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Testing in Humans Slated

Anticancer Effects of Platinum Demonstrate Value of Basic Research; Renew Interest in Metallic Drugs

One of the most promising drugs in recent years for the treatment of cancer has resulted from basic, noncancer research at Michigan State University. The drug, a platinum compound, is scheduled for preliminary human testing this summer and fall by the National Cancer Institute.

Dr. Rosenberg

The anticancer effects of certain platinum compounds were first noted in the laboratory of Dr. Barnett Rosenberg, professor of biophysics, six years ago. Since then, Dr. Rosenberg's group, as well as other researchers at MSU and scientists at the National Cancer Institute and several other laboratories, have shown that the platinum compounds demonstrate a remarkable ability to dissipate a wide variety of tumors in test animals. Side effects appear to be minimal and reversible.

"Dr. Rosenberg's work is an excellent example of the value of basic research and the danger inherent in its restriction," says Dr. Andrew D. Hunt, Jr., dean of the MSU College of Human Medicine.

"If a very intelligent and highly trained researcher had not been funded to pursue a basic research project on the effects of electrical fields on the growth of microorganisms, the world would still have no reason to suspect that platinum and other metallic compounds might be useful in the treatment of cancer."

Whether or not the particular compound now ready for human testing proves effective against cancer in people, the research firmly establishes the biological activity of platinum compounds, Dr. Rosenberg notes. He adds:

"It also opens the possibility that one or more of these compounds – or other metallic compounds – will eventually prove effective against human cancer and, perhaps, other diseases as well.

"It may even bring about a renewing of research activity on metallic drugs generally."

Prior to 1939, metals such as mercury, antimony and bismuth were used rather widely in medical therapy. But since the discovery of the sulfa drugs, nearly all research interest has been with organic compounds. Of the approximately 140,000 compounds that the National Cancer Institute has tested for antitumor activity over the past 15 years, only a dozen or so have been inorganic.

Discovery of the potential of platinum compounds came about when Dr. Rosenberg and his laboratory supervisor, Mrs. Loretta VanCamp, were using platinum electrodes to create an electrical field in order to study its effects on a culture of bacteria. They used platinum because it was understood to be relatively inert and therefore would not affect the chemical balance of the culture. When they applied the electrical field, the bacteria did not divide

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Anticancer Effects of Platinum

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but continued to grow and form long filaments. Detective work by Drs. Thomas Krigas and Andrew Thomson of the Biophysics Department revealed that platinum ions were combining with the bacterial culture medium to form a compound.

After learning that this compound and certain other platinum compounds were responsible for the unusual growth without division, Dr. Rosenberg decided to see what their effects would be on cell division in tumors. When initial tests against tumors in mice proved successful, he submitted the compounds to the National Cancer Institute for screening against other types of cancer.

Since then the compounds have been tested in a variety of ways by American, English, and Czechoslovakian researchers. Results of these efforts were reported at an international symposium on "The Bacterial, Viral and Antitumor Activities of Platinum Compounds" at MSU in September 1970. The reports revealed that the platinum compounds had one of the broadest spectrums of action of any class of antitumor agents yet discovered.

In addition, it was reported that while the platinum tends to concentrate in the filtering and excretory organs, such as the liver and the kidneys, the damage to these organs is negligible and reversible, while the tumor, which takes up less platinum, is destroyed.

One of the reports, by Dr. John Vendetti of the National Cancer Institute, showed that a platinum compound used in conjunction with cytoxan, an alkylating agent, on advanced leukemia L1210 in mice results in a synergistic effect – an effect greater than the sum of the effects of each drug when used singly.

Most of the testing to date has been carried out with the platinum compound *Cis*-dichlorodiammine platinum (II), and it is this drug which is slated for human testing.

RATINGS SHOW MSU STRONG; GAINING RAPIDLY IN SCIENCES

See the back page for an analysis of MSU's growth in scientific graduate programs.

Michigan State's national reputation in science is catching up to the growth it has enjoyed over the past 15 years.

This is the consensus of MSU administrators and scientists after reviewing *A Rating of Graduate Programs* by Kenneth Roose and Charles J. Anderson, published by the American Council on Education in December.

The study is based on a survey of more than 6,000 scholars who were asked to rate graduate programs at the various institutions as being "distinguished, strong, good, marginal or not sufficient for doctoral training."

In nearly all categories of the behavioral and biological sciences, Michigan State ranked "strong to distinguished" – the top category.

MSU's showing was particularly good considering that in a similar study by the American Council on Education, the university was unranked in most of the categories.

