**Title**
INFLUENCE OF TUMORS ON THE LIVER CONCENTRATION OF RADIO-ACTIVE STILBAMIDINE



**Authors**
Weaver, John C.
Tolbert, B.M.
Kreuckel, B.J.

**Publication Date**
1950-10-23

UCRL-963

UNCLASSIFIED



UNIVERSITY OF CALIFORNIA — BERKELEY

RADIATION LABORATORY

## DISCLAIMER

Copy 2

UCRL-963
Unclassified Distribution

UNIVERSITY OF CALIFORNIA

Radiation Laboratory

Contract No. W-7405-eng-48

UNCLASSIFIED

# INFLUENCE OF TUMORS ON THE LIVER CONCENTRATION OF RADIOACTIVE STILBAMIDINE

John C. Weaver, Bert M. Tolbert and Barbara J. Kreuckel

October 23, 1950

Berkeley, California

| INSTALLATION | Number of Copies |
|---|---|
| Argonne National Laboratory | 8 |
| Armed Forces Special Weapons Project | 1 |
| Atomic Energy Commission - Washington | 2 |
| Battelle Memorial Institute | 1 |
| Brush Beryllium Company | 1 |
| Brookhaven National Laboratory | 4 |
| Bureau of Medicine and Surgery | 1 |
| Bureau of Ships | 1 |
| Carbide and Carbon Chemicals Division (K-25 Plant) | 4 |
| Carbide and Carbon Chemicals Division (Y-12 Plant) | 4 |
| Chicago Operations Office | 1 |
| Columbia University (J. R. Dunning) | 1 |
| Columbia University (G. Failla) | 1 |
| Dow Chemical Company | 1 |
| H. K. Ferguson Company | 1 |
| General Electric Company, Richland | 3 |
| Harshaw Chemical Corporation | 1 |
| Idaho Operations Office | 1 |
| Iowa State College | 2 |
| Kansas City Operations Branch | 1 |
| Kellex Corporation | 2 |
| Knolls Atomic Power Laboratory | 4 |
| Los Alamos Scientific Laboratory | 3 |
| Mallinckrodt Chemical Works | 1 |
| Massachusetts Institute of Technology (A. Gaudin) | 1 |
| Massachusetts Institute of Technology (A. R. Kaufmann) | 1 |
| Mound Laboratory | 3 |
| National Advisory Committee for Aeronautics | 1 |
| National Bureau of Standards | 3 |
| Naval Medical Research Institute | 1 |
| Naval Radiological Defense Laboratory | 2 |
| New Brunswick Laboratory | 1 |
| New York Operations Office | 3 |
| North American Aviation, Inc. | 1 |
| Oak Ridge National Laboratory | 8 |
| Patent Branch - Washington | 1 |
| Rand Corporation | 1 |
| Sandia Corporation | 2 |
| Santa Fe Operations Office | 2 |
| Sylvania Electric Products, Inc. | 1 |
| Technical Information Division (Oak Ridge) | 15 |
| Armament Division, Deputy for Research and Development (Capt. Glenn Davis) | 1 |
| Assistant for Atomic Energy, Deputy Chief of Staff (Col. Robert E. Greer) | 1 |
| Chief of Documents and Disseminations Branch (Col. J. E. Mallory) | 1 |
| USAF Assistant for Research Director of Research and Development, Deputy Chief of Staff (Col. B. G. Holzman) | 1 |

