Phosphorus-32(half life 14 days), gold-198(half life 2.7 days) and iodine-131(half life 8 days) are referred to by the articles but pharmaceutical preparations of these radioisotopes were not manufactured in Australia by the AAEC until the mid - to late - 1960's. Hence Ansto had no connection with the early clinical experiments performed with these radioisotopes.

On the other hand, for the administration of sodium-24 to near-term expectant mothers, the main theme of several newspaper articles, the radioisotope would have been supplied by the AAEC. Sodium-24 has a half life of 15 hours which is too short to obtain

by import. Hence it may safely be presumed that this radioisotope originated from Lucas Heights.

The annual reports of the AAEC, from 1961 onwards, indicate the growing demand for short lived medical radioisotopes. The report for year ending 30 June 1961 of the operation of CXRL indicates that the AAEC was in a position to provide some radioisotopes for human use, and that where half life constraints applied, CXRL were prepared to authorise delivery direct from Lucas Heights. The CXRL Annual Report for 1962 states that 17 shipments of potassium-42(half life 12.5 hours) and 23 shipments of sodium-24 were supplied by the AAEC for medical research purposes. The National Health and Medical Research Council, Committee on Radioisotopes minutes of the 52nd meeting held in November 1961 report that approval had been sought by a group of medical researchers to use AAEC-produced sodium-24 in investigations carried over from similar studies in the UK which involved pregnant women. The AAEC was not involved in the approval-seeking process but was called on to supply the radioisotope on request. There was no secrecy involved and the results of the studies were published in appropriate medical journals.

There is a significant body of evidence in AAEC files, relating back to the period in question, which testifies to the fact that the human use of radioisotopes was an issue of extreme sensitivity to the organisation.(An example of the attitude prevailing at that time within the executive management of the AAEC was the decision to discontinue the supply of radioactive injections from January 1964 to July 1965 while facilities and procedures were modified to comply with newly drafted regulations concerning therapeutic substances-see later)

In the following segments of this information paper are provided :

- an historical review of the policies and practices for procuring, supplying and distributing radioisotopes for medical application in Australia, and

- a brief summary account of the production of medical radioisotopes by the AAEC during the period 1960 - 1970

It is intended that these chapters provide both the historical backgrounds to situations prevailing in Australia at the times referred to by the highly emotive newspaper articles and be of value in establishing the extent of the AAEC's contributions to the development of our national Nuclear Medicine Service.

An Historical Review of the Policies and Practices for the Procurement, Supply and Distribution of Radioisotopes in Australia

The first treatment involving a radioactive substance in Australia was performed by a Melbourne dermatologist in 1903; however most people at that time needed to go overseas to obtain this type of treatment. In 1928, recognising that it was intolerable for what was perceived as life-saving therapy, to be available only to the wealthy, the Commonwealth Government purchased 10 grams of radium-226, at a cost of more than $4M in present day values, and created a national radon-222 bank on the campus of the University of Melbourne. On June 1 1929, the Commonwealth Radium Laboratory, later to evolve into the Commonwealth X-ray and Radium Laboratory and then into the Australian Radiation Laboratory, was established to operate the radon bank and distribute therapeutic radiation devices to whomsoever was in need.

The first medical use of man-made radioisotopes (as opposed to radon-222 and other natural radioelements) occurred in Brisbane (1944) when US Services medical officers imported small quantities of phosphorus-32 for the treatment of blood disorders in some nineteen patients(presumably US servicemen). After the war (1946) trial shipments of phosphorus-32 arrived at the Commonwealth X-ray and Radium Laboratory(CXRL, name change 1935) from the USA but attempts to expand this to include iodine-131 and sulphur-35 were unsuccessful because there was no official mechanism by which the US authorities could export these materials.
In 1947 the National Health and Medical Research Council(NHMRC) established a Standing Committee on Radioactive Isotopes with responsibility for the coordination of research in the therapeutic use radioisotopes and their use in tracer studies. In effect, this committee acted as the national therapeutic trials committee but as interest became more widespread similar committees were set up in each State.

