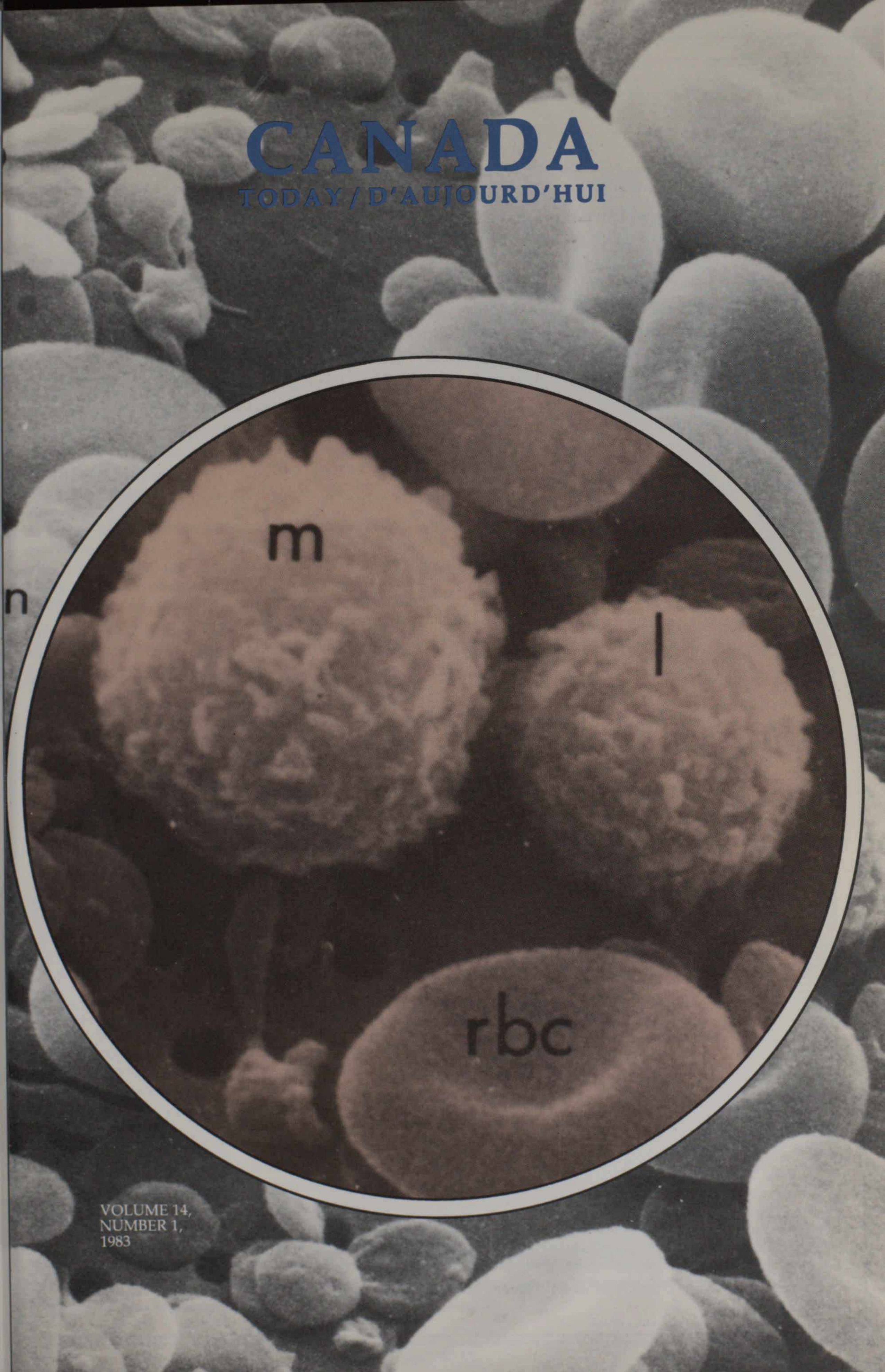
CANADA
TODAY / D'AUJOURD'HUI



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PHOTOS: COVER, BRUCE WETZEL AND HARRY SCHAEFER, NATIONAL INSTITUTES OF HEALTH;
PAGE TWO, LOU SCAGLIONE, THE HOSPITAL FOR SICK CHILDREN

Medical Research

Researchers have been working on the causes and cures of disease and painful death since Hippocrates took his oath.

This century there have been dramatic discoveries that have had swift and broad applications.

The insulin isolated in Canada in 1921 has saved millions around the world, and the vaccine developed by Dr. Salk in 1952 has saved children everywhere.

Since the early 1970s the advances in medical knowledge and technique have been coming rapidly, and scientists in Canada and the United States are in the vanguard. They have also developed a striking level of intra-continental cooperation. The breakthrough in one country is complemented in the other, the surgical technique developed in one hospital is refined someplace else.

In this issue of CANADA TODAY/D'AUJOURD'HUI we focus on the achievements of a few of the Canadians who are productively involved.

Diabetes

Dr. Michael Albisser and his insulin pouch.

Front Cover:
Normal circulating human blood, seen under a scanning electron microscope. Blood is made up of red blood cells (rbc); white blood cells including lymphocytes (l), monocytes (m) and neutrophils (n); and platelet cells (p) suspended in plasma, a straw coloured fluid composed of proteins, water and salts.

In the summer of 1921 Dr. Frederick Banting and Charles Best extracted insulin from the pancreas of a healthy dog, and the following winter they and two associates used insulin extracted from a beef pancreas to save the life of a young diabetic. (See box on page five.)

