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The history of nuclear medicine in the Republic of Slovenia – pioneering age from 1954 to 1968

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Early beginnings of the biomedical use of radionuclides in Ljubljana date back to the year 1954 when J. Satler at the Medical Clinic first used radioiodine (131-J) for diagnosis. In the '50s the institutions which used radionuclides appeared in the following sequence: In 1955 at the Institute of Oncology L. Šavnik injected 198-Au-colloid intraperitoneally for the treatment of malignant disease; at Orthopedic Clinic Thorium-X was used therapeutically; at Institute of Physics of the Medical Faculty dosimetry, and at Institute of Pathophysiology the transport of sodium and potassium ions through cellular membranes was studied by means of radioactive tracers (22-Na and 42-K).

In the year 1960 the Basic Laboratory for Work with Radioisotopes was established in Ljubljana with the aim to provide facilities and place for work as well as coordination to all five institutions which had been using radionuclides.

In fact, till 1968 only the Radium and Isotopic Laboratory of the Institute of Oncology and the Radioisotopic Laboratory of the Medical Clinic operated together in the same place. Research at the Institute of Physics found no clinical application, the therapeutic use of Thorium X at the Orthopaedic Clinic was completely abandoned and the Institute of Pathophysiology built in 1962 its own laboratory for radionuclide investigations.

During the period from 1954 to 1968 Slovenian nuclear medicine, which was in the beginning more or less research-oriented activity, gradually developed broadly into a clinically applicable science.

The year 1968 denotes the end of the pioneering period in Ljubljana and the beginning of a rapid development of nuclear medicine departments in regional hospitals out of Ljubljana.

Key words: nuclear medicine-history; Slovenia

Introduction

By the end of World War II, the use of radioactive isotopes in diagnostics and therapy which established nuclear medicine as a new medical speciality spread throughout Europe and also in Slovenia. Here, the development of this new speciality is presented from its first steps in 1954 till the beginning of rapid augmentation in 1968 which resulted in the establishment of seven nuclear medicine laboratories: two in Ljubljana and one each in the peripheral towns Maribor, Celje, Slovenj Gradec, Šempeter by Gorica and Ankaran. Further development showed that by 1974, these seven nuclear medicine departments sufficed for the needs of Slovenian health service, which was in charge of nearly two million of

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inhabitants, and since then there was no need to open any new ones.

In the first part of this presentation the pioneering age from 1954 till 1968 is described.

1952 – The Institute Jožef Stefan and The Slovenian Academy of Sciences and Arts

In 1952 The Institute Jožef Stefan and The Slovenian Academy of Sciences and Arts organized the first cycle of lectures on the use of radioactive isotopes in medicine, intended for medical doctors. These were followed by practical courses on the handling of unsealed radioactive sources, upon completion of which the attendants obtained legal rights to use these materials.

In the following years the location of these courses changed for a majority of Slovenian doctors, technicians and nurses who gained their theoretical and practical skills at the »School for Handling Radioactive Material« in The Institute Boris Kidrič, Vinča in Belgrade.[1]

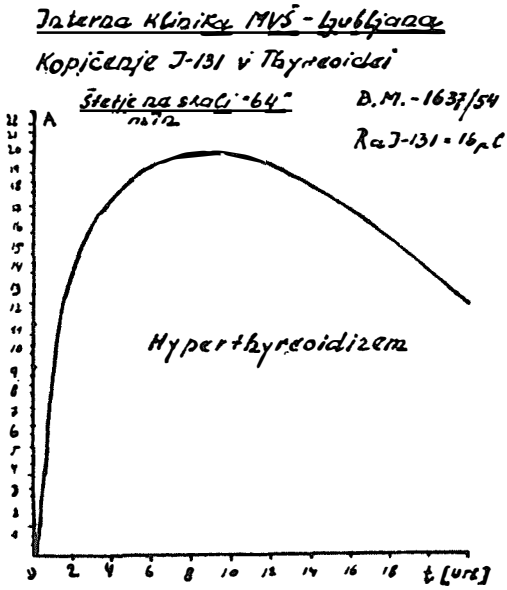

Figure 1. Time-activity curve of 131-I thyroid uptake in a patient with hyperthyrosis treated at Medical Clinic in Ljubljana in 1954 (3).

