Distribution of Tracer Doses of Methionine Tagged with Radiosulfur in Normal and Neoplastic Tissue*

ARNOLD J. KREMEM, M.D., PH.D.,** SAMUEL W. HUNTER, M.D., GEORGE E. MOORE, M.D., AND CLAUDE R. HITCHCOCK, M.D.

(**From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota)

It is well recognized by clinicians and experimentalists that tumor tissue will continue to grow while the organism as a whole loses weight and is unable to maintain itself in nutritional equilibrium. This suggests that growing tumor cells can more efficiently procure available protein building blocks than the remainder of the body. Since essential amino acids must be utilized for fabrication into new protoplasm, a study of the distribution in tumor bearing mice of tracer doses of methionine tagged with S\textsuperscript{35} has been undertaken in an effort to ascertain if by this means tagged radioactive substances might be introduced into tumor cells.

Schoenheimer (6) and his associates using isotopes of hydrogen, carbon, and nitrogen have demonstrated that every protein of the body is continuously changing and renewing its structure. Rapid amino shifts among the amino acids of the proteins of the body were observed. By measuring the concentration of isotopic nitrogen in a tissue at a certain time an index of the chemical activity of its proteins could be obtained. Serum proteins always contained the highest concentrations of isotopic nitrogen, and then in order of magnitude came viscera, muscles and skin. Shemin and Rittenberg (7) found the activity of the proteins of liver, plasma and intestinal tract to be high compared to the protein of muscle, skin and connective tissue. Rats inoculated with a transplantable sarcoma were fed labeled glycine. The highest immediate uptake of N\textsuperscript{14} was observed in liver tissue, with the tumor protein taking on the labeled glycine almost as rapidly as liver. However, the tagged protein of tumor was replaced at a rate only one-half as rapid as that of liver tissue, so that after twenty-four hours a higher concentration of N\textsuperscript{14} was observed in tumor tissue than in liver. A higher initial rise of N\textsuperscript{14} was observed at the periphery or rapidly growing portion of the tumor than in its central portion.

In studies on rats with transplanted lymphosarcoma given d-l-tyrosine labeled with radioactive carbon, Winnick and associates (10) found the uptake of isotope by tumor tissue to be somewhat less than that of intestinal mucosa, kidney and plasma protein, but greater than the other organs of the body. The tumor tissue again seemed to give up its isotope at a slower rate than the other tissues. Reid and Jones (5) studied the uptake of tyrosine tagged with radioactive carbon in mice with transplanted melanomasarcoma, and, although they observed appearance of the amino acid in the tumor, varying degrees of radioactivity were also found in the other tissues of the body. They state that the concentration of radioactivity found in tumor tissue was not sufficient to offer therapeutic possibilities.

Friedberg (2, 3), after giving d-l-methionine tagged with S\textsuperscript{35} to rats, observed the intestinal mucosa to have the highest specific activity. Next in activity were pancreas, kidney, plasma protein, liver, testes, heart, brain and muscle. The pattern was the same regardless of oral or intravenous administration of the methionine. The peak of the curve was reached at fifteen hours and then declined. However, at forty-two hours the relative distribution by organs remained as above. Tarver and Morse (8) observed in rats, after feeding labeled methionine, a tendency for the isotope concentration to approach a relatively constant level in the various tissues after five days. After fourteen days less than twenty per cent of administered methionine sulfur was excreted in the urine, and eight per cent had appeared in the feces.

METHODS

Two series of experiments were carried out using essentially the same methods in each. In Experiment 1 fifteen mice of “A” and “C\textsubscript{3}H” strain were inoculated subcutaneously with an ependy-
moblastoma two weeks before the start of the experiment. These mice, weighing approximately twenty grams, were then given by gastric intubation 0.2 cc. of a solution of d-l-methionine (1.5 mg.) tagged with S\textsuperscript{35} (0.75 microcuries). Two mice were sacrificed at six, twelve, forty-eight and seventy-two hour periods, and one mouse was sacrificed every forty-eight hours thereafter. All of the liver, brain, subcutaneous ependymoblastoma, gastric content, blood and striated muscle was removed, immediately minced and extracted with a fifty-fifty mixture of ethyl ether and ninety-five per cent ethyl alcohol. Following extraction, the tissues were baked, pulverized and weighed. Since S\textsuperscript{35} emits beta particles which will not penetrate more than 0.015 Gm./sq. cm., a layer of at least 15 mg./sq. cm. of dried powder was used in the counting containers. As the amount of radiation from tissue is constant after the critical thickness of 15 mg./sq. cm. is exceeded (1, 4, 9), the absolute radiation values of the various tissues were compared.

In Experiment 2, eight mice of "A" strain with spontaneous breast cancer were used, each receiving 0.92 microcuries of radiomethionine (1.8 mg.) administered as above. At twelve, twenty-four, forty-eight and seventy-two hours two mice were sacrificed, and kidney, brain, blood, stomach, intestine, colon, liver, breast cancer and muscle were studied. Also, urine and feces from two mice were collected separately for seventy-two hours.

---

1 These tumors were originally induced by methyl cholangrthine injection into the brains of mice of the same strains.
2 Methionine used in these studies was supplied through the courtesy of Dr. Paul Gyorgy, Professor of Clinical Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania.
3 Obtained through the courtesy of Dr. John Bittner, Professor of Cancer Biology, University of Minnesota, Minneapolis, Minnesota.

---

**RESULTS**

Figures 1 and 2 show the results of Experiment 1. The concentrations of S\textsuperscript{35} in liver and subcutaneous ependymoblastoma roughly paralleled each other at six hours, with the concentration in the tumor then exceeding that in the liver from twelve to seventy-two hours. After seventy-two hours the concentration of S\textsuperscript{35} in all tissues began to equilibrate and remained that way up to eighteen days. For the first seventy-two hours the concentration of S\textsuperscript{35} in the subcutaneous ependymoblastoma was roughly four times that of normal brain.

Figure 3 portrays the distribution of S\textsuperscript{35} in mice with spontaneous breast cancer. In this study the concentration in liver exceeded somewhat the activity of the breast cancer, which in turn was equalled by kidney and intestinal wall.

Figure 4 shows the rate of appearance of S\textsuperscript{35} in the urine. As will be noted, it is highest initially and gradually levels off at seventy-two hours. During this seventy-two hour period, twenty-six per cent of the total injected dose of S\textsuperscript{35} appeared...
that finds its way into the proteins of tumor cells may reside there longer than in the normal functioning organs of the body. Such a response seems to be suggested in Figure 1, as has also been noted by Shemin and Rittenberg (7) and Winnick and associates (10). However, with time the tracer substance in the tumor tissue did more or less equilibrate with the remainder of the protein tissues of the body as one would expect from the work by Schoenheimer (6), who demonstrated a continuous shifting of peptide linkages in the proteins of the body.

SUMMARY

1. The distribution of tracer doses of d-l-methionine tagged with radiosulfur has been studied in mice with spontaneous and transplanted neoplasms.
2. These studies indicate a high initial concentration of radiomethionine results in liver, tumor, kidney and intestinal wall.
3. Any therapeutic possibilities relating to introducing radioactive sulfur into tumor cells must await animal trial.

REFERENCES

Distribution of Tracer Doses of Methionine Tagged with Radiosulfur in Normal and Neoplastic Tissue

Arnold J. Kremen, Samuel W. Hunter, George E. Moore, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/9/3/174

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.