Insulin controls the level of blood sugar in the body and its use has saved tens of thousands of lives, but many diabetic patients have found daily single injections difficult and some have found them dangerous. The dose must be adjusted constantly since the blood sugar level can change from hour to hour. Each time the patient eats, for example, it goes up.

The problem of matching insulin dose to blood sugar level more easily and accurately is now being tackled with energy, ingenuity and some success by Dr. Michael Albisser and his colleagues at the Hospital for Sick Children in Toronto. Under a contract with the National Institutes of Health in Bethesda, Maryland, they have developed a computer-controlled pump which sends insulin into the bloodstream at measured intervals. The patient adjusts the dosage by pressing an appropriate button. As he sits down to a full meal he pushes one button; if he is about to eat a light snack he pushes another. There are twelve buttons in all.

Each pump has a dosage ceiling appropriate to the particular patient, and, in Dr. Albisser's

The 9:82 issue contained an error on page seven, under the heading "Burn Your Own Smoke." The first sentence of the third paragraph should read: "It sits on a chamber on top of the stove and reduces the ignition point of smoke from 1200° F to about 450° F."

phrase, it is "rather safe," even for children.

It weighs a pound, is twice the size of a Walkman radio and can be carried on the belt. It works well for most but not all—patients with kidney failure, for example, do not respond well.

Dr. Albisser says his model could be reduced to the size of a hockey puck and implanted in the patient's body. Experimenters at Yale and the University of New Mexico have developed one the size of a deck of cards, which holds a week's supply of insulin. They are also working on an implanted system of sensors which would monitor blood sugar levels and activate the pump to produce perfect levels at all times.

There are some technical problems in implanting—for example, the reservoir must be absolutely leak-proof—but the main one is the lack of a pure and flexible form of insulin. The type now generally available is taken from the pancreases of animals, and it has a number of shortcomings. For example, it does not adapt to the body temperature and "yolks up," or thickens so it cannot flow easily.

Dr. Albisser is pressing the commercial laboratories to develop an insulin that would work effectively under all circumstances, and there have been significant advances. Eli Lilly International Corporation recently began marketing an insulin produced by inserting human DNA blueprints of insulin into bacteria and reprogramming them.

Charles Best and Frederick Banting.

Dr. Anthony Sun of the Connaught Research Institute, seen here with technician Helen Van Rooy, is a leading researcher in the development of an artificial pancreas.

Canada's National Research Council has funded a sixteen-member team at Connaught Laboratories which is working to do likewise. Novo Industry, which dominates the market in Europe, introduced "humanized" insulin last June. It is pig insulin converted chemically to match the human variety.

Diabetics who depend on injections may have a number of serious secondary problems—they are twenty-five times more likely to go blind than other people, seventeen times more likely to develop gangrene and twice as vulnerable to heart disease.

Some of these difficulties probably develop when the insulin supplied does not match the amount needed, resulting in alternating high and low blood sugar levels. The use of animal insulin instead of human insulin may also contribute.

Researchers at Connaught Laboratories (where Banting and Best were working in 1921) are trying to develop a more ambitious implant that would eliminate these difficulties as well as those that hamper the pump makers.

Their implant is, in effect, an artificial pancreas. Living animal pancreas cells, suspended in a liquid in a small cylinder behind a plastic membrane, produce the hormones glucagon and somatostatin as well as insulin. The first raises blood sugar levels when needed, the second inhibits the release of either glucagon or insulin when necessary.

The cylinder—in one version it is the size and shape of a spool of thread—is connected to a vein or artery. The cells pass insulin and the other hormones through the membrane into the blood, providing exactly the amount required to metabolize the blood sugar present at the time. New cells can be injected into the cylinders as the old ones die. This device could be reduced in size, researchers believe, and implanted in a vein or artery and reseeded without being removed. It has been tested on monkeys and some problems have been identified. The plastic tubes carrying the blood tend to cause clotting, for example. Scientists at Joslin Research Laboratory in Boston working on the same problem have reduced the tendency by varying the tube sizes and winding them in new configurations.

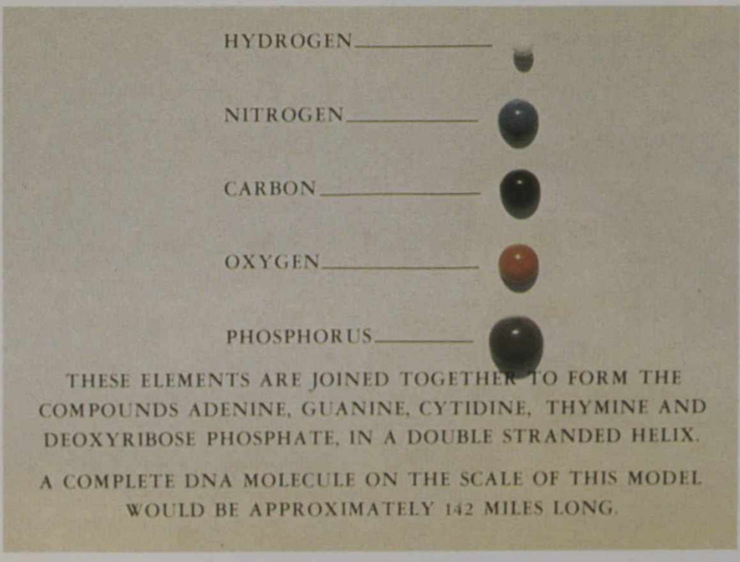
None of the problems seem insurmountable.