Many MSU officials feel that MSU would have ranked higher in both studies if it were not that reputation tends to lag behind actual accomplishment. Dr. James W. Butcher, assistant dean for research and graduate programs of the College of Natural Science, said:

"It is difficult to believe that so few of our disciplines were unranked in the 1964 evaluation compared with the 1969 survey.

"In virtually all of our (natural science) programs, we ranked in the top 10 to 30 percent of all universities in this country. Furthermore, our staff is very young, overall, with its most productive years ahead.

"Two things stand out in this report: (1) there are no weak programs but instead a relatively uniform level of excellence and (2) none of our programs has reached the peak.

"Most of the persons who evaluated us felt that our programs are better than they were five years ago."

Joint Administration a Factor

All but three of the graduate programs in which MSU ranked "strong to distinguished" are in departments which are jointly administered by two or more colleges.

In addition, most of the programs have strong ties with the College of Agriculture and Natural Resources in that they receive support from the Agricultural Experiment Station. For example, the microbiology and physiology departments are jointly administered by the Colleges of Human Medicine, Natural Science, and Veterinary Medicine and carry out Agricultural Experiment Station research projects.

"This indicates that joint administration works," says Dr. Robert D. Schuetz, acting director of the Institute of Biology and Medicine. "It also verifies the position taken by Michigan State in 1959 to the effect that a new medical school would both benefit from and contribute to related graduate programs.

"When the College of Human Medicine was organized in 1964, shared administration enabled it to begin with 12 departments – nine in the biological and three in the behavioral sciences – having graduate programs already in progress.

"Since then, the college, in turn, has helped to develop the departments in several ways, particularly through recruitment of new faculty who wanted to be involved in medical education and research."

MSU's new College of Osteopathic Medicine, Dr. Schuetz added, is scheduled to be organized along similar lines, with the expectation that it will likewise contribute to and benefit from joint administration.

Initial organization of the two medical colleges and general coordination of graduate and health professional programs has been the responsibility of the Institute of Biology and Medicine, which is a part of the Office of the Provost, the chief academic officer of the university.

WHY AND HOW PLATINUM COMPOUNDS WORK —Dr. Rosenberg's Theory

Dr. Rosenberg believes that the theoretical framework which he and his associates have constructed to explain the results of their experiments may prove useful in understanding the origin of tumors and in developing new ways of dealing with them.

The MSU scientist subscribes to the general theory that viruses sometimes invade cells leaving behind genetic material. This material, or viral genome, is thought to be normally repressed by the cell's regular genetic material, but may be partially liberated (derepressed) by chemical agents, radiation or other viruses. The partially liberated viral genome, the theory states, then begins to direct production by the cell of new proteins which transform the healthy cell into a tumor cell. The new protein is foreign to the body and, therefore, stimulates the production of antibodies which may or may not successfully combat the new cells.

From the data collected from experiments in conjunction with Drs. Scarlett Reslova and Jaroslav Drobnik of Czechoslovakia, Dr. Rosenberg tentatively concludes that the platinum compounds cause lesions in molecules of cellular DNA, leading to more complete liberation of the viral genome. The cell then produces a great deal of new protein which, in turn, gives the body's defense mechanisms a well-defined target. The result is a massive antibody reaction that eventually overwhelms the tumor.

One of the pieces of evidence for this speculation is a finding that the platinum compounds which are active against tumors also cause destruction of bacteria that are known to contain viral genomes. These findings indicate that the drugs affect the normal DNA, allowing the viral genomes to take over.

