Saskatchewan's role in radiotherapy research

C. Stuart Houston, MD and Sylvia O. Fedoruk, MA

ew Canadians, much less the rest of the world, realize that Saskatchewan has led other jurisdictions in North America in several aspects of health care.

Saskatchewan's list of firsts include

- the first municipal doctor in the rural municipality of Sarnia (1914)
- the first union hospital district legislation (1916)
- the first municipal doctor legislation (1919)
- the first free tuberculosis treatment (1929)
- the first bacille Calmette Guerin (BCG) protection of student nurses (1938)
- the first province-wide radiographic survey for tuberculosis (1941)
- the first province-wide medical care plan for indigents, old age pensioners and mother's allowance recipients (1945)
- the first province-wide Medicare medical plan in the Swift Current region (1946)
- the first province-wide hospital plan (1947)
- the first province-wide medicare plan (1962).

Such developments arose from the cooperation and mutual help necessary among pioneer settlers, sparsely distributed in a relatively hostile environment. House-raising, barnraising and the building of community amenities, such as schools and rinks, made it logical for other cooperative developments to occur.

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However, what is not well known is that Saskatchewan led the world in the development of high technology cancer treatment. This was due to the foresight of Dr. Allan Blair, director of cancer services for Saskatchewan and Dr. E.L. Harrington, professor of physics at the University of Saskatchewan.

The first correspondence, from Blair to Harrington on Dec. 12, 1944, suggested that a full-time physicist should be hired jointly by the Saskatchewan Cancer Commission and the university. Harrington replied 6 days later, offering his full cooperation.

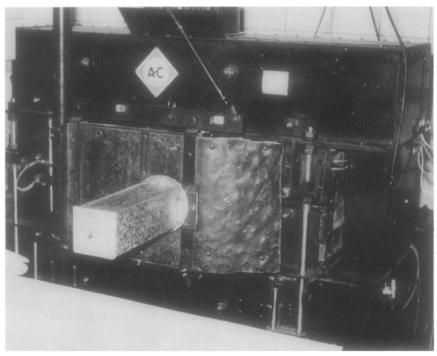
Harrington displayed great wisdom in his choice of a suitable physicist Dr. Harold E. Johns, then at the University of Alberta, was offered the joint position. Johns was offered \$1800 per annum as half salary by Blair on Mar. 26, 1945 and was "to give half-time to supervision of the radium and x-ray therapy equipment of the two cancer clinics". In May 1946, Johns was awarded a travelling scholarship of

\$800, allowing him to visit the leading centres of radiation physics in the United States and Canada. Shortly thereafter, Johns gained permission from the university and Saskatchewan Premier T.C. (Tommy) Douglas to purchase a betatron.

However, the project required further support from higher levels. University of Saskatchewan President James S. Thomson wrote to Blair on Nov. 18, 1946: "I called last week upon Dr. C.J. Mackenzie, National Research Council president, to discuss the use of a betatron in connection with the cancer treatment in this province. Dr. Mackenzie expressed some doubts as to whether research was fully advanced to make such a project practicable

Matters affecting the use of atomic energy are really under the control of the Atomic Energy Commission of which General A.G.L. McNaughton is the chairman."

Blair then wrote to Mackenzie on Dec. 11, 1946 concerning the possible betatron installation: "It is not



The Allis-Chalmers 24 million volt betatron, University of Saskatchewan

planned to use it for any actual treatment until the physical measurements have been completed to everyone's satisfaction". (This principle of exact calibration before patient treatment became the cornerstone of all future development of radiation treatment facilities in Saskatchewan. Depth-dose data produced in Saskatoon were used around the world for many years.)

Meanwhile, other centres viewed this development in Saskatchewan with suspicion, as shown by a letter from Harrington to Thomson on Feb. 10, 1947: "In the earlier part of the discussion regarding the betatron, it appeared that a certain member of the Atomic Energy Commission, to which this matter must be referred for decision, had expressed the belief that if the reason for the betatron was mainly medical it would be in the interest of the country as a whole to locate it in a large medical centre, say in Toronto. In the mind of Dean Mackenzie, the chance of obtaining a favourable action on our request for this equipment would be better if any possible uses in medicine of the betatron were given but little emphasis".