In September 1947, President Truman announced that the US Atomic Energy Commission(USAEC) would accept requests for radioisotopes from other countries providing those countries were

capable of dealing with them safely and effectively and that all requests could be channelled through a central procurement agency in each recipient country. With such an infrastructure already in place, Australia satisfied the conditions set out in the Presidential statement and therefore regular consignments of phosphorus-32 and iodine-131 were soon being received at the CXRL in Melbourne for sub-division and then national redistribution. Although the source of supply was subsequently switched from the USA to the UK (to benefit from shorter delivery times and the saving of US dollars) CXRL was consolidated as the sole authority for the importation and use of medical radioisotopes in Australia.

Initially, it was proposed that no charge be made for radioisotopes issued for clinical use in public wards while private patients would be charged at cost. Eventually it was agreed no patient would be charged for any radioisotope used in well-established clinical procedures of diagnosis or therapy. The costs for this service were borne, firstly, by the Commonwealth Department of Health but later were met from the National Welfare Fund.

In 1953 the Australian Atomic Energy Commission(AAEC) came into being with an interest, inter alia, in identifying the benefits of domestically produced radioisotopes. A liaison was created between CXRL and the AAEC and new procedures were agreed for the procurement and distribution of radioisotopes in Australia. CXRL maintained their authority to regulate and supply radioisotopes to all medical applications(including medical research). The AAEC was limited to servicing the industrial and non - medical markets.

The Australian use of radioisotopes in medicine, particularly for diagnostic purposes, increased rapidly, and, coinciding with its increasing technological competence, the AAEC was encouraged by CXRL to use its facilities for import replacement. In 1961 the AAEC began to satisfy the medical demand for radioisotopes; subsequently the AAEC was given first refusal on all radioisotope products that CXRL planned to procure. By 1977 this demand covered some 25,000 consignments per annum of which nearly 95% originated from the AAEC. During the whole of this development period the AAEC only supplied radioisotopes to the medical market according to case - by - case directions from CXRL from whom also came the authority for reimbursement from the National Welfare Fund. However there was one regulatory responsibility incumbent on the AAEC in responding to a CXRL request to supply direct to the end-user (as half lives of

radioisotopes used in medical applications got progressively shorter, more and more deliveries from Lucas Heights went directly to the user instead of via CXRL). That responsibility was to check that the recipient organisation/medical practitioner possessed a valid licence from the State authorities to hold and use that particular radioisotope.

In respect of those radioisotopes in demand but not produced in Australia, responsibility for procurement and customs clearance was divided. Until the end of 1977 CXRL maintained their traditional control over radioisotopes destined for medical application; the AAEC only authorised the importation of industrial radioisotopes

Two acts of deregulation occurred in nuclear medicine on the 1 January 1978. The Commonwealth Government decided to transfer CXRL's function of procurement and distribution of radioisotopes for medical applications to the AAEC and other Australian agents. The free issue of radioactive materials to patients was discontinued. (No change occurred to the States' requirement for user-licensing.)

Since that time the nuclear medicine market in Australia has had to respond to the forces of commerce where questions of supply were limited only to:

- The radioisotope/radiopharmaceutical must be approved and licensed by the Commonwealth Department of Health before it may be offered for sale to public or private medical organisations (as is common with all therapeutic substances).

- The medical organisation's financial capability to meet costs

Clinical trials are only performed in accordance with regulations established by the National Health and Medical Research Council and the Therapeutic Goods Administration. These regulations bind the drug supplier and the research organisation to a strict code of practice.

Radiopharmaceuticals in routine use are listed in the Pharmaceutical Benefits Schedule and charges incurred by a patient undergoing a nuclear medicine investigation are transferable, in part at least, back to the Commonwealth in the same way as are most other medical procedures.

The AAEC Production of Medical Radioisotopes in the Period 1960 - 1970

The production of radioisotopes for medical application utilising the Australian nuclear reactor, HIFAR, commenced in 1960. These activities were initially limited to the production of cobalt - 60 for the treatment of cancer and the first Australian-made teletherapy source, containing 2600 Curies, was delivered to St. Vincent's Hospital in November 1961. However within a short period sodium-24 was also being produced for applications in medical research.

