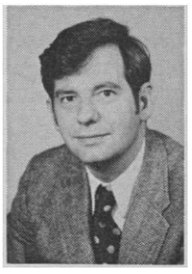
oped over the next decade. The director of the DBS should have responsibility for organizing the research program as well as the regulatory activities of the division.

In addition, federal responsibility for vaccine development should be clarified, in a way that ensures the DBS does not develop vaccines in-house. There should be some court of appeal against the director's decisions. Since the DBS acts, in effect, for the academic community on behalf of the public, there should be a stronger connection with the academic world than occasional ad hoc conferences and a rubber-stamp board of scientific counselors. Standing committees of scientists might be established—one to oversee research and another for regulations—so as to buttress the director's posture toward manufacturers. Problems with vaccines should be more openly discussed, and herd immunity should be sought by means other than treating the public as one. Most importantly, the boat in which the DBS director sits should be strong and flexible enough to withstand the occasional rocking.—NICHOLAS WADE

APPOINTMENTS



W. G. Bowen

M. H. Bernstein

William G. Bowen, provost, Princeton University, to president of the university. . . . **Marver H. Bernstein**, professor of politics and public affairs, Princeton University, to president, Brandeis University. . . . **David R. Derge**, dean for administration, Indiana University, to president, Southern Illinois University, Carbondale. . . . **Timothy W. Costello**, professor of psychology and management, New York University, to president, Adelphi University. . . . **N. Ferbee Taylor**, vice president for administration, University of North Carolina system, to chancellor, University of North Carolina, Chapel Hill. . . . **Ivan L. Frick**, president, Finlay College, to president, Elmhurst College. . . . **Harold P. Hanson**, dean, Graduate School, University of Florida, to vice president for academic affairs at the university. . . . **Archie R. Dykes**, chancellor, University of Tennessee, Martin, to chancellor, University of Tennessee, Knoxville. . . . **Victor Jones**, professor of engineering and applied physics, Harvard University, to dean, Graduate School at the university. . . . **Thomas G. Cook**, assistant professor of education, University of Wisconsin, to dean, School of Education, Ferris State College. . . . **William Happ**, operations research analyst, U.S. Army Corps of Engineers, to dean, School of Engineering, Sacramento State College. . . . **Leonard E. Goodall**, vice chancellor, University of Illinois, Chicago Circle, to chancellor, University of Michigan, Dearborn. . . . **Conrad T. Burriss**, professor of chemical engineering, Manhattan College, to dean, School of Enginering at the college.

RESEARCH NEWS

Cancer Radiation Therapy: Potential for High Energy Particles

Although the causes of cancer are still unknown, treatment with radiation therapy alone or in combination with chemotherapy and surgery helps to save hundreds of thousands of lives a year. Large doses of radiation, however, damage healthy tissues in addition to destroying tumors and thus may cause severe side effects. The use of high energy particles instead of the conventional x-rays or gamma rays may make possible significant improvements in radiation therapy, according to a growing number of physicists and radiotherapists, and the preliminary results of several laboratory and clinical trials seem to support this belief.

Both the physical and radiobiological properties of energetic particles indicate that they may be able to alleviate some of the problems of conventional radiotherapy, although clinical trials are needed to ascertain that new and untoward effects do not occur. The potential uses of particle radiation may be restricted to localized cancers—a category of diseases that does not include some of the most common, such as lung and breast cancer. Nonetheless, the use of particle radiation, if its potential advantages turn out to be clinically significant, may be able to help the large number of patients who now die from localized cancers despite treatment with conventional radiotherapy.

Practical applications of particle radiation in cancer therapy may be slow in coming. Except on a small scale, the necessary clinical trials are not now being conducted in this country, and there appears to be little likelihood of systematic trials with many types of particles in the near future. Despite the large increases in funding for cancer research, relatively little support is available for radiotherapy research, including particle radiation. National Cancer Institute support for investigations of particle radiation totaled less than $1 million in fiscal year 1971, a figure that NCI officials estimate may rise to $2.5 million by fiscal 1973. One reason, according to NCI, for the relatively low level of funding is a shortage of qualified radiotherapists who are interested in particle radiation. Research proposals have been rejected by the peer review system for lack of scientific merit—a consequence, according to one NCI official, of the naiveté in radiobiological matters on the part of the physicists who proposed them.