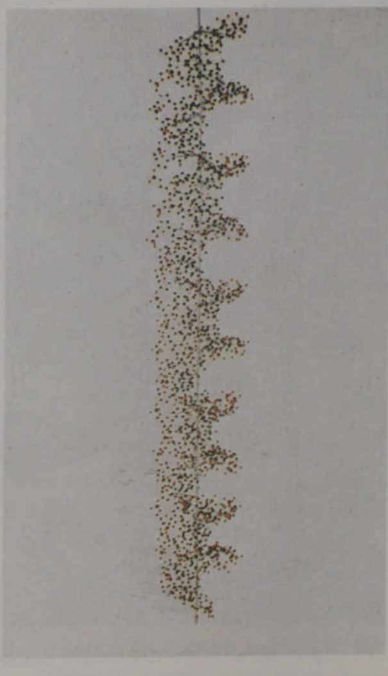
Basic Blueprints

The DNA double helix was identified some thirty years ago.

Current research on DNA, deoxyribonucleic acid, has produced a new understanding of cancer, and the secrets of cell structure have been unraveling with extraordinary speed.

The body has billions of cells, and each one contains five feet of tightly coiled DNA. If the strands in a single body were stretched and laid end to end, they would reach 400 times to the sun and back. Each strand has some 100,000 genes, and these include all the basic blueprints of the body. Particular cells use only the ones appropriate to their own function: red blood cells produce





The model at right represents a section of deoxyribonucleic acid, including all of its elements.

PHOTO: COURTESY OF DR. TAN

Discovery

It has been generally assumed for decades that insulin was discovered, exclusively, by Banting, a surgeon, and Best, a medical student.

The legend was shaped by Paul De Kruif's best-selling book, *Men Against Death*, and it had villains as well as heroes. The major villain seemed to be Dr. Banting's boss, J.J.R. Macleod, the head of the physiology department at the University of Toronto, who was on vacation in Scotland the summer that Banting and Best did the vital work. Lesser villains included the Nobel Prize committee which gave its 1923 medical award to Banting and Macleod instead of Banting and Best.

Banting reacted to the award by publicly announcing that he would share his half of the award money with Best anyway. Macleod responded by sharing his with James B. Collip, a young biochemist who joined the research team some months after what was assumed to be the significant summer.

Michael Bliss, an historian at the University of Toronto, has now published *The Discovery of Insulin*, which greatly changes the picture.

According to Bliss, Macleod had given Banting and Best detailed technical advice and explicit instructions before going to Scotland. When he returned and insisted on extensive further tests, Banting threatened to quit. He didn't, and Macleod put the entire laboratory staff to work on the project. Banting asked for the services of a skilled chemist, and Macleod assigned Collip. The next January a diabetic boy, Leonard Thompson, was given first an injection prepared by Banting and Best, which failed, and then one by Collip, which worked.

Bliss believes Banting and Best could not have "carried the work to a successful conclusion" without the aid of Macleod and Collip.

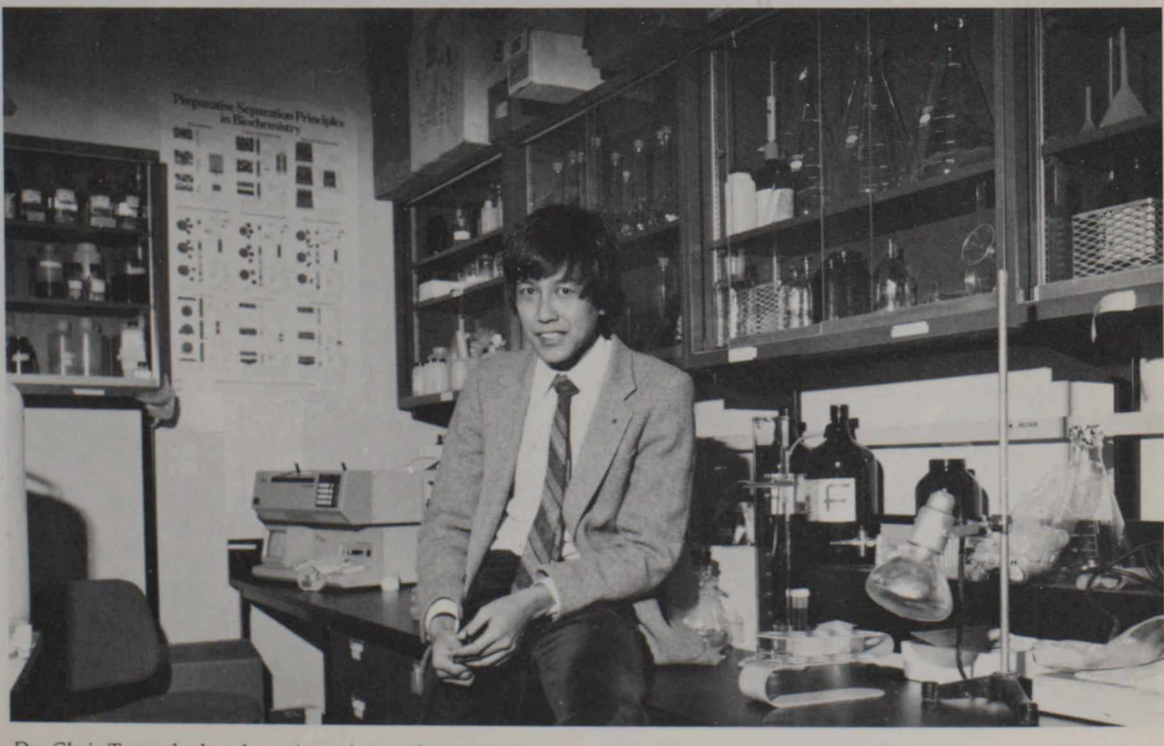
the globin protein for hemoglobin, pancreatic cells produce insulin.

