drugs. However, in the presence of alcohol, such agents may overwhelm the homeostatic mechanisms of the cell by permitting an influx of lethal amounts of calcium. Such a mechanism might also explain alcohol-induced disease in organs that do not metabolize alcohol, including the heart, pancreas, and central nervous system.

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References and Notes

1. H. A. Edmondson and L. Schiff, in *Diseases of the Liver*, L. Schiff, Ed. (Lippincott, Philadelphia, ed. 4, 1975), p. 256; J. T. Galambos, *Prog. Liver Dis.* **4**, 567 (1972); H. A. Edmondson, R. L. Peters, T. B. Reynolds, O. T. Kuzma, *Ann. Intern. Med.* **59**, 646 (1963); J. T. Galambos, *Gastroenterology* **63**, 1026 (1972).
2. H. Popper, in *Alcohol and the Liver*, M. M. Fisher and J. G. Rankin, Eds. (Plenum, New York, 1977), p. 289.
3. E. Rubin and C. S. Lieber, *N. Engl. J. Med.* **290**, 128 (1974).
4. J. Moreland and A. Bessensen, *Biochim. Biophys. Acta* **474**, 312 (1977); K. D. Konrad and G. B. Reed, *Exp. Mol. Pathol.* **26**, 425 (1977).
5. J. Rosa and E. Rubin, *Lab. Invest.* **43**, 366 (1980).
6. E. Rubin, *N. Engl. J. Med.* **301**, 28 (1979).
7. H. Sarles, J. C. Sarles, R. Camatte, R. Muratore, M. Gaini, C. Guien, J. Pastor, F. LeRoy, *Gut* **6**, 545 (1965).
8. M. W. Hill, *Biochim. Biophys. Acta* **356**, 117 (1974); J. H. Chin and D. B. Goldstein, *Science* **196**, 684 (1977); M. Curran and P. Seeman, *ibid.* **197**, 910 (1977).
9. H. Rottenberg, D. E. Robertson, E. Rubin, *Lab. Invest.* **42**, 318 (1980).
10. F. A. X. Schanne, A. B. Kane, E. E. Young, J. L. Farber, *Science* **206**, 700 (1979); F. A. X. Schanne, F. G. Pfau, J. L. Farber, *Am. J. Pathol.* **100**, 25 (1980).
11. A. B. Kane, E. E. Young, F. A. X. Schanne, J. L. Farber, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 1177 (1980).
12. O. Strubelt, *Biochem. Pharmacol.* **29**, 1445 (1980).
13. F. A. X. Schanne, D. Glazer, J. L. Farber, unpublished results.
14. M. Frimmer, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **269**, 152 (1971); T. Wieland and O. Wieland, *Microbiol. Toxins* **8**, 249 (1972).
15. T. Wieland and H. Faulstich, *Crit. Rev. Biochem.* **5**, 185 (1978); A. M. Lengsfeld, I. Low, T. Wieland, P. Dancker, W. Hasselbach, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 2803 (1974); I. Low and T. Wieland, *FEBS Lett.* **44**, 340 (1974).
16. K. Decker and D. Keppler, *Prog. Liver Dis.* **4**, 183 (1972).
17. M. K. Roach, in *Biochemistry and Pharmacology of Ethanol*, E. Majchrowicz and E. P. Noble, Eds. (Plenum, New York, 1979), vol. 2, p. 67; J. W. Williams, M. Tada, A. M. Katz, E. Rubin, *Biochem. Pharmacol.* **24**, 293 (1970).
18. R. C. Reitz, W. Helsabeck, D. P. Mason, *Lipids* **8**, 80 (1973); J. M. Littleton and G. John, *J. Pharm. Pharmacol.* **29**, 579 (1977); J. H. Chin, L. M. Parsons, D. B. Goldstein, *Biochim. Biophys. Acta* **513**, 358 (1978); J. A. Thompson and R. C. Reitz, *Lipids* **13**, 540 (1978); A. J. Waring, H. Rottenberg, E. Rubin, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
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Astatine-211–Tellurium Radiocolloid Cures Experimental Malignant Ascites