1954 – The Medical Clinic in Ljubljana

The first diagnostic application of radioiodine in a patient was performed at The Medical Clinic in Ljubljana in the year 1954 by J. Satler. He remembers:[2]

»In the spring 1954 I attended a three-month course on the use of radionuclides in medicine at the Institute Jožef Stefan in Ljubljana, and in the same year the first diagnostic applications of radioiodine (131-J) were performed. I reported about this at The Second Slovene–Chroatian Meeting in Ljubljana and had the article published by Zdravstveni vestnik in 1955. That was probably the first report[3] on the practical use of radioactive isotopes in medicine that appeared in Yugoslav medical press«.

Figure 1 taken from the above mentioned article[3] shows a diagram of 131-J accumulation in the thyroid gland of a patient with hyperthyreosis.

Between the years 1954 and 1960, when the first laboratory for nuclear medicine was opened, the pioneers of nuclear medicine in Slovenia did not have a fixed location of their own. Thus, for example, the Radioisotope Laboratory at the Medical Clinic moved in that period through four different rooms, and accordingly it had to be rearranged, reequipped, reorganized and reopened four times.[1]

J. Satler, who established nuclear medicine practice at the Medical Clinic in Ljubljana, was after some months succeeded by B. Varl while the former moved to Etiopia where he functioned as an expert of World Health Organisation. In that time nuclear medicine staff consisted of only two persons: a doctor (B. Varl) and a technician (B. Rozman). Their measuring equipment was borrowed from the Institute Jožef Stefan: a Geiger–Mueller counter which served for the radioactivity measurements of urine, plasma and erythrocytes, and a scintillation detector with binary and decade counter used for radioiodine thyroid uptake test.[1]

After the introduction of radioiodine thyroid uptake test in 1954 at the Medical Clinic, the frequency of that test had been increasing linearly until the end of 1969, when it reached the

annual number of 2400. By that time radioimmune thyroid tests appeared, and *in vitro* measurement of thyroxine in serum almost completely replaced *in vivo* thyroid radioiodine uptake test.

Besides radioiodine (131-J), the following radiopharmaceuticals were used also: radioactive chromium (51-Cr) served as an erythrocyte marker in the measurements of blood volume, whereas radioactive phosphorus (32-P) was injected for the therapy of polycythemia rubra vera and chronic lymphatic leukemia.[1]

Soon after functional radioiodine diagnostics had been introduced, B. Varl made his first attempts in localisation diagnostics which enabled imaging of radiotracer distribution in the patient's body.[4] As the Geiger–Mueller counter proved insufficient for that purpose, it was gradually replaced by a better detector, i.e. scintillation counter equipped with a specific collimator.

The simplest information on radiotracer distribution in the body was achieved by drawing the radioactivity profile of the body (Figure 2). Better, but much more complicated and time consuming was elaboration of a map of e.g. the neck map with isoactivity lines (Figure 3). The best localisation diagnostics at that time was thyroid scanning with an automatic rectilinear scanner. It was, however, available only after 1962 when the then *Basic laboratory for work with isotopes* was equipped with Nuclear Chicago scintiscanner.

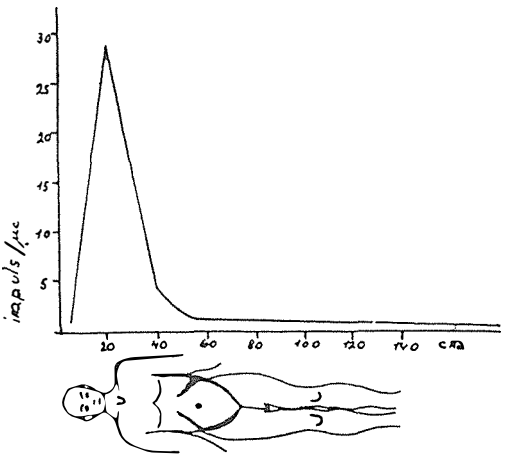

Figure 2. Radioactive prophyle of a patient treated at Medical Clinic in Ljubljana in 1957 with 131-I (4).

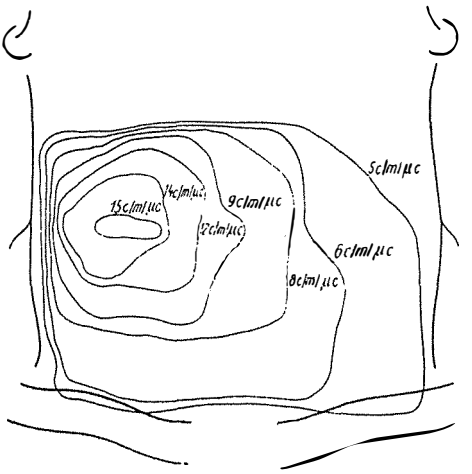

Figure 3. Isoimpulse-drawing of the 131-I uptake in the neck of a patient with anaplastic thyroid cancer – The Institute of Oncology in Ljubljana in 1958 (6).