When the person is fully mature the genes stop growth, but some may be activated in a way that produces cancer.

There are more than a hundred diseases called cancer. All are believed to be caused by errors in the DNA. Some are inherited and a few are caused by viruses, but most result from damage to the DNA.

The body has its built-in defences—antigens, proteins that attach themselves to the outside of damaged or diseased cells and to disease-causing intruders such as viruses and bacteria, and antibodies that seek out cells tagged by antigens. In combination with other kinds of cells, antibodies can help kill the damaged or diseased cells and the intruders. (The description here is greatly simplified. The immune system is complex, and its parts interact in ways that are not easily described.)

Scientists can now sometimes manufacture



Dr. Chris Tan, who has done pioneering work on interferon.

defence materials that attack specific targets. Dr. Chris Tan of the University of Calgary's department of medical biochemistry patented a method for the large-scale production of one type of the protein interferon in 1973. Then, after years of effort, he and his colleagues broke its genetic code, determining which genes produce it and which control its effects. They found it to be effective against viruses. Some researchers had hoped that interferon would prove to be a "magic bullet," a broad-scale remedy for cancer, but it has not. Researchers hope it may prove effective in treating specific cancers, but it will take years of clinical trials to determine that.

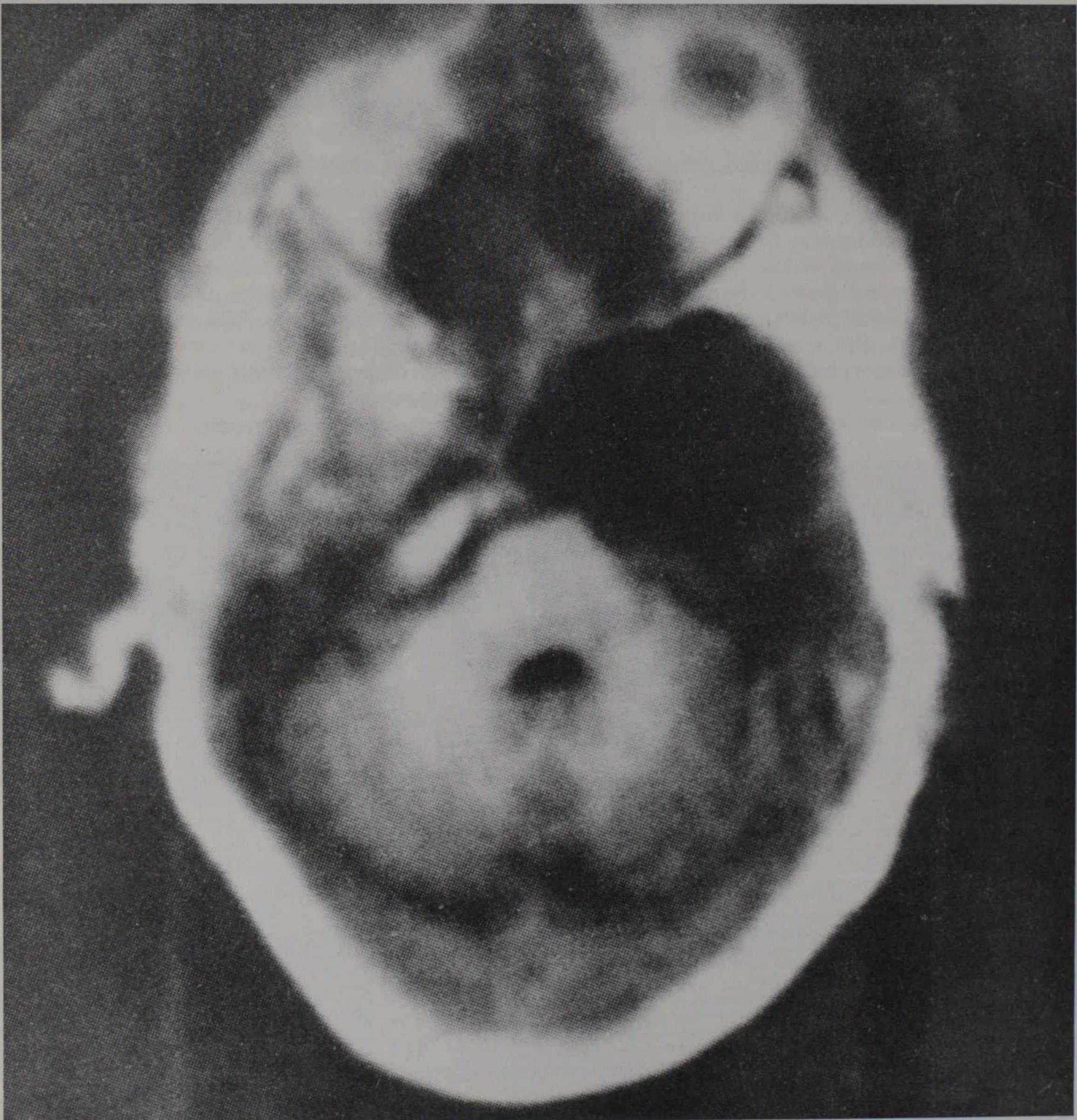
It has had promising results in the treatment of tumors caused by viruses and of viral diseases such as herpes and the common cold.