Abstract. *An investigation of the efficacy of astatine-211–tellurium colloid for the treatment of experimental malignant ascites in mice reveals that this α-emitting radiocolloid can be curative without causing undue toxicity to normal tissue. By comparison, negatron-emitting phosphorus-32 as colloidal chromic phosphate had no antineoplastic activity. The most compelling explanation for this striking difference is the dense ionization and short range of action associated with α-emission. These results have important implications for the development and use of α-emitters as radiocolloid therapy for the treatment of human tumors.*

Although the potential of directed but unsealed sources of radiation for cancer therapy was recognized early (*1*), the therapeutic potential of such sources remains largely unrealized. The shortcomings have been both physical and biological; not only must the radionuclide deposit its energy within a short range of action, but it must also be localized preferentially within or in close proximity to tumor cells. If appropriate carriers can be devised and labeled with α-emitting radionuclides, these requirements should be satisfied.

The α-particles emitted in the process of radioactive decay (i) are directly ionizing, (ii) have energies (E_α) of 5 to 8 MeV, (iii) have a range of several cell diameters, and (iv) have a high linear energy transfer which results in high specific ionization; their radiobiological effects are largely independent of cellular oxygenation. Among the available α-emitters, ^{211}At appears the most promising (*2*). The average E_α is 6.8 MeV, and the range in water is 60 μm; the average linear energy transfer is 113 keV/μm. The chemical properties of astatine are quite different from those of iodine, its nearest halogen neighbor; nonetheless, astatine is concentrated by thyroid tissue, albeit less avidly than iodine (*3*).

We have prepared ^{211}At-tellurium colloid and investigated its therapeutic efficacy in a malignant ascites tumor model. The therapeutic ratio should be highly favorable in this system because the radionuclide is administered directly into the peritoneal cavity and is brought directly into contact with tumor cells. The decay characteristics of ^{211}At emissions are such that the critical normal tissue, intestinal mucosa, is largely spared the cytotoxic effects of the emitted α-radiations because of the thickness of the serosa and muscularis relative to the α-particle range. This model provides a quantitative experimental system in which to assess risk-benefit considerations that may be directly applicable for evaluating human radiocolloid therapy.

The ^{211}At was produced on the 60-inch cyclotron of the Brookhaven National Laboratory. Targets were prepared by melting bismuth-209 onto circular aluminum disks. These water-cooled targets were irradiated with α-particles (21 to 28 MeV) to produce the reaction ^{209}Bi(α,2n)^{211}At. The beam current was 10 to 15 μA, and the irradiation time was 2 to 6 hours. We isolated the ^{211}At from the target by distillation at 700°C and collected it in a trap containing 0.1*N* sodium hydroxide and 0.01*N* sodium bisulfite. Preparations were determined to be chemically pure by elemental analysis

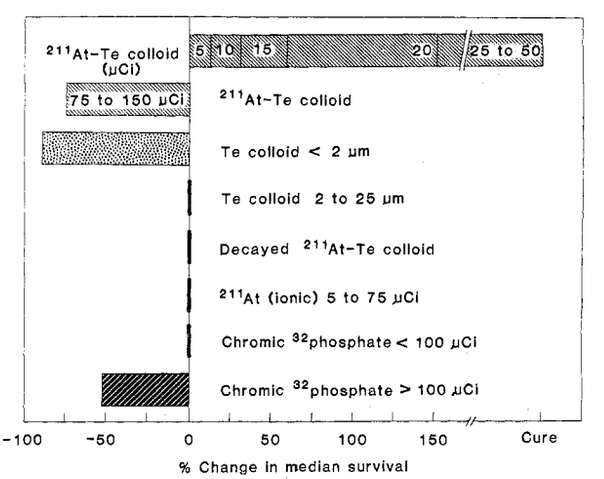

Fig. 1. Results of radiocolloid therapy on experimental malignant ascites in mice, expressed as the percentage of change in median survival. Each experimental group contained 10 to 12 mice; experiments were performed three times. Nonradioactive tellurium colloid < 2 μm in size is uniformly lethal in 3 days, presumably the result of pulmonary insufficiency.