1955 – The Institute of Oncology in Ljubljana

From its very establishment in 1938, the Institute of Oncology in Ljubljana was dedicated to the comprehensive care of cancer patients in Slovenia. The newest achievements were used in the diagnostics and therapy and therefore it is not surprising, that some of the pioneers of Slovenian nuclear medicine could be found there also.

From the very beginning, therapy with radionuclides was the most intriguing item for oncologists. First they used sealed radioactive sources such as 60-Co-seeds, later they included in their repertoire unsealed radioactive sources such as 198-Au-colloid, which was injected intraperitoneally since 1955 by L. Šavnik to some patients with disseminated ovarian cancer.[5]

Radioiodine-131 was used in patients with thyroid cancer for diagnostic and therapeutic purposes by S. Plesničar since 1957.[5,6]

Among the instruments used in the beginning, Geiger–Mueller counter intended for localization diagnostics played the main role. Initially, they measured the distribution of radiotracers in the patient's body by means of a body mould with openings arranged in rows; a Geiger–Mueller detector was sequentially inserted into the holes and the obtained measurements written on a body map.

Later on, the procedure was greatly improved by the use of scintillation detector purchased for that purpose. Figure 3 shows a drawing of radioiodine distribution in the neck of a patient with anaplastic thyroid cancer. In that time the bio-distribution of radioiodine was studied in excised specimens by means of autoradiography as well.[6]

1957 – Center for The Use of Isotopes in Medicine

This Center was established on the initiative of the Federal Commission for Nuclear Energy, as a cooperative association of institutions in order to unite and rationalize all efforts related to introducing of radioactive isotopes in biomedical research, diagnostics and therapy. The same commission founded similar centers in the capitals of all six Yugoslav republics. The institutions which had been already using or intended to use radioisotopes for biomedical research, diagnostics and therapy were also included. In Ljubljana the members were: Institute of Medical Sciences at the Slovenian Academy of Sciences and Arts, Medical Clinic, Orthopedic Clinic, Institute of Oncology, Institute of Pathophysiology and Institute of Physics at the Medical Faculty.[5]

Later development showed that this cooperation was partly accepted only by Medical Clinic and the Institute of Oncology mainly with reference to prospective room facilities made available by the building of *Basic Laboratory for Work with Isotopes.*

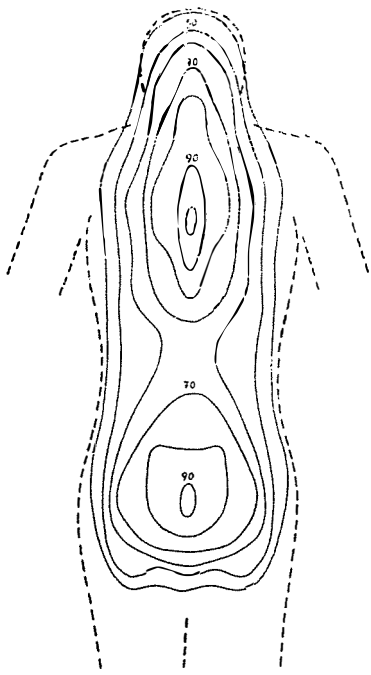

Figure 4. Isoimpulse-drawing of the 85-Sr uptake in the trunk of a patient with bone metastases – The Institute of Oncology in Ljubljana in 1961.

1960 – Basic Laboratory for Work with Isotopes in Ljubljana

In 1960, the Basic Laboratory for Work with Radioisotopes was established in Ljubljana with the aim to provide facilities together and working place as well as coordination for all five institutions of the above mentioned Center, which had begun with the use of radionuclides.

It was located in a brand new extension accomplished during one of the several reconstructions of the buildings where the Institute of Oncology was located in the adapted old Saint Peter's barrack from 1748.