Beyond the Cat Scanner

Dr. Donald Boisvert, associate surgical research professor at the University of Alberta, and his colleague, Dr. Peter Allen, a physicist formerly at the University of Nottingham, U.K., head a ten-person Nuclear Magnetic Resonance Research Unit at the University of Alberta.

NMR uses magnetic fields to produce pictures of the internal organs that are more detailed than those produced by the CAT (Computer Axial Tomography) scanner, which uses x-rays.

Here's how it works: Hydrogen is abundant in the human body in the form of water, H_2O. Its nuclei are tiny magnets, which, placed in a



This NMR image clearly shows recurrence of a facial tumor following partial removal.

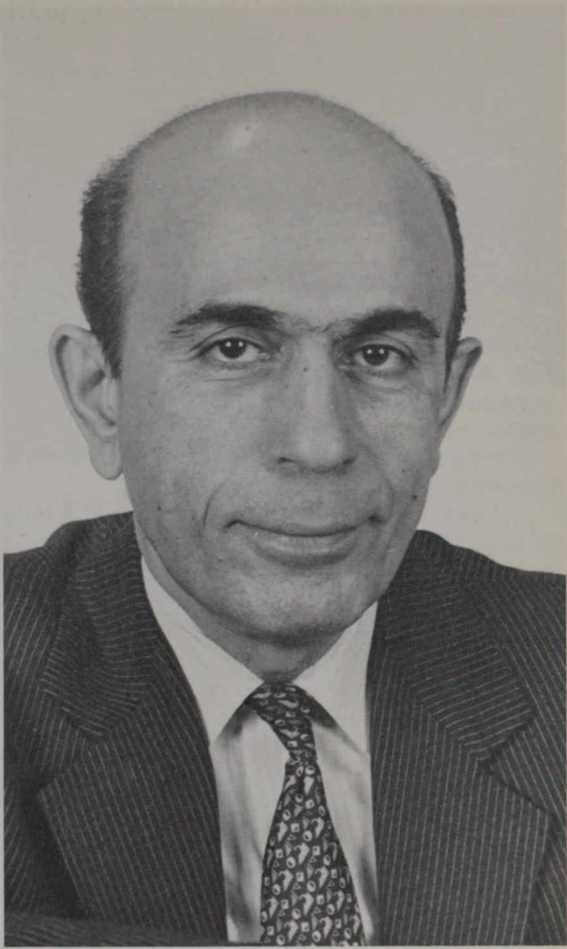
magnetic field, fall into line. Stimulated by radio waves, they give off absorbed energy in the form of radio signals which vary in strength according to their positions. When fed into a computer, the variations produce a high-resolution image of the organ in question. NMR can detect a tumor only two or three millimeters in diameter. The images produced by a CAT scanner give information about tissue, but NMR gives information about the physiology (or function) of the tissues too.

The nuclei of some other elements such as phosphorous, which plays an important metabolic role in the human body, also respond to NMR. Researchers can study, without surgery, how basic processes differ in normal and diseased cells. They can observe how a tumor grows or how diseased bones deteriorate.

The University of Alberta team will install its $2.2 million custom-made super-conducting magnet NMR system this summer. It will concentrate on cancer research, first with small animals, later with people.

An NMR system has also been installed at the University of British Columbia in Vancouver, and one is planned in Quebec. The Ontario government has approved the purchase for hospitals in Toronto and London.

Short-term Dynamic Psychotherapy



Dr. Habib Davanloo

Dr. Habib Davanloo, associate professor of psychiatry at McGill University in Montreal and director of outpatient psychiatric services at Montreal General Hospital, is the founder of a new school of psychotherapy.

The technique—short-term dynamic psychotherapy—shortens therapy time from years to months, and, even its detractors acknowledge, produces extraordinary results.

One patient, for example, who had been unable to drive a car, fly in a plane, board a subway, ride in an elevator, go to a movie or eat in a restaurant and who had been in conventional therapy for seven years, was free of all these governing fears after thirty-two, hour-long sessions.

The therapy has three distinctive characteristics: it is confrontational—the therapist challenges the patient aggressively; it is recorded—each session is videotaped and reviewed by both therapist and patient; and it is compact—the patient is forced to plumb the source of his behaviour in fifteen to forty sessions.

Prospective patients are evaluated in two sessions with different therapists and are not accepted for treatment if they exhibit a low tolerance for anxiety. Its proponents claim that it can be used successfully in 35 per cent of cases.

Dr. Davanloo, who describes himself as "a relentless healer," began applying the technique in the early 1960s.

Dava Sobel, writing in *The New York Times Magazine*, described the theory behind it:

"A major reason for the challenging [of the patient by the therapist] is . . . to prevent the formation of the so-called transference neurosis. In classical analysis, the silence [by the therapist] allows the patient to breathe his own life into the person of the therapist, embroidering elaborate fantasies about what the doctor thinks, feels and does. Typically, his thoughts about the doctor and his reaction to the doctor repeat all the troubled relationships of his life. The creation and resolution of this transference neurosis are the essence of psychoanalysis. In short-term dynamic psychotherapy, however, the doctor works constantly to bring the patient's feelings toward him to the surface."