At the end of April 1948, Johns, accompanied by Drs. R.N.H. Haslam and L. Katz of the physics department, left Saskatoon to visit the Allis-Chalmers Plant in Milwaukee where they examined their betatron. Johns wrote back to Blair on



Dr. Harold E. Johns

'Apresoline' tablets

(hydralazine hydrochloride) Antihypertensive Agent

Hydralazine hydrochloride exerts its hypotensive action by reducing vascular resistance through direct relaxation of vascular smooth muscle.

APRESOLINE Oral: Essential hypertension.
APRESOLINE is used in conjunction with a diuretic and/or other antihypertensive drugs but may be used as the initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a vasodilator.

APRESOLINE Parenteral: Severe hypertension when

the drug cannot be given orally or when there is an urgent need to lower blood pressure (e.g. toxemia of pregnancy or acute glomerulonephritis). It should be used with caution in patients with cerebral vascular accidents.

Contraindications

Hypersensitivity to hydralazine, coronary artery disease, mitral valvular rheumatic heart disease, and acute dissecting aneurysm of the aorta.

Warnings

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus in such cases treatment should be discontinued immediately. Long-term treatment with adrenocorticosteroids may be necessary. Complete blood counts, LE. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine and if patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. If the results of these tests are abnormal, treatment should be discontinued. Usage in Pregnancy

Animal studies indicate that high doses of hydralazine are teratogenic. Although there is no positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the benefit clearly justifies the potential risk to the

Caution is advised in patients with suspected coronary-artery disease, as it may precipitate angina pectoris or congestive heart failure, and it has been implicated in the production of myocardial infarction. The "hyperdynamic" circulation caused by APRESO-LINE may accentuate specific cardiovascular inadequacies, e.g. may increase pulmonary artery pressure in patients with mitral valvular disease. May reduce the pressor resonness to exicate the control of the control May reduce the pressor responses to epinephrine. Postural hypotension may result.
Use with caution in patients with cerebral vascular

accidents and in patients with advanced renal damage. Peripheral neuritis has been observed and published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias consisting of reduction in hemo-globin and red cell count, leukopenia, agranulocytosis and purpura have been reported. In such cases the drug should be withdrawn. Periodic blood counts are advised during therapy. MAO inhibitors should be used with caution in patients receiving hydralazine. Slow acetylators should probably receive no more than 200 mg of APRESOLINE per day. When a higher dose is contemplated, and, whenever possible, it may be advisable to determine the patient's acetylation phenotype.

Adverse Reactions

Within the first day or two: headache, palpitations, tachycardia, anorexia, nausea, vomiting, diarrhea, and angina pectoris. They are usually reversible when dosage is reduced or can be prevented or minimized by administering reserpine or a beta-blocker together with hydralazine.

Less Frequent: nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranu-locytosis, thrombocytopenia with or without purpura; hypotension; paradoxical pressor response

Late Adverse Reactions: Long-term administration at relatively high doses may produce an acute rheumatoid state. When fully developed a syndrome resembling disseminated lupus erythematosus occurs. The frequency of these untoward effects increases with dosage and duration of exposure to the drug and is higher in slow than in fast acetylators. Antinuclear antibody and positive L.E.-cell tests occur.

Symptoms and Treatment of Overdosage Symptoms: hypotension, tachycardia, headache, generalized skin flushing, myocardial ischemia and cardiac arrhythmia can develop. Profound shock can occur in severe overdosage.

Treatment: No known specific antidote. Evacuate gastric content, taking adequate precautions against aspiration and for protection of the airway; if general conditions permit, activated charcoal slurry is instilled. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized. since they might precipitate cardiac arrhythmias or increase the depth of shock.

Support of the cardiovascular system is of primary importance. Shock should be treated with volume expanders without resorting to use of vasopressors, if possible.

If a vasopressor is required, a type that is least likely to precipitate or aggravate cardiac arrhythmia should be used, and the E.C.G. should be monitored while they are being administered.

Digitalization may be necessary. Renal function must be monitored and supported as required. No experience has been reported with extracorporeal or peritoneal dialysis.

Dosage and Administration

Adjust dosage according to individual blood pressure

Orally: Initial: 10 mg 4 times daily for the first 2 to 4 days, 25 mg 4 times daily for the remainder of the first week, 50 mg 4 times daily for the second and subsequent weeks of treatment.

Maintenance: adjust dosage to lowest effective levels. Following titration, some patients may be maintained

on a twice daily schedule. Usual maximum daily dose is 200 mg, up to 300 mg daily may be required in some patients. In such cases a lower dosage of APRESOLINE combined with a thia-zide, reserpine or both, or with a beta-adrenergicblocking agent may be considered. When combining therapy, individual titration is essential to ensure that the lowest possible therapeutic dose of each drug is administered.

