between 0.1 and 0.15 mill/kWh of nuclear electricity produced. This cost approximates only one to two per cent of the cost of nuclear power in an 8 - 10 mill/kWh economy. The ORNL engineering and economic studies indicate that the total cost of interim liquid storage, pot calcination, and shipping over a 3000 mile round trip can be as low as 0.02 mill/kWh(e). Tentative costs for a large-scale disposal operation for calcined solids in salt deposits are estimated at 0.01 mill/kWh(e). Based on past laboratory and engineering scale cold unit operation data, and on an expected successful field demonstration and testing programme with high activity wastes, it is firmly believed that waste management operations should not constitute a major obstacle to the development of economical nuclear power."

MEDICAL USES OF RADIOACTIVE CALCIUM

REVIEW OF AN IAEA PROGRAMME TO PROMOTE THE APPLICATIONS OF CALCIUM-47

Calcium plays a number of biologically essential roles, which have long been under investigation by various techniques available to medical science. One of the most important of these techniques is radioactive tracer analysis, i.e. study of the functions of calcium within the body with the help of a radioactive isotope of the element.

The calcium-47 programme of the International Atomic Energy Agency is intended to promote these investigations by facilitating the production and use of this isotope. The importance attached to calcium-47 is due to the special properties of this isotope, which make it the most valuable tool for many calcium studies by the radioactive tracer method.

Calcium as found in nature is a stable element and has six isotopes. The most common of these six stable isotopes is calcium-40, which constitutes about 97 per cent of natural calcium. The other stable isotopes are rare, and calcium-46, a stable isotope which is of particular interest in the production of the radioactive isotope calcium-47, has an abundance of only 0.003 per cent.

Advantages of Ca^{47} and Methods of Production

Apart from the stable isotopes, at least six radioactive isotopes of calcium have been artificially produced. Three of these have properties which make them of possible use as radioactive tracers. Calcium-45 has been the most prominent of these three, and has been used extensively during the last 15 years. Calcium-49 has also been employed. But for many purposes the most suitable is calcium-47. Why this is so is explained by a comparison of the physical characteristics of these three isotopes.

Calcium-45 has a half-life of about 160 days and emits low energy beta radiation which is completely absorbed in a layer of matter less than 1 mm thick. The relatively long half-life of the isotope results, in most human studies, in an undesirably prolonged irradiation of the subject and the isotope is therefore considered rather hazardous for internal administration. Also, the low energy level of its radiation often makes measurements difficult. Calcium-49, on the other hand, has a half-life of only nine minutes, which is too short for biological tracer applications, although convenient for certain other purposes. Calcium-47 has a half-life of about five days, which is long enough for numerous biological investigations and short enough to ensure that the person subjected to the investigation is not under prolonged irradiation. It emits gamma rays in addition to beta rays, and since the gamma rays are capable of penetrating many centimeters of tissue, determination of calcium-47 in the body is possible by external measurements. Furthermore, measurement of the calcium-47 content even of isolated samples, such as a few milliliters of blood, is far more convenient than that of calcium-45. Thus calcium-47 has distinctive properties which allow its use in biological investigations where calcium-45 would be unsuitable, and some of these uses are of considerable medical significance.

Unfortunately, calcium-47 is difficult to produce. The irradiation of ordinary calcium in a nuclear reactor, of course, results in the capture of some neutrons by the stable isotope calcium-46, which thereby is converted to calcium-47. However, because calcium-46 is extremely rare, the amount of calcium-47 produced in this way is insignificant compared with the amount of calcium-45, which is produced from calcium-44, a more abundant stable isotope. There are several other reactions by which calcium-47 can be produced, but they are all very expensive. At present the most economic approach is a sequence of two steps. First, calcium-

46 is separated from other natural calcium isotopes in isotope separation machines. Secondly, this nearly pure calcium-46 is then irradiated in a reactor to produce nearly pure calcium-47. It should, however, be remembered that very few centres in the world have machines for isotope separation.

Importance of Calcium Studies

It might be worth while to examine at this point the reasons for the special interest in the production of radioactive tracers for calcium studies. The reasons lie in the physiological importance of calcium, which - as is well known - is a primary constituent of the skeleton; in fact, the skeleton contains more than 99 per cent of the body's calcium. What is not so well known is that the element has other essential physiological functions. A continuous and rapid exchange of calcium goes on between the blood and other soft tissues on the one hand, and the reserves in the skeleton on the other.

Before the advent of radioactive tracers it was virtually impossible to investigate the metabolic path of calcium in the body: its absorption through the walls of the intestine into the blood, its deposition in the skeleton, its return to the blood and possible incorporation into complex molecules, and its excretion. All these steps are subject to interference by disease and by nutritional conditions, and defects in the body's handling of the isotope may in turn cause illness. The isolation of metabolic pathways and the identification of disorders in any of these are possible only when the scientist is able to administer a "tracer" under chemical or physiological conditions appropriate to the study. Radioactive isotopes of calcium are particularly suitable as such tracers.

A somewhat different calcium-47 application, which cannot be done with any other calcium isotope, is the detection and localization of bone tumours. These tumours, whether originating in the skeleton or transferred there from a soft tissue tumour, are usually characterized by comparatively rapid growth and deposition of increased amounts of calcium. If detected in time, their progress can be greatly retarded by suitable treatment. When calcium-47 is injected into a patient thought to be suffering from or vulnerable to bone tumours, the existence and location of tumours can be established from the abnormal concentration of the isotope at any place, the concentration being detected by scanning of the gamma rays emitted by the isotope. It appears that it is sometimes possible to detect skeletal tumours by this technique earlier than by radiography.