Whatever the reason, several physics laboratories that have an interest in using their particle accelerators for cancer research may find it impossible to do so, and in one case the lack of other sources of funding may result in the closing of the laboratory.

The current interest in medical uses for particle radiation contrasts strongly with the attitudes that have prevailed

for much of the past 30 years. Early, and what proved to be premature, trials of fast neutrons took place at Berkeley in the early 1940's. At the time, little was known of the biological effects of radiation, and, as a result, the patients were exposed to too large a total dose, so that a few patients were severely burned. The incident discouraged further work with particle radiation for many years. More recently the combination of improvements in conventional radiotherapy techniques—the use of high energy x-rays and gamma rays—and the unavailability of beam time on major accelerators because of the higher priority that was given to physics experiments provided little incentive for radiobiological investigations with high energy particles. Nevertheless, considerable work was done with obsolete machines at a few laboratories, notably Berkeley and Harvard. Now that physics research funds are scare, however, quite a few accelerators are available, and there is something of a rush for physicists to get into cancer research. Neutrons, protons, alpha particles (helium ions), heavy ions such as nitrogen or neon, and the pi minus meson or pion are among the particles being considered for radiotherapy.

Compared to 30 years ago, considerably more is known now about the effects of radiation on tissue. Two factors in particular seem to be important for the prospects of particle radiation: (i) the dose delivered to the tumor in comparison to that inflicted on healthy tissue, and (ii) the biological effectiveness of the radiation in the tissue.

X-rays and gamma rays are exponentially attenuated by interacting with electrons as they travel through tissue, so that, except for an initial buildup just below the skin, the dose reaching the tissue decreases with depth. Thus a deep-seated tumor receives a smaller dose than the healthy tissue above it. The tissue behind the tumor also receives a substantial, although smaller, dose.

Heavy charged particles also lose energy in tissue by scattering electrons, but in contrast to x-rays and gamma rays, their energy loss occurs at a rate proportional to the square of their nuclear charge and inversely proportional to their energy (at nonrelativistic velocities), so that a nearly constant amount of radiation is deposited along most of the particle path. As the particle comes to a stop, however, the amount of radiation deposited rises sharply to a maximum, known as the Bragg peak. Hence if the initial energy of a beam of charged particles is adjusted so that the Bragg peak occurs in the tumor, the intervening normal tissue above the tumor receives less radiation than does the tumor. Tissue behind the tumor receives almost none, since most of the particles have stopped in the tumor.

Hence charged particles, because they allow the radiation to be concentrated in the tumor, appear to offer an improvement over conventional radiotherapy. That this improvement in dose localization is clinically significant has not been demonstrated for particle radiation, and some radiotherapists are skeptical; but one step in this direction, for which there is clinical evidence, is the successful use of high energy x-rays and gamma rays that have better dose localization than low energy x-rays do.

The Oxygen Effect

The amount of radiation delivered to the tumor is not the only consideration, however, because the biological response of cells to radiation varies with the condition of the cell and the type of radiation. Many tumors, for example, appear to be undifferentiated tissue with inadequate blood supply, and hence may contain a small proportion of hypoxic cells. For conventional radiation, the dose required to kill such oxygen-poor cells is about three times that which will destroy normal, oxygenated cells—an effect that is believed by many radiotherapists to be due to the high reactivity (within normal cells) of the free radicals created when unbound oxygen is ionized by the radiation. The radiosensitivity of cells also appears to vary with cell cycle, although less is known about why this should be so. Both effects may increase the advantage of the tumor over normal tissue. The magnitude of both of these effects, however, seems to be less with particle radiation than with conventional radiation.