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and by γ- and α-spectrometry. Finely ground elemental tellurium was chosen as the colloidal material because of its strong affinity for astatine at neutral and acidic *p*H (*4*). We prepared the tellurium particles just before use by first grinding elemental tellurium to a fine powder. Particles between 2 and 25 μm were obtained by a series of sedimentations, centrifugations, and filtrations. Then we acidified the ^{211}At with 2*N* nitric acid, added it to the tellurium colloid, and shook the mixture for 1 minute at room temperature. The radiocolloid was washed in distilled water; supernatants from these washes contained < 0.5 percent unbound ^{211}At.

The tumor used in these experiments arose spontaneously in the ovary of a C3H mouse and has been maintained in its ascitic form by serial intraperitoneal transplantation in female C3HeB/FeJ mice (*5*). A regular relationship has been observed between the size of the tumor cell inoculum and the median time to death (*6*). Consequently, therapeutic efficacy can be expressed not only as the percentage increase in median survival but also as a cellular surviving fraction. Such a calculation implies little or no repair of radiation damage, an assumption that is substantiated by in vitro studies (*7*).

Single graded doses of the ^{211}At-tellurium colloid were administered into the peritoneal cavity 24 hours after intraperitoneal injection of 10^6 tumor cells (Fig. 1). Mice treated with < 50 μCi of radiocolloid demonstrated a dose-related increase in median survival; furthermore, doses of 25 to 50 μCi were curative in all animals so treated. Although some mild morbidity was manifested by weight loss and change in fur nap with doses of 25 to 50 μCi, there were no acute deaths. Doses of radiocolloid ≥ 75 μCi were uniformly fatal in 5 to 7 days, presumably the result of gastrointestinal injury. When the cellular surviving fraction after treatment with ^{211}At colloid was expressed as a semilogarithmic function of dose (Fig. 2), a linear relationship with no shoulder in the low-dose region was observed at doses < 20 μCi.

Cured animals observed for at least 200 days were sleek, agile, and alert. Histological sections of major organs showed no evidence of tumor and were unremarkable as compared to those of untreated mice except for the thyroid. Thyroid tissue, which was identified with much less frequency in treated mice, contained considerable fibrosis as well as granular and refractile material. These findings probably reflect some in vivo release of ^{211}At from the tellurium colloid. No second tumors were identified; however, the number of cured animals was small and the duration of follow-up relatively short. Although intravenous injection of ionic ^{211}At in comparable doses has been reported to induce mammary tumors, endometrial polyps, and endocrine adenomas in immature rats (*8*), these adverse effects may be minimized under conditions of directed colloidal administration. Moreover, thyroid uptake and other potentially adverse effects of ^{211}At may be prevented by preliminary treatment with iodide.

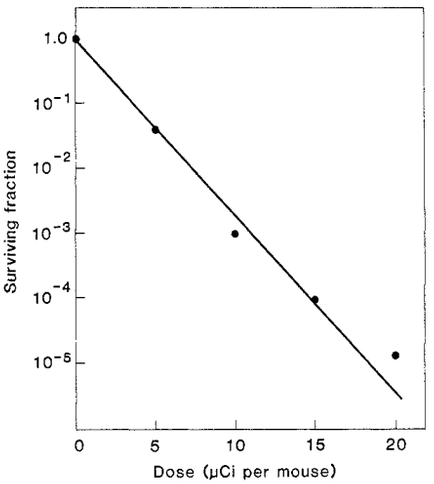

Fig. 2. Results of ^{211}At colloid therapy expressed as cellular survival fraction. The slope of the line was determined by semilogarithmic linear regression analysis. The correlation coefficient is > .99. The dose to reduce survival to 0.37 is 1.6 μCi.