Parenterally: patients should be hospitalized. Usual dose is 20-40 mg I.M. or by slow I.V. injection or I.V. drip, repeated as necessary. Patients with marked renal damage may require a lower dosage.
For I.V. drip, the ampoule(s) should be added to 5%

sorbitol solution, physiological saline or Ringer solution; glucose solution is not suitable for this purpose. Blood pressure levels should be monitored. It may begin to fall within a few minutes after injection, with an aver age maximal decrease occurring in 10 to 80 minutes. In cases with a previously existing increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia

Most patients can be transferred to oral APRESOLINE within 24 to 48 hours.

AvailabilityTablets of 10 mg: yellow, uncoated, biconvex, scored, and imprinted "FA" on one side and "CIBA" on the

Bottles of 100 and 500.

Tablets of 25 mg: blue, coated, printed "GF" on one side and "CIBA" on the other. Bottles of 100 and 500.

Tablets of 50 mg: pink, coated, printed "HG" on one side and "CIBA" on the other. Bottles of 100 and 500.

Ampoules: 1 ml, each containing 20 mg hydralazine hydrochloride, 103.6 mg propylene glycol, 0.65 mg of methyl-p-hydroxybenzoate and 0.35 mg of propyl-p-hydroxybenzoate in water for injection.

Boxes of 10. Complete Prescribing Information available on request.

1. The Pharmacological Basis of Therapeutics, Sixth Edition, Pages 799-801 – Goodman and Gilman 1980. 2. Gifford, R.W., Isolated systolic hypertension in the elderly. Postgraduate Medicine, Vol. 71, No. 3, March 1982. 3. Finnerty, F.A., M.D., Hypertension in the elderly: Special considerations in treatment. Postgraduate Medicine, Vol. 65, No. 5, May 1979. 4. Scriabine, A. Pharmacology of Antihypertensive Drugs, Methyldopa, page 48, 1980.





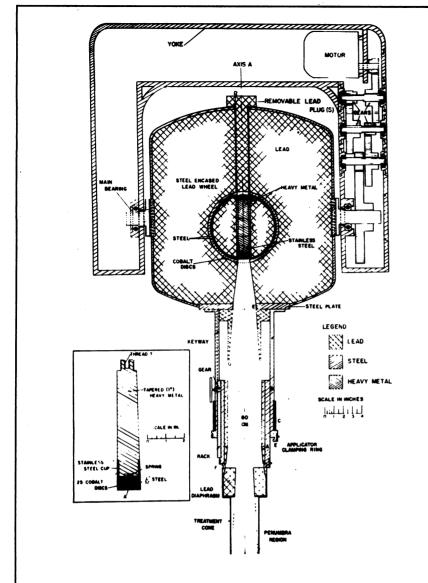


Diagram of a cobalt unit, University of Saskatchewan. The central wheel was rotated to bring radioactive cobalt opposite the open port.

May 12, 1948: "The betatron is finished but has not been tested . . . the machine which we are getting is the one ordered by the University of Pennsylvania but they have no building finished to house it and have allowed us to have it . . . We reached the University of Illinois on Monday, May 3 (1948) where we have been since Professor Kerst has been more than cooperative. First he introduced us to all his men and gave us full access to all blueprints, all reprints, keys to the building, . . . Kerst then presented us with two doughnuts for nothing and one electron doughnut

for a nominal sum . . .

"Dr. Kerst is amazed at the rapidity with which we have pursued our program and in the fact we are getting the first betatron to be installed in any university or hospital.... The University of Illinois medical school gets the third betatron (second to the University of Pennsylvania) and I heard yesterday that the University of California medical school is getting one, at Berkeley."

Dr. D.W. Kerst, of the physics department of the University of Illinois at Urbana, had developed a small 2.3 million volt betatron by

1940 and 2 years later had developed a device which accelerated electrons to 20 million volts, the prototype of the Allis-Chalmers machine. Kerst had, with Dr. Henry Quastler, treated his first patient just 4 days before the Saskatchewan physicists arrived.

An addition to the University of Saskatchewan physics building was built quickly. The 24 million volt betatron was installed in the summer of 1948 and the first Saskatchewan patient was treated on Mar. 29, 1949. As M.D. Schultz said in a historical review in the American Journal of Roentgenology in 1975, "... thus started the really first concerted clinical investigation of the usefulness of the multimegavoltage as a radiotherapeutic tool".