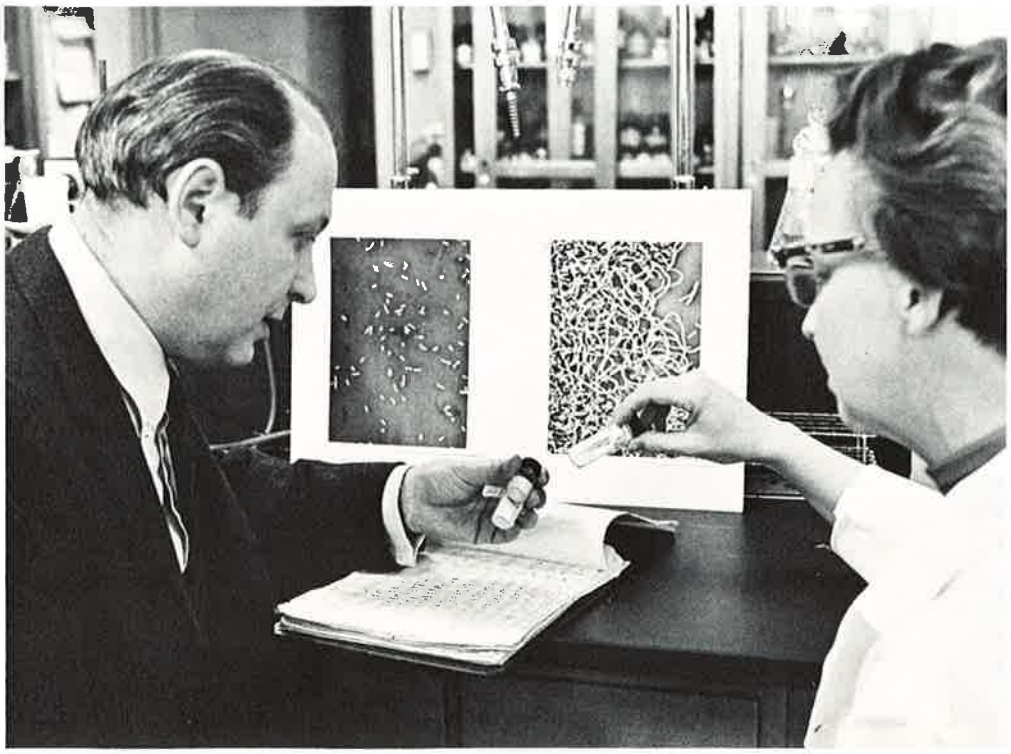
MOLECULAR BASIS

Molecular studies conducted by Dr. Harold Harder of the biophysics department indicate that platinum compounds cause lesions in DNA molecules in a manner similar to the action that other scientists have postulated for antitumor alkylating agents.

Dr. Rosenberg thinks one type of lesion is caused when two active chloride groups on the outside of the platinum compound molecule are replaced by bonds between two of the purine bases attached to one strand of the DNA molecule. Inasmuch as the spacing between the two active chloride groups is 3.3 angstroms, and the space between the two purine bases is about 3.4 angstroms, a snug fit is possible.

If the DNA molecule is thought of as a helical ladder, the theoretical action of the platinum compounds is comparable to a connection from one rung to the next. By the same analogy, the theoretical action postulated for alkylating agents would be comparable to an extra rung running diagonally from one side to the other so that it connects the end of a regular rung with the opposite end of the next rung up.

These concepts account for a key finding in early testing — the synergistic effects that result when a platinum compound is used in conjunction with an alkylating agent. Under these conditions, any repair mechanism operating within the cell would be less effective because it would be dealing with two types of lesions.



Dr. Rosenberg and Mrs. VanCamp study photomicrographs showing how certain platinum compounds cause bacteria to grow and enlarge without multiplying. This finding led to use of the compounds for tests which show that the compounds are remarkably potent against many forms of cancer in test animals.

Michigan State's "Strong to Distinguished" Graduate Programs

GRADUATE PROGRAM	COLLEGE*	NATIONAL RANKING 1964	NATIONAL RANKING 1969	CHANGE IN 5 YEARS BETTER	SAME	WORSE
BIOCHEMISTRY	HM, NS, ANR	U**	28	31	16	0
BOTANY	NS	13	9	27	40	2
CHEMISTRY	NS	U	24	28	35	1
ENTOMOLOGY	NS	U	12	31	26	5
MICROBIOLOGY	HM, NS, VM	U	25	30	19	0
MOLECULAR BIOLOGY	HM, NS	NI***	29	21	19	0
PHYSIOLOGY	HM, NS, VM	U	25	28	9	0
POPULATION BIOLOGY	HM, NS, ANR	NI	13	28	27	4
PSYCHOLOGY	HM, SS	22	20	23	35	2
SOCIOLOGY	HM, SS	17	17	20	44	3
ZOOLOGY	HM, NS	U	18	24	19	1

Listed above are the MSU graduate programs that were rated in the top category in a study sponsored by the American Council on Education. The numbers under "National Ranking" indicate MSU's standing in relation to other universities throughout the nation. For example, botany ranked 13th in the nation in 1964 and 9th in 1969. Only graduate programs in the "strong to distinguished" category received numerical ratings. The three columns to the right indicate the numbers of respondents who felt the MSU programs were better, the same or worse than five years ago.

* Colleges that jointly administer departments in which the graduate programs are taught: ANR – Agriculture and Natural Resources, HM – Human Medicine, NS – Natural Science and VM – Veterinary Medicine.

** U – program was unranked in 1964 survey.

*** NI – program was not included in 1964 survey.

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East Lansing 48823

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Robert D. Schuetz, Ph.D. — Acting Director

Charles R. Downs—Editor

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