| INSTALLATION | Number of Copies |
|---|---|
| Electronic Systems Division (Mr. E. C. Trafton) | 1 |
| Chief of Scientific Advisors (Dr. Theodore von Karman) | 1 |
| USAF, Eglin Air Force Base (Major A. C. Field) | 1 |
| USAF, Kirtland Air Force Base (Col. Marcus F. Cooper) | 1 |
| USAF, Maxwell Air Force Base (Col. F. N. Moyers) | 1 |
| USAF, NEPA Office | 2 |
| USAF, Offutt Air Force Base (Col. H. R. Sullivan, Jr.) | 1 |
| USAF Surgeon General, Medical Research Division (Col. A. P. Gagge) | 1 |
| USAF, Wright-Patterson Air Force Base (Rodney Nudenberg) | 1 |
| U. S. Army, Atomic Energy Branch (Lt. Col. A. W. Betts) | 1 |
| U. S. Army, Army Field Forces (Captain James Kerr) | 1 |
| U. S. Army, Commanding General, Chemical Corps Technical Command (Col. John A. MacLaughlin thru Mrs. Georgia S. Benjamin) | 1 |
| U. S. Army, Chief of Ordnance (Lt. Col. A. R. Del Campo) | 1 |
| U. S. Army, Commanding Officer, Watertown Arsenal (Col. Carroll H. Deitrick) | 1 |
| U. S. Army, Director of Operations Research (Dr. Ellis Johnston) | 1 |
| U. S. Army, Office of Engineers (Allen O'Leary) | 1 |
| U. S. Army, Office of the Chief Signal Officer (Curtis T. Clayton thru Maj. George C. Hunt) | 1 |
| U. S. Army, Office of the Surgeon General (Col. W. S. Stone) | 1 |
| U. S. Geological Survey (T. B. Nolan) | 2 |
| U. S. Public Health Service | 1 |
| University of California at Los Angeles | 1 |
| University of California Radiation Laboratory | 5 |
| University of Rochester | 2 |
| University of Washington | 1 |
| Western Reserve University | 2 |
| Westinghouse Electric Company | 4 |
| R. F. Bacher (California Institute of Technology) | 1 |
| Cornell University | 1 |
| Total | 140 |

Information Division
Radiation Laboratory
University of California
Berkeley, California

# INFLUENCE OF TUMORS ON THE LIVER CONCENTRATION OF RADIOACTIVE STILBAMIDINE

John C. Weaver, Bert M. Tolbert and Barbara J. Kreuckel

Donner Laboratory of Medical Physics and
Radiation Laboratory, University of California, Berkeley.

October 23, 1950

## ABSTRACT

A series of normal and tumor mice were injected with stilbamidine-amidine-$C_2^{14}$. After 96 hours, the livers were removed and analyzed for radioactivity. Much higher and distinctly abnormal concentrations of $C^{14}$ were found in the tumor-bearing A and dba strain mice as compared to the controls. Some data for C57, Bagg and McDonnel strain mice are also present.

The relation of this phenomenon to possible abnormalities in nucleic acid concentration in tumor-bearing mice is discussed.

UCRL-963

# INFLUENCE OF TUMORS ON THE LIVER CONCENTRATION OF RADIOACTIVE STILBAMIDINE*

John C. Weaver, Bert M. Tolbert and Barbara J. Kreuckel

Donner Laboratory of Medical Physics ** and

Radiation Laboratory, University of California, Berkeley.

October 23, 1950

During the course of studies with radioactive stilbamidine, certain findings have appeared that are of sufficient interest to warrant a preliminary report.

Kopac (1) reported that stilbamidine destroyed the neoplastic cells in cultures of rat mammary adenocarcinoma and transplanted lymphosarcoma. Snapper (2) further studied this drug and found inclusion bodies containing stilbamidine in the cytoplasm of plasma cells in patients with multiple myeloma. Accordingly, $C^{14}$-labeled stilbamidine was prepared and its metabolic distribution in normal mice and a patient with multiple myeloma was undertaken (3,4). These experiments established that the oxidation to $C^{14}O_2$ of stilbamidine by the body is negligible.

These studies suggested the possibility of investigating the localization and distribution of activity in mice with various types of tumors. Accordingly, normal and tumor bearing mice were injected intraperitoneally

---

* Supported in part by the Atomic Energy Commission.

** Division of Medical Physics, Department of Physics.

with 0.4 mg. ($4.50 \times 10^6$ dis./mg.) of stilbamidineamidine-$C_2^{14}$ dissolved in 0.05 ml. saline. The $C^{14}$-labeled stilbamidine used for this experiment was synthesized by Dr. J. C. Reid (5).

Ninety-six hours after injection the mice were killed with ether and autopsied. Liver, spleen, kidneys, pancreas and tumors were removed, dried in vacuum, weighed and burned over copper oxide and the resulting carbon dioxide was converted to barium carbonate and the radioactivity measured with a proportional counter*(6). The mice were kept in separate cages designed to prevent contamination of food and water with excreta.