The greater biological effectiveness of particle radiation in destroying tumor cells—and the potentially lower dependence on the oxygen content or on the cycle of the cell—is apparently due to the higher density of ionization, compared to x-rays, that the particles produce along their path through tissue. The higher the ionization density or the amount of energy transferred to the tissue per unit of path (linear energy transfer or LET) of a particle, the greater the tissue damage. The greater effectiveness of high LET radiation for some types of particles has been demonstrated in animal studies. But whether anoxic tissue is a significant factor in human tumors or whether the oxygen effect is a limiting factor in radiation therapy remains to be clinically proved.

One indication that high LET radiation may indeed be very effective in human tumors comes from clinical trials of fast neutrons under way at the Hammersmith Hospital in London. After several years of careful and detailed radiobiological studies, a team at the hospital began investigating the clinical effects of neutrons in human cancers in 1969. Preliminary trials with a neutron beam, obtained by bombarding beryllium with deuteron particles showed that the response of patients treated with neutrons did not differ in any observable way from those treated with x-rays; the skin reaction to a total dose of about 1440 rads of neutron radiation, however, was judged to be equal to that produced by 4100 rads of high-voltage x-rays (*1*).

Neutrons are exponentially attenuated in tissue, and so distribute radiation with depth in a manner similar to x-rays. In radiobiological experiments, however, the damage that neutrons cause is only about half as sensitive to the oxygen content of cells as that caused by x-rays. Preliminary and informal reports of the clinical trials that are continuing at Hammersmith (with more than 150 patients) indicate that the oxygen effect may be very significant clinically; after irradiation there appear to be almost no recurrences of tumors in treated tissue among the surviving patients, a degree of success that, if confirmed, would be remarkable. One U.S. radiotherapist who is familiar with the work described it as "startling, if the preliminary indications hold up." Several U.S. teams are now preparing to start clinical trials with neutrons; and other teams, with support from the National Cancer Institute, are working on the development of new types of neutron generators.

Unlike neutrons, the damage that protons and conventional radiation cause are about equally sensitive to the oxygen effect. Because of the Bragg peak effect, however, protons are superior to neutrons in localizing the dose within the tumor; the proton beam can be so sharply focused that a major limitation in making use of protons is the lack of a sufficiently accurate means of locating tumors within the body—techniques for which there was no need with the broad

beam used in conventional radiotherapy. Nonetheless, therapeutic work with protons has been going on at Harvard and at Uppsala, Sweden, for more than a decade, although no full-scale clinical trials have been conducted. Another advantage of protons is that they are inexpensive to accelerate; the Harvard cyclotron has been supported largely by patient fees for pituitary irradiation since 1967.

Alpha particles appear to combine many of the advantages of both neutrons and protons. The energy loss of the particles is concentrated in a pronounced Bragg peak at the end of the particle path, so that radiation can be concentrated in the tumor, and the oxygen dependence within the Bragg peak is substantially lower than that of x-rays (although not quite so low as that of neutrons). The Bragg peaks of alpha particles and of heavier ions are too narrow to allow a large tumor to be completely irradiated, unless the range of the beam is varied or the width of the Bragg peak is broadened by inserting a variable absorber in the path of the beam. It had been thought that, within such a broadened Bragg peak, the advantageously low oxygen dependence of the alpha particles would be lost. But recent experiments with cultured cells indicate that there is a still significant reduction in oxygen sensitivity within a broadened Bragg peak (*2*). Systematic clinical trials with alpha particles have not been done, although the 184-inch (1 inch = 2.54 cm) cyclotron at Berkeley has been used for pituitary irradiation since 1956. Several other accelerators that can produce alpha particles of sufficiently high energy are either available or are in the process of being modified for alpha particle work, including the NASA synchrotron in Newport News, Virginia.

Neutron, proton, and alpha particle accelerators that would be suitable for clinical studies are already available, and substantial information on the radiobiological behavior of these particles has already been obtained. Less is known about heavy ions and pions, so that their relative advantages are still somewhat unclear. Nonetheless, some radiotherapists believe that these particles have significant potential for radiotherapy applications.