The Saskatchewan betatron installation was used as much for physics research as for patient treatment. Until the new university hospital was completed in 1955, patients were brought across the South Saskatchewan River from Saskatoon City Hospital. Thereafter, it remained difficult to move patients several hundred metres across the campus from the hospital to the betatron in the physics building. In 17 years, only 301 patients were treated.

The operating costs of the betatron were considered exorbitant in the 1940s. Dr. T.A. Watson, now director of cancer services at Saskatoon, reported on Nov. 10, 1949 that each doughnut cost \$3800 and, although guaranteed to last for 150 hours, "No doughnut which has so far been used has lasted nearly as long as this . . . the cost of the doughnut alone is \$25.70 an hour . . . Eleven patients were treated at an average cost of \$224 per patient."

Nevertheless, Johns reported to the president of the Saskatchewan division of the Canadian Cancer Society that the betatron offered "a method of delivering easily a high dose to tumours at a depth, without appreciably affecting the overlying skin Radiation sickness and blood changes are much less likely".

Johns and his coworkers were not content with development of the betatron for clinical use. In June 1949, Johns visited the Chalk River reactor and had discussions with Drs. Cipriani and Lewis of the Atomic Energy Project. The Chalk River reactor was the only installation in the world capable of producing large quantities of radioactive cobalt. Johns felt cobalt would offer even better and more economical opportunities for cancer therapy.

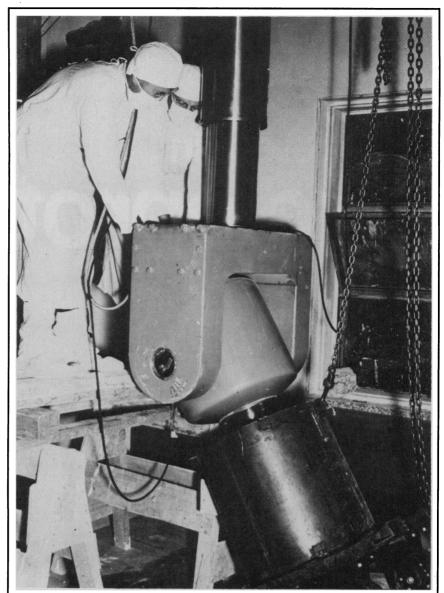
Johns wrote to University of Saskatchewan President Walter P. Thompson on July 15, 1949, presenting his proposal. He wanted an effective source of 1000 curies of cobalt 60, about 100 times the activity of any previously designed radium unit, which would allow treatment of a patient at a large focalskin distance. Johns estimated the total cost of construction to be about \$3000 and asked for "between \$2500 and \$7000 to cover this expense". Johns, Cipriani and Lewis agreed that this project would receive greater priority if it were considered as a research project.

A quick visit to Premier Douglas in Regina obtained assent for this expenditure. The cabinet, the treasury and the university board of governors were bypassed; there were no visits from outside accreditors. Saskatchewan's simple two-page, three-copy application for the isotope was sent to the National Research Council at Chalk River on Aug. 13, 1949.

Lewis, the father of the Canadian nuclear energy program, praised the strong case made in the application but mentioned skepticism: "Doubts have been expressed in some quarters about the wisdom of applying cobalt in this way for therapeutic work".

Three radioactive cobalt sources had been put in the Chalk River pile to "cook" in the fall of 1949. The first of these sources was delivered to the University of Saskatchewan on July 30, 1951 and the second to the University of Western Ontario (UWO) on Oct. 16, 1951. The third source, destined for the United States, was not released until 1952.

Each cobalt source was 2.5 cm in diameter and 1.25 cm thick and, as Johns had forecast, had an approximate strength of 1000 curies. The Saskatoon unit was designed by Johns and Lloyd Bates, a graduate student; it was built by Johnny MacKay, the proprietor of Acme Machine and Electric in Saskatoon;



The installation of radioactive cobalt on Aug. 18, 1952. "Wearing specially treated smocks and masks as protection against deadly gamma rays..."

and was installed in Room 167 in the newly constructed cancer wing, adjacent to the medical college, on Aug. 17, 1951. The room was hardly ready for use; the walls were still being plastered, the concrete floor yet to be poured.