Tables I and II show the total concentration of radioactivity present in the livers of normal and tumor mice 96 hours after injection. The total liver activity is given as percent of injected dose. It is evident that very much higher and distinctly abnormal concentrations of radioactivity are present in the livers of the tumor bearing mice as compared to the controls for the A and dba strains. With the number of animals used, no correlation between tumor weight and liver concentration of radioactivity can be established. However, there appears to be some correlation between mouse weight and liver concentration of radioactivity. Thus, there is a small increase in liver concentration in the normal group with increasing mouse weights. Conversely, there appears to be a drop in liver concentration in tumor mice with increasing mouse weights. The number of such mice is inadequate to definitely establish this correlation. The three mice with lymphatic leukemia were found to have elevated levels of radioactivity in the liver, but

---

* Nucleometer, Radiation Counter Laboratories, Chicago, Illinois.

TABLE I

Activity Found in the Livers of Tumor Mice 96 Hours after Injection of Labeled Stilbamidine

| No. | Strain | Sex | Age (Months) | Mouse Weight, gms. | Tumor Weight, wet, gms. | Liver Weight, dry, gms. | Total Liver Activity (% of Injected Dose | Type of Tumor |
|---|---|---|---|---|---|---|---|---|
| XS1 | A | male | 6 | 24 | 4.45 | 0.272 | 40 | Sarcoma |
| XCW1 | A | male | 6 | 23 | 2.09 | 0.265 | 23 | Mammary |
| X2S1 | A | male | 5 | 23 | 4.45 | 0.321 | 23 | Sarcoma |
| X3S1 | A | male | 5 | 21 | 3.39 | 0.310 | 30 | Sarcoma |
| X4S1 | A | male | 5 | 22 | 4.26 | 0.299 | 31 | Sarcoma |
| X5S1 | A | male | 5 | 24 | 4.76 | 0.326 | 31 | Sarcoma |
| X6S1 | A | male | 6 | 21 | large | 0.176 | 19 | Sarcoma |
| X7S1 | A | male | 6 | 21 | large | 0.184 | 21 | Sarcoma |
| XG2 | dba | male | 10 | 24 | 2.27 | 0.407 | 19 | Melanoma |
| XG3 | dba | male | 8 | 32 | 4.67 | 0.559 | 12 | Melanoma |
| XG4 | dba | male | 8 | 29 | 7.06 | 0.547 | 11 | Melanoma |
| XLL1 | McDowell | female | 6 | 26 | 0.06 | 0.430 | 12 | Lymphatic leukemia |
| XLL2 | McDowell | female | 18 | 20 | 0.30 | 0.296 | 35 | Lymphatic leukemia |
| XLL3 | McDowell | female | 6 | 19 | 0.16 | 0.258 | 33 | Lymphatic leukemia |
| XML1 | C57 | male | 6 | 30 | 0.58 | 0.573 | 24 | Myelogenous |
| XCB1 | C57 | female | 6 | 36 | 6.03 | 0.659 | 41 | Mammary |

TABLE II

Activity Found in the Livers of Normal Mice 96 Hours after Injection of Labeled Stilbamidine

| No. | Strain | Sex | Age (Months) | Mouse Weight, gms. | Liver Weight, dry, gms. | Total Liver Activity (% of Injected Dose) |
|---|---|---|---|---|---|---|
| SC43 | A | male | 10 | 24 | .356 | 2.5 |
| SC48 | A | male | 12 | 27 | .496 | 7.7 |
| SC49 | A | male | 6 | 24 | .535 | 7.7 |
| SC50 | A | male | 6 | 24 | .539 | 7.5 |
| SC57 | A | male | 5 | 20 | .336 | 4.4 |
| SC58 | A | male | 5 | 22 | .380 | 4.8 |
| SC59 | A | male | 5 | 22 | .389 | 2.0 |
| SC60 | A | male | 5 | 22 | .408 | 3.0 |
| SC40 | Bagg | male | 10 | 32 | .512 | 5.1 |
| SC41 | Bagg | male | 10 | 34 | .513 | 7.5 |
| SC42 | Bagg | male | 10 | 32 | .579 | 6.4 |
| SB1 | dba | female | 18 | 28 | .336 | 8.0 |
| SC46 | dba | male | 8 | 23 | .473 | 4.6 |
| SC47 | dba | male | 8 | 25 | .517 | 5.0 |
| SC51 | C57 | female | 6 | 23 | .406 | 30. |
| SC52 | C57 | female | 6 | 21 | .420 | 17. |
| SC53 | C57 | male | 6 | 24 | .459 | 24. |
| SC54 | C57 | male | 6 | 24 | .443 | 34. |
| SC55 | C57 | male | 13 | 32 | .575 | 36. |
| SC56 | C57 | male | 13 | 32 | .57 | 30. |

the significance of this group is not known since no control determinations have been made for mice of the C-58 strain.