Heavy ions with energies suitable for radiobiological studies have only recently became available at the Princeton synchrotron and at the Berkeley bevatron. Both nitrogen and neon ions are of interest, and both have exceedingly intense Bragg peaks—an indication of the possibly high biological effectivenesss of such radiation within this region. What is not known, however, is the extent to which the biological effectiveness will be decreased when the Bragg peak is broadened to widths comparable to those of real tumors. Nor is the physics of heavy ions—including what secondary particles are produced in tissue—known with any precision. Both laboratories are modifying their accelerators to increase their intensity to that required for clinical work and are planning therapeutic facilities. The Princeton facility, however, will be forced to close down if it does not receive additional funding this spring—about $700,000 a year is needed to operate the laboratory and to continue the radiobiological and preclinical studies now in progress.

No pion beams of sufficient intensity for therapeutic work are yet available, although the Los Alamos meson facility is expected to be completed in 1973, and similar facilities are being constructed in Vancouver, B.C., and in Zurich, Switzerland. A superconducting electron accelerator at Stanford, which could be used to make pions, will be completed at about the same time. The Los Alamos facility includes a special beam channel for therapeutic work, now being built with support from the National Cancer Institute.

Pi Meson Radiation

Some radiobiological experiments have been done with pions, but at dose rates far below those needed for preclinical studies. Pions are believed to act like conventional radiation in tissue until the end of their path, where they are captured by an atomic nucleus and decay, releasing a localized burst of secondary particles. Thus pions, like heavy ions, also deposit a highly localized dose of radiation that is theoretically very effective biologically, although by a mechanism different from that which causes the Bragg peak of a heavy ion. Pions have the disadvantage, however, that they are expensive; they also produce, among other secondary particles, three energetic neutrons per pion, many of which will pass through the patient but may cause a radiation hazard within the treatment room.

With conventional radiation, healthy tissue often receives a larger dose than the tumor does, and to the extent that the tumor contains anoxic cells, it takes more radiation to destroy the tumor cells than it does healthy cells. Conventional radiotherapy thus depends on the preferential recovery of healthy tissue for its success. Charged particle radiation, on the other hand, can deliver higher doses to the tumor than to the normal tissue around it, and, for some particles, is much less sensitive to the oxygen content of the cell.

The radiobiological properties of proton, neutrons, and alpha particles are relatively well known, and similar information about heavy ions and pions could be available within a few years. There is some clinical evidence that dose localization is important, and if the preliminary results from the Hammersmith trials are confirmed, there will be clinical evidence that the oxygen effect is significant in human tumors (there is already evidence that it is in animal studies). There appears to be a consensus among radiobiologists and radiotherapists who have worked with particle radiation that it is time for systematic clinical trials of particle radiation. Cancers of the oral cavity, the bladder, the cervix, and the pancreas are among those for which radiotherapists would like to try heavy particle radiation (*3*).

The policy in regard to supporting research on particle radiation of the National Cancer Institute, however, has some apparent contradictions. Instead of encouraging the use of available facilites for preclinical and clinical trials of protons or alpha particles, for example, the NCI has supported the development of new facilities for generating fast neutrons and for therapeutic applications of pions. And although clinical trials of fast neutrons (with NCI support) seem likely to move ahead in the next year, it is clear that NCI has been content to follow at a safe distance the British lead in this research.

Even ardent supporters of particle radiotherapy agree, however, that it would be a mistake to divert too much money from basic research on cancer to the sophisticated technologies required for studying the effects of particle radiation. Nor are miracles likely to happen, they caution; but they do believe that particle radiation therapy is well worth trying.—ALLEN L. HAMMOND

References and Notes

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2. M. R. Raju, M. Gnanapurani, B. I. Martins, J. Howard, J. T. Lyman, *Radiology* **102**, 425 (1972).
3. Some of the information presented here was gathered from those who participated in a meeting in Albuquerque, New Mexico, 19 to 21 February 1971, sponsored by the American College of Radiology and the National Aeronautics and Space Administration.