Dr. Davanloo spends much of his time training psychiatrists. Institutes for training have been established in Montreal, London, New York City, Hartford, Connecticut, Woodcliff Lake, New Jersey, and Charlottesville, Virginia, and one is planned in Madrid. It takes two years of rigorous effort to master the technique.

Lung Transplant

Early last September James Franzen, 31, a nursery gardener in Marietta, Georgia, was lying in a hospital hours from death, his lungs destroyed after inhaling paraquat, a weed killer.

His physician, Dr. Harold Alpert, flew with him to Toronto General Hospital, which is the only hospital with a membrane oxygenator (artificial lung) where surgeons transplant lungs alone without transplanting the heart. (Transplanting both at the same time is technically easier.) The oxygenator could keep him alive for, possibly, two weeks.

A thirty-member surgical team led by Dr. Joel Cooper was standing by.

A potential donor—a man with healthy lungs who had just died—was found back in Georgia and his body was rushed north. As his lung was removed in one operating room, Franzen was being prepared in a room next door.

The operation was a clinical success—the patient survived the operation though dangerously high levels of the herbicide remained in his blood. He received a second lung transplant, but died of a stroke some two months after his surgery when the tube carrying oxygen from the ventilator broke through a major blood vessel.

Dr. Cooper said afterwards that he is encouraged about the future of lung transplants but not for victims of paraquat poisoning, which causes widespread damage to other muscles of the body as well as the lungs. Both transplanted lungs were working when Mr. Franzen died. A new drug called cyclosporine played a role in the operation's limited success.

When a body receives a transplanted organ, cells known as T-lymphocytes, a major part of the body's natural immune system, react as they would to any other foreign body—they attack and reject. This has been the greatest problem in the transplanting of organs. Cyclosporine contains a rare amino acid which suppresses the production of T-lymphocytes.

Sick Children

Canada's researchers and its research institutions have long had a particular focus on sick children. The first diabetic saved by insulin was a teenage boy. Since then the lives of thousands of children have been enlarged by innovative treatments. One recent example concerns an eight-year-old who had his life broadened by surgery at Toronto's famed Hospital for Sick Children.

The following description of his adventure is adapted from a report by Diane Wilson in *Saturday Night* magazine.

Michael O'Brien had a rare defect called *pectus excavatum*, a hole in his chest, about three inches long, two inches wide and two inches deep. He had been born with it, and it had deflected his ribcage and pushed his heart to the left.

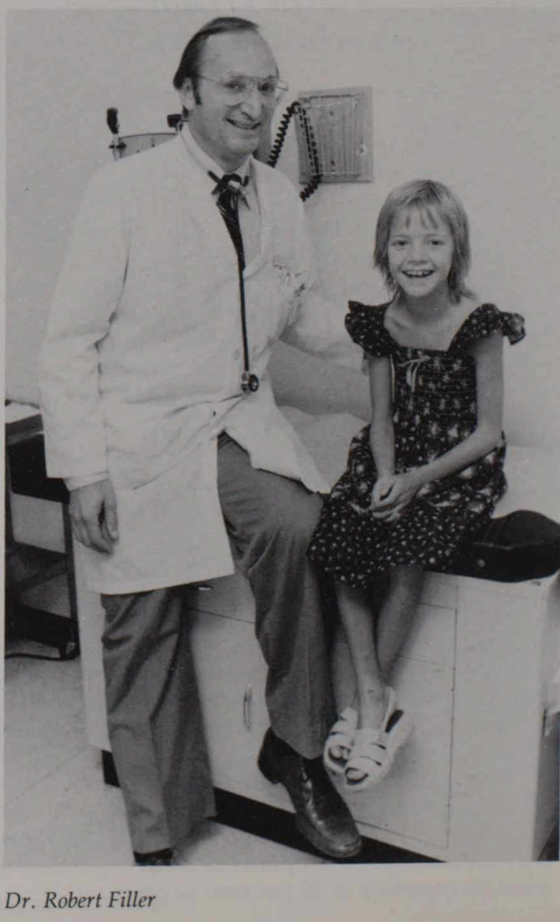
He was in the Hospital for Sick Children, about to be operated on by a team headed by Robert Filler, the hospital's surgeon-in-chief.

Nurses had demonstrated heart surgery for Michael and other young patients, unzipping a puppet and exposing its internal organs, but that was not particularly reassuring to Michael.

On the morning of the operation he was awake early and scared.

First Dr. Filler came to visit him in the pre-operating room where he and several other frightened children were waiting. The doctor exuded confidence.

Michael was then rolled into the operating room and wired to an electrocardiogram monitor. The nurse explained that this was done so that Jeremy Sloan, the anaesthetist, could listen to his



Dr. Robert Filler

heart. Michael was told he would soon be asleep. When he was, Dr. Sloan connected him to a ventilator so he'd have an easy supply of oxygen.

Dr. Filler and his senior resident, Rick Superina, arrived, freshly scrubbed. A nurse helped them into gloves and gowns, and Michael's small body was draped in sterile green towels.

The team of seven—surgeon, anaesthetist, residents and nurses—took their places around the table under circular lamps. Jeremy Sloan stood at the top watching Michael's heart rhythm, body temperature and heart rate wiggle across the screen in green lines.

Filler exposed Michael's sternum and lower rib cage. He and Superina planned their next move.

"Now, that cartilage has to go," Filler said. "Just cut it. That rib there can stay. Do you agree?"

The residents agreed.

With effort Filler took out a two-inch piece of rib and handed it to a nurse. He worked his way over Michael's right side, removing cartilage. A nurse mopped his face with a green towel. He took out parts of five ribs on the right and moved over to the left. Parts of five more came out there.