In addition to its interest in intrinsic calcium metabolism and in the detection of skeletal tumours, medical science has a special interest in another aspect of the behaviour of the skeleton, and this is an aspect which has a bearing on IAEA's functions in the field of radiation safety. Many long-lived radioisotopes, having once gained entry into the body, are retained in the skeleton and therefore irradiate the skeleton more than any other organ. Notable among these is strontium-90. In order to devise an effective method of eliminating these isotopes from the skeleton, it is necessary to have a detailed understanding of the metabolism of the skeleton, and in particular of calcium.

Start of IAEA Programme

IAEA's attention was focussed on calcium-47 during a scientific meeting in 1958 when it became apparent that several doctors were interested in using this isotope, but that at the time only one or two in the whole world were able to do so on account of its scarcity and exceedingly high price. Later that year the Agency's own scientific staff and its consultants, after a study of the problem, determined that the demand for this isotope far exceeded its current supply, and that production possibilities existed which would be much more economical if production in quantity could be undertaken. Much of the Agency's work thereafter has been directed towards the stimulation of cheaper production and the demonstration of the usefulness of the isotope if it could be more cheaply available.

In 1959 a second meeting of Agency consultants examined production techniques in detail and certain lines of action emerged from these discussions. One research contract was negotiated, with financial assistance from the United States Atomic Energy Commission, to develop cheaper methods of enriching calcium in the isotope calcium-46, i.e. increasing artificially the calcium-46 content of natural calcium. The existing producers of calcium-47 were stimulated to improve their techniques; in particular, several additional machines for the enrichment of calcium with the calcium-46 isotope were put into operation at the Oak Ridge National Laboratory in the USA. Recommendations were also made concerning the radiochemical purity of calcium-47 for human applications.

The research contract on enrichment techniques was partially successful in developing new methods, although they have not yet been utilized due to the simultaneous improvement in the supply of enriched calcium from existing methods. Since 1958 the price of calcium-47 has been reduced from over $1400 per millicurie to $200 per millicurie, and its degree of purity has been increased.

By the end of 1960 eleven more research contracts had been negotiated by the Agency on the application of calcium-47 in medical diagnosis and research. Most of these contracts financed only the cost of the isotope itself, so as to remove an important barrier to its use and thus to encourage competent and otherwise suitably equipped investigators to explore its potential applications. The contracts have been placed in the following countries: Austria, Belgium, Denmark, France, Poland, South Africa, Sweden and the United Kingdom.

Most of these studies have now been in progress for nearly two years, and it is expected that they will be continued for one more year. It is foreseen that thereafter the cost of calcium-47 will not be excessive in comparison with the other costs of radioactive tracer investigations of medical and biological problems, and that the existence and possibilities of this isotope will be widely recognized by the medical profession. The isotope would then, perhaps, be treated like any other useful radioisotope and not need any special subsidy.

Results of Research

Throughout this programme, an important goal has been to make the Agency serve as a clearing house for information concerning calcium-47. A study of the special problems in the assay of calcium-47 and the most economic means of performing the task was undertaken by the Agency's scientific staff, and its conclusions were made available to those interested. In December 1961 the Agency convened a panel of experts to review the progress of Agency-sponsored research contracts; all Agency contractors for calcium-47 research and a few other interested scientists were invited to the meeting. Each scientist reported on his experience with calcium-47 in comparison with other calcium isotopes and in the light of his medical problems.

It was clear from the discussions that the distinctive characteristics of calcium-47 make it the isotope of choice in a variety of applications, and, by joint use with calcium-45, extend the power of the calcium tracer technique. One group of investigators had employed the isotope in studies of calcium absorption through the intestinal wall. It was demonstrated that calcium absorption is modified in the presence of several diseases, particularly - as could be expected - those that affect the skeleton. It was also shown that calcium absorption is to some extent influenced by the amount of calcium in the diet and by the character of the diet. A number of investigators had concentrated on the elucidation of the metabolic pathways within the body. After injection of the isotope, the concentration in the blood and excretions was followed in quantitative detail, and attempts were made to describe mathematically the size and turnover rates of the several metabolic pools of calcium. Correlations were attempted between these findings and disease states, or treatment routines in particular diseases. At several laboratories calcium-47 had been extensively tested in tumour localization studies, and specific examples were given in which this isotope had permitted particularly early recognition of tumours.

One interesting finding was the difficulty experienced in accurate measurement of stable calcium by chemical techniques, which in turn made it difficult to interpret some of the results of the tracer investigations. This illustrates the need for well-established conventional measuring techniques to enable the effective utilization of radioactive tracers.

The proceedings of this meeting have recently been published by the Agency as a booklet entitled "Medical Uses of Ca^{47}" (Technical Reports Series No. 10).

In summary, the Agency has for four years been engaged in a comprehensive effort to bring calcium-47 into routine medical use. To this end, it has surveyed the need for this isotope, stimulated its cheaper production, encouraged the investigation of its medical possibilities, and arranged for the dissemination of the information thus obtained. The fact that calcium-47 is no longer considered an exotic isotope is at least partly due to the Agency's efforts, in co-operation with interested scientists throughout the world.