The unit, weighing approximately 0.9 tonnes, consisted of a steel-encased cylinder suspended from an overhead carriage; a rotating circular platform, flush with the floor, permitted rotation therapy. A variety of treatment fields could be obtained by using interchangeable lead plugs which were manufactured by MacKay.

How to turn the machine on and off caused problems, but Johns rediscovered the wheel with his solution. The radioactive cobalt source was mounted on the circumference of a wheel near the centre of the head. By rotating the wheel, the source could be moved 180° from its shielded resting position until it was opposite an opening through which the radiation emerged.

The Saskatoon Star Phoenix, on Aug. 18, 1951, printed a photograph of the installation with the caption: "[W]earing specially treated smocks and masks as protection against deadly gamma rays, Dr. H.E. Johns

use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which has been reported to be useful.

Hypotension

Use sympathomimetic pressor drug therapy, such as levarterenol or epinephrine. In refractory cases the use of glucagon hydrochloride has been reported to be useful. Bronchospasm

Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

Hypoglycemia

Intravenous glucose and/or intramuscular glucagon.

An in vitro hemodialysis study, using C¹⁴ timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids.

It should be remembered that BLOCADREN* is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of BLOCADREN*. However, the complications of excess isoproterenol, such as tachycardia, headache, flushing of the skin, arrhythmias, nausea, weakness, tremor and sweating, should not be overlooked.

DOSAGE AND ADMINISTRATION

HYPERTENSION

BLOCADREN* is usually used in conjunction with other anti-hypertensive agents, particularly a thiazide diuretic, but may be used alone (see INDICATIONS).

The dose must always be adjusted to the individual requirements of the patients, in accordance with the following guidelines.

When BLOCADREN* is given to patients already receiving other antihypertensive agents, the initial dose should be 5 to 10 mg twice a day. If after one to two weeks an adequate response is not observed, dosage may be increased by increments of 5 mg twice daily, at intervals of two weeks. A 60 mg daily dose should not be exceeded.

When BLOCADREN* is used alone the initial dose should be 10 mg twice a day and dosage increased if required, following the regimen described above.

In those patients who are found to be adequately controlled on daily doses of 20 mg or less, the administration of the total dose in the morning should be tried as studies show adequate response to this dose regimen.

ANGINA

The recommended dosage range of BLOCADREN* is 15 mg to 45 mg per day. The majority of patients respond to a daily dosage of 35 mg to 45 mg. Therapy should be initiated with 5 mg two or three times a day. Depending on response, increases in dosage may be necessary. The first increase should not exceed 10 mg per day in divided doses. Subsequent increases should not exceed 15 mg per day in divided doses. A total daily dose of 45 mg should not be exceeded. There should be an interval of at lease three days between increases in dosage.

After the titration period, some patients may be maintained on a b.i.d. schedule.

PREVENTIVE USE IN ISCHEMIC HEART DISEASE

For long-term preventive use in patients who have survived the acute phase of myocardial infarction, the maintenance dose is 10 mg twice daily. Therapy should be initiated with 5 mg twice daily and the patient observed carefully. In no adverse reaction occurs, the dosage should then be increased after 2 days to 10 mg twice daily. In the studies evaluating BLOCADREN* following myocardial infarction, treatment was begun 7 to 28 days after the acute phase.

AVAILABILITY

8911 — Each white, flat, bevelled-edge tablet, scored one side, marked Frosst on other, contains 5 mg of timolol maleate. Available in bottles of 100.

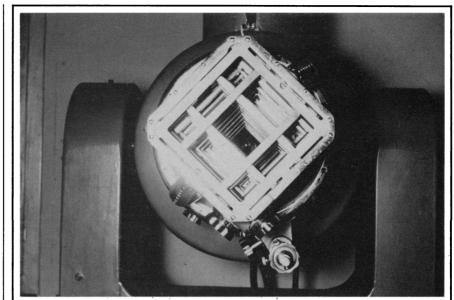
8866—Each light-blue, flat, bevelled-edge tablet, scored one side, marked Frosst on other, contains 10 mg of timolol maleate. Available in bottles of 100 and 500.

8945 — Each light-blue capsule shaped tablet, scored one side, marked Frosst on other, contains 20 mg of timolol maleate. Available in bottles of 100.

FULL PRODUCT MONOGRAPH AVAILABLE ON REQUEST







The final version of the MacKay-Johns collimator was a system of fixed and moving steel-encased lead bars that provided rectangular and square fields by simply twisting two dials.

and Mr. J.A. MacKay are shown here carefully transferring a small piece of radioactive cobalt from a lead container to a treatment head..."