The year 1962 was the first full year of radioisotope production at Lucas Heights when it responded to a four-fold increase in demand from the medical community. Consistent with its original mission statement, a special feature of local production was a concentration on short lived radioisotopes which were difficult (or impossible) to obtain from other sources. Examples of these were sodium-24, potassium-42, copper-64 and gold-198.

In 1963, special medical preparations containing chemically processed short-lived radioisotopes were increasingly sought after and consequently the AAEC initiated a development program to increase its product range. Doubling the capacity to activate targets for short-lived radioisotopes was achieved in 1964 but their use in medical applications in Australia, in fact, dropped away.

This reversal in the trends being experienced elsewhere in the developed world was due to a decision to cease the production of radioactive injections.

Prior to this, preparations intended for parenteral administration were subjected to terminal autoclaving before dispatch. The newly drafted Therapeutic Substances Regulations now required that all injections must also be tested for sterility before being released for use. Because the time taken to perform standard sterility testing far exceeded the useful life of medically used radioisotopes, the initial understanding at Lucas Heights was that this requirement did not apply to radiopharmaceuticals. Advice from the Crown Solicitor, however, suggested that very substantial legal liabilities rested on the AAEC should this regulatory requirement be ignored.

As a result a decision was taken in January 1964 to discontinue the supply of radioactive injections until suitable sterility testing standards could be agreed with the National Biological Standards Laboratory and then incorporated into the AAEC's production infrastructure.

In the course of the next eighteen months phosphorus-32 was added to the list of products of potential value in medicine and improved equipment was installed to facilitate the routine sterilisation of radioactive solutions. Comprehensive testing schedules (including sterility testing) were established in conformity with the Pharmaceutical Substances Regulations and in July 1965, very short-lived radioisotope preparations for administration by intravenous injection became routinely available once again. The number of shipments from Lucas Heights almost doubled and planning commenced on new processing facilities.

A five year plan (1965-1970) was developed with several new radioisotope products included; for example - technetium-99m, fluorine-18, iodine-131 and mercury-197. The need to cope with the close programming of production, distribution and use of such products as technetium-99m (half life 6 hours) and fluorine-18 (half life 110 minutes) was seen as likely to limit their availability to Sydney and its environs. For the first time the Australian Department of Health permitted the AAEC to establish direct contact with medical users of radioisotopes providing that the discussions were limited to technical detail and were not used as a means to press for a wider general usage of radioisotopes in medicine.

In 1967 the new radiochemical production laboratories were commissioned and this coincided with the growing and world-wide interest in technetium-99m for imaging studies in nuclear medicine. Technological developments at Lucas Heights and the new facilities provided the AAEC with the opportunity to produce large amounts of technetium-99m at just the right time to sustain a rapid growth in nuclear medicine in Sydney. When the AAEC produced its prototype molybdenum-99:technetium-99m generator in 1968, a similar growth in nuclear medicine was made possible in the other Australian centres.

In 1969 iodine-131 production was established and fluorine-18 was being regularly delivered to Adelaide and Melbourne(as well as Sydney) despite its half life of less than 2 hours. In 1970 extensive research was underway to produce a wide range of technetium-99m radiopharmaceuticals.

The cumulative sales from radioisotopes (1960 - 1970) exceeded S1M (about half of which had been generated in the last two years of the decade). Very short lived medical products (mainly technetium-99m based) constituted 85% of all deliveries. These products were delivered before 9.00am daily to hospitals in Sydney, Melbourne, Brisbane, Adelaide, Perth, Hobart and Launceston. Production activities were conducted around the clock and deliveries were made according to very tight schedules with a high success rate.

The national delivery system developed by the AAEC to provide short lived radiopharmaceuticals throughout the Commonwealth of Australia was quite unique internationally and it did much to contribute to an early leading position in nuclear medicine that Australia enjoyed at that time.

The medical radioisotope products manufactured by the AAEC during this period were used with great effect by medical specialists in the investigation of various internal regions of the body and were all authorised and funded by agencies of the Australian Department of Health.