The therapeutic efficacy of ^{211}At colloid was compared with that of chromic phosphate labeled with ^{32}P, a radiocolloid that is used as adjuvant therapy to surgical treatment in early stage human ovarian cancer (*9*) and has been used to perform radiation synovectomies in patients with rheumatoid arthritis (*10*). In this tumor model, the labeled chromic phosphate had no antineoplastic activity (Fig. 1); doses > 100 μCi were uniformly fatal within 5 to 7 days, the result of gastrointestinal toxicity (*11*).

The ^{211}At-tellurium colloid is highly effective in the treatment of experimental malignant ascites. Not only is the prolongation of median survival dose-related, but this α-emitting radiocolloid can also be curative without serious morbidity. The most compelling reason for this increased efficacy is the direct and densely ionizing character of the emitted α-radiations. In comparison with ^{32}P, ^{211}At radiations have 1/100 of the length but ten times the energy deposition per unit path length. Thus, the indirect and sparse ionizations of ^{32}P appear to be insufficient to kill tumor cells in this system despite their close physical proximity to tumor cells. Because 1-day-old ascitic tumor cells are considered to be well oxygenated, the increased radiobiological effectiveness of ^{211}At relative to ^{32}P probably reflects differences in linear energy transfer rather than hypoxic cell sensitization by the emitted α-radiations.

These experiments form the basis for further investigations and development of α-emitting radiocolloids. The most obvious applications of such radiocolloids are in the therapy of ascites and surface-spreading abdominal and pelvic malignancies. Another use may be in the treatment of rheumatoid arthritis, particularly in selected joints where the synovial thickness does not exceed the α-particle range.

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References and Notes

1. C. Regaud and A. Lacassagne, *Radiophysiol. Radiother.* **1** (fascicle I), 95 (1927).
2. D. R. Corson, K. R. MacKenzie, E. Segré, *Phys. Rev.* **58**, 672 (1940).
3. A. K. Lavrukhina and A. A. Pozdnyakov, *Analytical Chemistry of Technetium, Promethium, Astatine, and Francium* (Ann Arbor–Humphrey Science, London, 1970), pp. 227–260; J. G. Hamilton and M. H. Soley, *Proc. Natl. Acad. Sci. U.S.A.* **26**, 483 (1940).
4. M. Bochvarova, D. K. Tyung, I. Dudova, Y. V. Norseev, V. A. Khalkin, *Sov. Radiochem.* **14**, 889 (1972).
5. E. Fekete and M. A. Farringno, *Cancer Res.* **12**, 438 (1952).
6. W. D. Bloomer and S. J. Adelstein, *Nature (London)* **265**, 620 (1977).
7. C. R. Harris, S. J. Adelstein, T. J. Ruth, A. P. Wolf, *Radiat. Res.* **74**, 590 (1978).
8. J. M. Hollander, I. Perlman, G. T. Seaborg, *Rev. Mod. Phys.* **25**, 469 (1953); P. W. Durbin, C. W. Asling, M. E. Johnston, M. V. Parrott, N. Jeung, M. H. Williams, J. G. Hamilton, *Radiat. Res.* **9**, 378 (1958).
9. R. D. Pezner, K. R. Stevens, Jr., D. Tong, C. V. Allen, *Cancer (Philadelphia)* **42**, 2563 (1978).
10. M. A. Winston, R. Bluestone, A. Cracchiolo III, W. A. Blahd, *J. Nucl. Med.* **14**, 886 (1973).
11. A. G. Huvos, E. E. Rogoff, B. S. Hilaris, E. W. Hahn, *Radiology* **113**, 203 (1974).

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