The Saskatoon unit was officially commissioned on Oct. 23. Rigorous measurements continued until Nov. 8 when the first patient was treated by Watson. Watson played down attempts to publicize the importance of Saskatoon's achievement, saying this was but a device that might prove more efficient and economical to operate.

Meanwhile, Canada's second cobalt source had been installed at UWO on Oct. 23. Dr. Ivan H. Smith quickly treated the first patient in London, Ont., on Oct. 27.

This first cobalt treatment at UWO was widely publicized in the Canadian press. The Saskatoon Star Phoenix commented on the "cobalt race" in an editorial on Nov. 7, 1951: "We hope Messrs. Truman, Stalin, Peron et al won't think someone is trying to steal their thunder, but we think they ought to know theirs is not the only atomic race going on in the world. Another has been declared by the London Free Press which claims editorially 'the world's first cobalt bomb' for . . . the Ontario city. With all due respect to the preservation of national peace and goodwill, that is a boast which this newspaper cannot allow to go unchallenged — especially since the *Free Press* is brazen enough to remark that a cobalt bomb 'is also being installed at Saskatoon, Sask.' One is indeed. Or, to be more accurate, one has been installed."

Eldorado Mining and Smelting had built the second unit for installation at Victoria Hospital in London, but they used a somewhat different design. Their unit consisted of a head pivoted between the arms of a horizontal "Y" which could be raised and lowered. The beam was turned on and off by an air compressor that forced mercury in and out of the reservoir. The radiation beam was turned off when a pool of mercury was introduced between the source and a conical opening in the head. The field size was varied by means of four lead blocks at right angles to each other. This was the prototype of the Atomic Energy of Canada Limited (AECL) cobalt

The first formal publication giving details of cobalt therapy appeared in the Dec. 15, 1951 issue of *Nature*. The authors were H.E. Johns, L.M. Bates, E.R. Epp, D.V. Cormack and S.O. Fedoruk, all from Saskatchewan, and three Uni-



Saskatchewan cobalt unit with initial lead plug collimator system. From left to right: Johns, John MacKay and Dr. T.A. Watson admiring their handiwork.

versity of Saskatchewan graduates (A. Morrison, W.R. Dixon and C Garrett) from the radiology laboratory in the physics division of the National Research Council in Ottawa. This paper described both Canadian cobalt units. More detailed papers on the calibration and use of the two units and the Saskatchewan betatron filled an entire issue of the Journal of the Canadian Association of Radiologists in March 1952. Isodose curves were made available and the Saskatchewan cobalt 60 depth-dose data were included in a special supplement to the British Journal of Radiology in June 1952.

It was obvious to the Saskatoon group that the collimation system had to be redesigned, as therapists wanted a smaller penumbra. The technicians did not like the interchangeable lead plugs that were 5 cm to 8 cm thick and very heavy MacKay turned his attention to designing a new collimator system.

using a large number of interleaved diaphragms rather than a single diaphragm in one plane. The final version of the MacKay-Johns collimator was a system of fixed and moving steel-encased lead bars that provided rectangular and square fields from 4 cm × 4 cm to 20 cm × 20 cm by simply twisting two dials. MacKay's small engineering firm in Saskatchewan single-handedly produced these collimators for over 100 Picker Cobalt units that were distributed world-wide.

The Journal of the Canadian Association of Radiologists presented the medical world with the first 5-year report on the clinical application of cobalt 60 therapy units in a special issue in June 1957. The original Saskatoon cobalt unit was in service until 1972, treating 6728 patients over 21 years. Finally, it was replaced by a commercial AECL machine.

The first Saskatoon patient who

completed her full course of treatments for carcinoma of the cervix on Nov. 29, 1951 is still alive and well. The first UWO patient's disease was far advanced and she died within a few months of treatment. No doubt she was chosen for this reason since the London cobalt machine had not yet been fully calibrated.

Saskatchewan physicists were in the forefront of development of the cobalt 60 teletherapy units Although one highly respected commercial consultant predicted in 1952 that in 10 years there would only be 30 cobalt machines in use worldwide, these machines proved to be not only compact but economical to purchase and maintain. There are about 2500 units in routine use in the free world, 1500 of which have been built in Canada by AECL.

Though born of war-time nuclear research, the cobalt bomb was in practice a ploughshare rather than a sword.