In fact, only the Radium and Isotopic Laboratory of the Institute of Oncology and the Radioisotopic Laboratory of the Medical Clinic had been operating there together until they separated in 1968. The activities of other members of

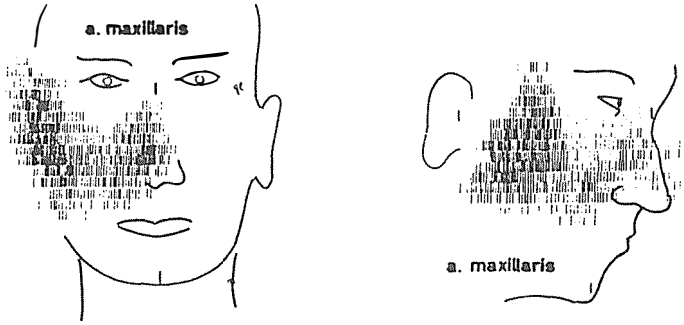

Figure 5. Scan of the area perfused through a catheter inserted into the right maxillary artery, taken after the injection of tracer dosis of macro-aggregates of radioiodinated albumin (131-J-MARA) at the Radium and Isotopic Department of the Institute of Oncology in 1968 (10).

the Center, who did not express any interest in sharing the available facilities, were as follows: in the '50s there were only a few attempts at Orthopaedic Clinic to use Thorium-X therapeutically. Later, however, this sort of therapy was completely abandoned. At the Institute of Physics of the Medical Faculty the study of dosimetry remained at academic level, and so did also the research carried out at the Academy of Science and Arts. At the Institute for Pathophysiology the transport of sodium and potassium ions through cellular membranes was studied by means of radioactive tracers (22-Na and 42-K). This studies continued and in 1962, this institute built its own laboratory.[7]

Even though medical and oncological nuclear medicine were performed in the same place using the same facilities and instruments, the collaborators from that time claim that their work was strictly separated.

Chief of medical nuclear medicine **B. Varl** described their work as follows:[1] »The staff of **Radioisotopic Laboratory of the Medical Clinic** comprised two residents in internal medicine, three technicians, a senior medical nurse, a secretary and an orderly – all of them employed full-time. For me, as chief of the radioisotopic laboratory, nuclear medicine was still a part time job.

In nuclear medicine *equipment* has always been playing a major role in comparison with other factors (e.g. available pharmaceuticals, personnel and other capacities) in determining the type, quality and quantity of operations.

The laboratory equipment was obtained gradually. First instruments were donated by the Federal Commission for Nuclear Energy and by Slovene enterprises; part of the equipment was purchased by Medical Clinic also. We had scintillation detectors with electronic scalers and printers which were used for kinetic in vivo studies. Further, we had a well-type scintillation detector, a Geiger–Mueller counter (for radioactivity measurements in feces and urine), a scanner for electrophoretic and chromatographic tapes as well as an automatic system for scintigraphy and radioactivity measurements of liquids«.

An enormous qualitative step forward in clinical nuclear medicine was made possible by the purchase of scintiscanner Nuclear Chicago; the unit was bought by the Institute of Oncology in 1961 with a loan from Boris Kidrič Foundation.[5] The device enabled automatic morphological nuclear medicine investigations that had been extremely time consuming before as they had been based on manual scanning, i.e. measurements of radioactivity in discrete points and presented as the body map of isoactive lines (Figures 3 and 4).

So, since 1961 static automatic scanning of the thyroid, liver, kidneys, spleen, and after 1967 also pancreas scanning was performed.[1]

Accordingly, a step forward in the annual num-

ber of renal examinations was noted after the purchase of renaltron in 1967.[1]

All this pioneering period was characterized by a steep increase in the annual number of diagnostic and therapeutic procedures. The total figure of annual diagnostic and therapeutic applications of radionuclides to patients in Slovenia was in 1958 between 140 and 150.[5]

In 1964, the Radioisotopic Laboratory of Medical Clinic, performed alone 1750 investigations and by 1970, the annual number at the Institute of Nuclear Medicine, which developed from the previous Radioisotopic Laboratory, increased to 7500.[1]

The time after the year 1960 was the period of first research projects in nuclear medicine based on the contracts with Federal Commission for Nuclear Energy and with the Research Council of Slovenia, the Boris Kidrič Foundation.

On the other hand, a major part of our work was dedicated to clinical and outpatient thyrology including two phase radioiodine test, first manual and afterwards automatic thyroid scanning, thyroid TSH test, thyroid suppression test, and therapy of hyperthyroidism with radioiodine«.