The team was now ready for the next phase.

Filler cut across the sternum so the depressed bone could be bent upward and sewn in place. He placed a few stitches and set free the skin and muscles that had been held back with retractors.

Filler put a plastic drain in Michael's chest and closed the muscle and skin incisions. The nurses counted the gauzes to make sure none had been left inside, and Filler and Superina wiped off his chest, painted it with tincture of benzoin and sealed the incision with tape.

The two-hour operation was over. Sloan removed the breathing tube and Michael began breathing on his own.

Michael took a walk down the corridor the next day and went home four days later.

The Hospital for Sick Children

The Hospital for Sick Children, which is attached to the University of Toronto, is the biggest children's hospital in the western world and one of the best. It attracts first-rate researchers from around the globe.

It was founded in 1875, and it established Toronto's first pasteurization plant in 1909. Alan Brown, the physician-in-chief from 1919 to 1951, pushed his associates to develop proper food for infants, and two of them, Theo Drake and Frederick Tisdall, combined vitamins and minerals and produced both Sun-Wheat biscuits and Pablum.

In 1953 the hospital established the Research Institute, and research is now the hospital's essence.

Aser Rothstein, director of the Research Institute and a professor of medical biophysics and pediatrics at the University, was in charge of the primary toxicology lab at the Manhattan Project

Dr. Aser Rothstein

and chairman of radiation biology and biophysics at the University of Rochester's medical school. He directs research and recruits researchers.

He says the capacity to pick good researchers is the key to the Institute's success.

"Research is a very elitist occupation. One brilliant guy might do something twenty mediocre guys could never do."

The Institute has sixty-two full-time researchers, a $15 million annual budget and 180 current projects.

Much of the research is basic, and a lot of it has to do with congenital diseases. Biotechnologists are busy here, as elsewhere, on strands of DNA.

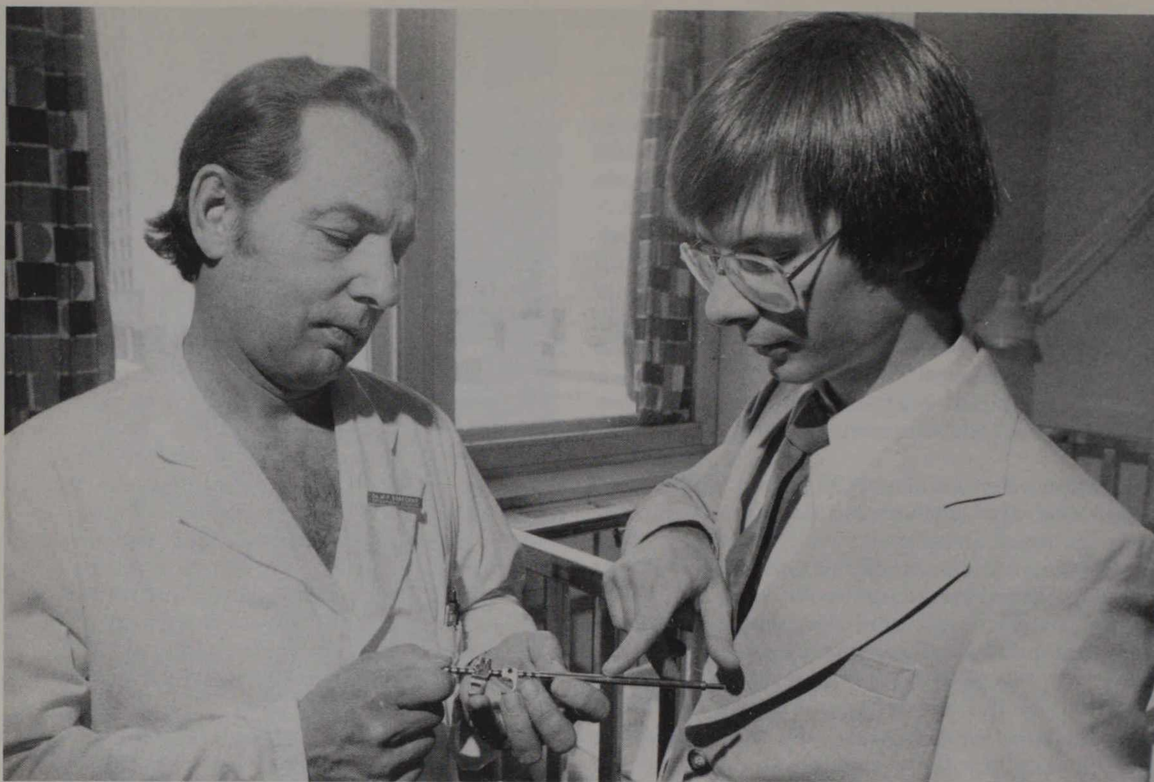
("You have to identify the good gene and the sick gene," Rothstein says, "and replicate them in bacteria. You then put the good gene into the sick gene. This can be done in the test tube right now. We're going to attempt to be at the very forefront of genetic engineering.")

There is also a great deal of research going on in other fields. There are regular advances in surgical techniques and post-operative care. There are innovations every day.

Spinal Pacemaker

Dr. Walter Bobechko, chief of orthopedic surgery at the Hospital for Sick Children, and his col-

PHOTO: LOU SCAGLIONE, THE HOSPITAL FOR SICK CHILDREN



Dr. Walter Bobechko and his son Kevin, with the super stability system they designed.

leagues have found two extraordinary solutions to scoliosis, a curvature of the spine that afflicts many teenage girls. The traditional treatments have involved the wearing of neck braces for years and, in some cases, body casts for months.