It is of considerable interest that the normal C-57 strain mice have liver concentrations of radioactivity in the same range as mice with neoplasms. Whether this is unique for mice which develop spontaneous non-epithelial neoplasms or whether it is coincidental remains for further study. Here increasing mouse weights appears to be associated with increasing liver concentrations of radioactivity following the pattern of the other normals in this respect. More mice with tumors will need to be studied before the effect of tumors on liver concentration in this strain can be known.

The specific activity of liver for the tumor mice averaged 3,464 dis./mg./min. and for the strains A, dba and Bagg controls 498 dis./mg./min. For the normal strain C-57 mice the specific activity averaged 2,726 dis./mg./min. No definite correlation could be established between tumor weight or mouse weight and specific activity.

The concentrations of activity in the kidneys and spleens of the tumor mice averaged 7.5 and 0.24 percent of injected dose respectively and are a little greater than in the normals, but the differences are not significant for the number of animals studied to date. The concentration of radioactivity in the pancreas was found to be intermediate between spleen and kidney and is in the same range for both control and tumor mice. None of the tumors contained more than traces of activity which compares with Snapper's qualitative results in which he found no evidence of localization of stilbamidine in transplantable lymphosarcoma and mammary carcinoma (7).

Kopac has shown that stilbamidine dissociates protamine-nucleate complexes with the release of partially denatured protamine molecules and the formation of an insoluble stilbamidine-nucleate complex (8). Snapper and his group have presented evidence that stilbamidine is capable of specifically combining with ribose nucleic acid in the cytoplasm of myeloma cells (2). Kelly and Jones (9) have found a considerable increase in turnover rates of desoxypentose nucleic acid in the liver, spleen and kidneys of tumor mice with transplanted mammary cancer as compared with turnover rates in normal mice. The behavior of ribose nucleic in this regard is not known.

It seems possible, then, that stilbamidine precipitates in the liver cells as an insoluble stilbamidine-nucleate complex and the increased amounts present in tumor bearing animals are related to increased formation of certain nucleic acids in these livers. Studies are being made to determine the chemical nature of the stilbamidine complex or derivative that has concentrated in these livers and in what elements of the liver this material is located.

In a patient with multiple myeloma, who was injected with $C^{14}$-labeled stilbamidine, it was found that an unexpectedly high concentration of radioactivity was present in the liver at autopsy three months later (4). While this fits the pattern of the mouse results, more studies of humans with and without malignant disease will be necessary before significance can be attached to this isolated finding.

The authors wish to thank Professors J. H. Lawrence, H. B. Jones and M. Calvin for their interest and help in this work and Mr. Saburo Ikeda for radioactive measurements.

## BIBLIOGRAPHY

1. Kopac, M. J., Cancer Res. (Proc.) 1946, 6, 491.

2. Snapper, I., Mirsky, A. E., Ris, H., Schneid, B. and Rosenthal, M., Blood, 1947, 2, 311.

3. Reid, J. C. and Weaver, J. C., (to be published).

4. Weaver, J. C., Reid, J. C., Krueckel, B. J., and Lawrence, J. H., (to be published).

5. Reid, J. C., A.E.C.U. 586, 1949.

6. Dauben, W. G., Reid, J. C. and Yankwich, P. E., Anal. Chem. 1947, 19, 828.

7. Snapper, I., Schneid, B., Greenspan, E. and Lieben, F., Bull. N. Y. Acad. Med. 1950, 26, 269.

8. Kopac, M. J., Trans. N. Y. Acad. Sci. 1945, 8, 5.

9. Kelly, L. S. and Jones, H. B., Science 1950, 111, 333.