Investigations of other organic systems included testing of the absorption of fats, vitamin B_{12} and iron. Among the investigations performed were also other hematologic tests with radioactive chromium (51-Cr) and iron (59-Fe) as well as radionephrography with 131-I-hippurate, functional liver investigations with colloidal radioactive gold (198-Au) and 131-I-Rose Bengal.[1]

Between 1960 and 1968, the **Radium and Isotopic Department of the Institute of Oncology** shared the same rooms and facilities with the Radioisotopic Laboratory of Medical Clinic, was headed by **M. Erjavec.** He has described that period as follows:

«Regular work probably started by 1960. In that pioneering period it developed in the following six major directions:

1. *Therapy with sealed radioactive sources:* First attempts were made in 50's with 60-Co-seeds. After 1960 we have introduced artificial radionuclides in brachyradiotherapy in form of »after-load« technique which was revolutionary for that time. First we used gold seeds. Later on we developed a genuine modification of French therapy with iridium wires and original graphical dosimetry. Even later we developed our own pencil-sized apparatus for implantation of iridium seeds, which replaced Italian »wardrobe«. That pencil-sized apparatus was copied and commercially produced by the international radiopharmaceutic company Sorin.

2. *Therapy with open radioactive sources:* Treatment with 198-Au-colloid, which was injected intraperitoneally since 1955 by L. Šavnik to some patients with disseminated ovarian cancer,[5] was followed by 131-J-iodine[6] in patients with thyroid carcinoma though first in a rather simple form and not at a high professional level. The technique was upgraded only 15 years later.

Though the use of radioactive phosphorus (32-P) for the treatment of bone metastases from different tumors was introduced relatively early, this therapeutic method was soon abandoned owing to its severe toxicity. Later on it was replaced by radioactive strontium (89-Sr) in the treatment of non-curable osteoblastic metastases.

3. *Radiopharmaceutical labelling,* first with radioactive iodine (131-I) and later on with indium (113m-In) was a must if we wanted to keep abreast of the work performed elsewhere in the world.

In the beginning, radiolymphography by means of radioiodinated oils appeared very promising and therefore in 1967 we even developed our own method of production of this radiopharmaceutical. Clinical application of the method, however, was not successful, so that it was abandoned after a few years.

Actually, most of the efforts were directed into the development of labelling of radioiodinated microparticles which were initially used for lung scanning and finally for lymphography and scintigraphic monitoring of the position of intraarterially inserted catheters for later intraarterial chemotherapy application. Figure 5 shows perfusion through catheter inserted into the right maxillary artery.

4. *Skeletal scintiscanning* has always been a model achievement of our laboratory. Our first, pioneering attempts in this respect, by means of strontium (85-Sr) date back to the year 1961; not aware of the fact that two other groups from America were developing the same method, at that time we were among the beginners of those investigations. Figure 4 shows a body map of radiostrontium (85-Sr) distribution in a patient with bone metastases. Had it not been just a day to late, our report submitted for presentation at the IAEA Congress (Athens, 1964) would have been the first of the kind in the world.

5. Measuring devices have been technically upgraded and modified along with the development of skeletal scintiscanning. The first commercially available scintiscanner Nuc-Chicago was modified to such extent that even the producer could not recognize it any longer. A special collimated detector enabled imaging by means of high-energy gamma rays of 510 KeV energies emitted by radioactive strontium (85-Sr) and fluorine (18-F).

6. *Renography,* i.e. measuring of kidney clearance has always been in the first plane of our laboratory work, first as a «hobby» activity and later on because of the increased demand related to the expanding use of chemotherapy at the Institute of Oncology.

The method has been frequently changed and upgraded until it reached its ideal form in the recent years. Presently, the investigation is completely automated, blood-sample taking is unnecessary, and kidney clearance of 131-I hippurate is obtained simultaneously with standard renography«.[8]

Due to the growing scope of work, the capacities of the Basic Laboratory in Ljubljana became too small to house medical nuclear medicine and oncological nuclear medicine under the same roof.

As a result, the former activity was moved from the mutual premises back to the west wing of the old Clinic of Internal Medicine.[1] After that time The Basic Laboratory served for the needs of Radium and Nuclear Medicine Department of the Institute of Oncology only.

By that time the first nuclear medicine laboratory in a regional hospital, i.e. in the Health Center in Celje, was established.[9]

The year 1968 marked the end of the pioneering period and the beginning of a rapid development of nuclear medicine departments in regional hospitals out of Ljubljana.

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