If the disease, which is genetic, is detected in its early stages, before any curvature has taken place, Dr. Bobechko and his team implant a pacemaker next to the spine. The pacemaker is a radio receiver, and a transmitter by the child's bed sends out radio signals at night while the child is sleeping. The signals trigger electrical impulses which stimulate the spinal muscles and prevent curvature. The child does not feel the treatment in any way, and, in Dr. Bobechko's enthusiastic phrase, it's "good-bye to neck braces" once the pacemaker is in place. The implanting has been taking place in Toronto for ten years, and other hospitals around the continent have mastered the technique.

The second process involves children who have a degree of curvature already. The condition can be corrected by surgery, using a technique known as the Harrington operation, but post-operative treatment requires that the patient wear a body cast for six to twelve months.

Dr. Bobechko and his son Kevin, an engineering student, recently designed three-dimensional "super-stability" spinal clamps. These are attached internally to the spine, and the patient can walk unaided shortly after the operation and needs no body cast.

The Kids Who Drowned But Didn't Die

Since 1970, 140 children who had drowned or almost drowned have been brought to the Hospital for Sick Children.

Thirty-four of them appeared to be dead.

By the experience of centuries, most of the larger and all of the smaller group should have died. Most of the larger group recovered completely, and so did 30 per cent of those who showed no signs of life at all.

Dr. Alan Conn, who directed the hospital's intensive care unit for ten of those years, attributes the extraordinary success to a precise series of co-ordinated processes designed to get the heart going and to prevent the brain from swelling.

First, the apparently drowned child is given mouth-to-mouth resuscitation at the scene and rushed as soon as possible to a hospital.

Once there, five steps are followed if he is in a coma:

1) His intake of fluid is greatly restricted.
2) He is hyperventilated—given a greater level of oxygen than a person normally requires.
3) His body is cooled to thirty degrees centigrade, seven degrees below normal.
4) He is given large doses of phenobarbital and heavily sedated even though he is already in a coma.
5) He is kept totally paralyzed, so he cannot twist, turn or cough.

The theory behind the treatment is that when a person appears to have drowned, some of his brain cells are destroyed and many more are damaged.

If he is not treated properly the brain will swell and the damaged cells will also be destroyed. If the brain does not swell, however, these can recover.

The treatment is designed to prevent or at least retard the swelling—the cooling of the body is an essential step and so is the induced paralysis. A cough could jar the head and bump damaged cells against the skull. The pressure inside the skull is monitored while the child is in intensive care.

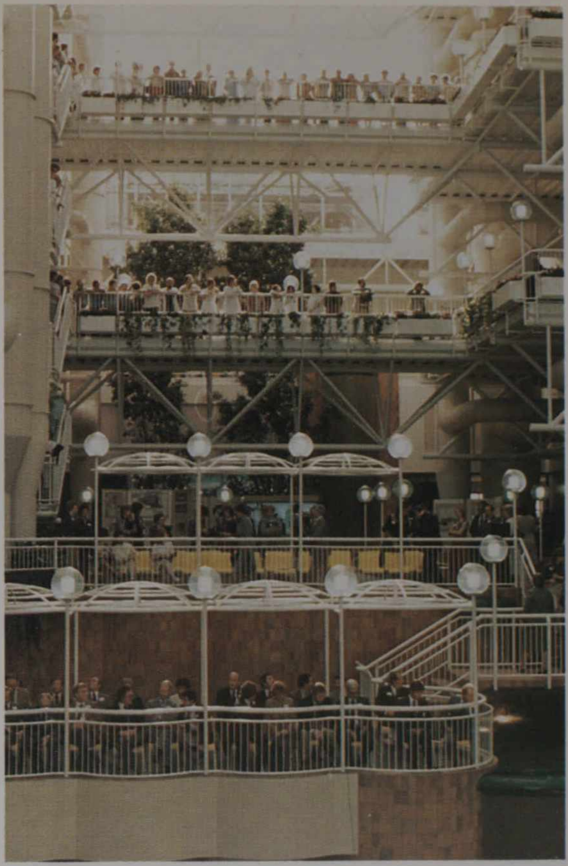
Dr. Conn recently spent a sabbatical year in San Antonio, Texas, at the University of Texas Health Sciences Center, doing further research on drowning. He found, among other things, that the water drowning people take into their lungs has a beneficial as well as an adverse effect since it cools the oxygen that is going to the brain.

The principal lesson learned from the accumulated research may be that a person should be assumed to have a spark of life even if he has been underwater for fifteen minutes or more. One child who had been under for forty-five minutes before getting the full, intensive treatment recovered completely.

Dr. Alan Conn and a patient who made a total recovery after being submerged for an estimated twenty minutes.

PHOTO : UNIVERSITY OF ALBERTA HOSPITALS COMPLEX

Dedication of the Walter C. Mackenzie Health Sciences Centre, of the University of Alberta Hospitals Complex in Edmonton, in October 1982. The Centre, designed by Toronto architect Eberhard Zeidler, has three parallel wings grouped around a glass-domed courtyard with benches, window boxes, trees and a waterfall. Six-foot spaces between each floor contain heating and electrical equipment so that the building can be renovated with minimal disruption to hospital activities. The Centre was funded through the Alberta Heritage Savings Trust Fund, established with revenue from the province's natural resources.



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