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May 26, 1964


REPOSITORY OAK RIDGE / ENERGY SYSTEMS / ONC X-10

COLLECTION OFFICE OF RADIATION PROTECTION

BOX No. K2 MORGAN'S FILES (PAST DIV. DIR. OF HEALTH PHYSICS)

FOLDER BCD 45000, WING 4 ATTIC


Dr. Eugene P. Cronkite
Medical Department
Brookhaven National Laboratory
Upton, Long Island, New York

Dear Dr. Cronkite:

Enclosed is a copy of a report dealing with estimation of dose from tritiated thymidine in humans. You will recall that I discussed this with you at the Radiation Research Society meeting in Miami Beach and you suggested that I send it to you to look over.

You will note the authors conclude that the average total dose received by cell nuclei from tritiated thymidine is about 7100 times greater than that from an equal injection of tritiated water, while the average initial dose rate is 450 times higher than tritiated water. Thus, for the case of injected tritiated thymidine, a permissible level would be 1/7100 the permissible level of tritiated water. Do you agree with this method of estimating a level for injected tritiated thymidine?

Also, the authors discuss the case of ingestion, and here it is indicated that the MPC would be approximately 1/100 of that for tritiated water. Do you agree that this would be a permissible level for ingestion of tritiated thymidine?

The authors make these estimates on the basis of dose to cell nuclei, and, as you pointed out, the ingestion of the thymidine will result in the labelling of the cells in the gut. As far as I can see, in this report the authors have not made any dose estimations for the gut.

In view of the fact that the ICRP Committee 2 is going to meet in New York during the week of June 22 and discuss this problem, would it be possible for you to comment on these estimations before that time?


1026274

A-00132

Human Subjects Project

Dr. Snyder has not yet returned from Europe, but if he agrees that I should come and work on your data for estimating an MPC, I would probably come before this meeting if this is convenient and agreeable with you.

Very truly yours,

Original Signed By

S. R. Bernard
Health Physics Division

P.S. I have written to Verly for his data too.

Enclosure:
"A Comparison of the Risk from Tritiated Thymidine and Tritiated Water," by Myers and Vennart

SRB:ss

bc: K. Z. Morgan
W. S. Snyder

1026275

AUTHOR: Geigy Pharmaceuticals

Termatrex Number _____

TITLE: CHEMICAL COMPOSITION OF THE BODY AND SOME OF ITS ORGANS

JOURNAL: DOCUMENTA GEIGY SCIENTIFIC TABLES, page 282, Basle, Switzerland (1959)

REPORT No:

FILED:

Abstracted by: C. F. Holoway Date: 31 July 1964

KEY WORDS:

ANIMAL:
man
cow
dog
goat
guinea pig
monkey
mouse
pig
rabbit
rat
sheep
other mammals
other vertebrates
Cells and Microorganisms

AGE:
embryo
feotus
*infant
young
adult
aged

SEX:
male
female

CONDITION:
pathological
grossly normal

METHOD:
single
multiple
continuous
inhalation
oral
IV
IM
IP
SC
IT
submersion
surface absorption

ISOTOPE:
$Sr^{85}$, $Pu^{239}$, etc.

ELEMENT:
Sr, U-nat, etc.
Sulfur

LEVEL:
tracer
chronic
toxic
high

CHEMICAL FORM:
acetate
carbonate
citrate
halide
nitrate
oxide
phosphate
sulphate
thymidine
organic
Other form
carrier free

PHYSICAL FORM:
aerosol
gas
particle data
solid
solution (suspension or colloid)

LENGTH OF EXPERIMENT:
hour; day; week; month; year

SOLUBILITY:
Soluble - acid; blood; GI tract; Lung; Water
InSoluble - acid; blood; GI tract; Lung; Water

STANDARD ANIMAL DATA:
Intake/day: air; food; water
Elimination/day: air; food; water; elements
Composition: whole body; body organs
Mass: whole body, body organs
Radius: body organs

DIET DATA:
food; water
Diet: composition (elements)
Diet: % water; % solid

OTHER DATA (discussed):
Chemical toxicity
Radiotoxicity
Uptake
RBE and/or MF
MPC's
Power Function
Exponential
Variability

OTHER DATA:
bibliography
$f_1$ (fraction from GI tract to blood)
$f_2$ (fraction in organ of reference of that in total body)
$f_2'$ (fraction from blood to organ of reference)
$f_a$ (fraction in organ of reference by in halation)
$f_w$ (fraction in organ of reference by ingestion)
$T_b$ (biological half-life)
$T_r$ (radioactive half-life)
T (effective half-life)
$f_f$ (fraction in feces)
$f_u$ (fraction in urine)
fecal to urine ratio
blood to urine ratio

OTHER DATA:
* New-born

| WHOLE BODY AND BODY ORGANS | %deposited | %retention | Burden | distribution | Elimination Urine | Elimination Fecal | Time |
|---|---|---|---|---|---|---|---|
| WHOLE BODY | | | | | | | |
| Adrenal | | | | | | | |
| Aorta | | | | | | | |
| Blood | | | | ✓ | | | |
| Bone | | | | ✓ | | | |
| Brain | | | | ✓ | | | |
| Breast | | | | | | | |
| Gastrointestinal tract | | | | ✓ | | | |
| Esophagus | | | | | | | |
| Stomach | | | | | | | |
| Duodenum | | | | | | | |
| Jejunum | | | | | | | |
| Ileum | | | | | | | |
| Cecum | | | | | | | |
| Sigmoid colon | | | | | | | |
| Rectum | | | | | | | |
| Heart | | | | ✓ | | | |
| Kidney | | | | | | | |
| Larynx | | | | | | | |
| Liver | | | | ✓ | | | |
| Lung | | | | ✓ | | | |
| Muscle | | | | ✓ | | | |
| Diaphragm | | | | | | | |
| Pectoral | | | | | | | |
| Psoas | | | | | | | |
| Omentum | | | | | | | |
| Ovary | | | | | | | |
| Pancreas | | | | | | | |
| Prostate | | | | | | | |
| Skin | | | | ✓ | | | |
| Spleen | | | | ✓ | | | |
| Testis | | | | | | | |
| Thymus | | | | | | | |
| Thyroid | | | | | | | |
| Tongue | | | | | | | |
| Trachea | | | | | | | |
| Urinary bladder | | | | | | | |
| Uterus | | | | | | | |
| Vagina | | | | | | | |

June 18, 1964

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TX-3514 (6-64)

Abstract:

Data needed for calculating μg S/gm. wet tissue for Table 7, page 150, ICRP Handbook, are given:

| | |
|---|---|
| Skeleton: | 11.6% of body weight |
| Total skeleton fat | 10 % |
| Sulfur content of fat-free skeleton | 0.137 g. S/100 g. fat-free bone |
| Skin | 17.4% of body weight |
| Total skin fat | 15 % |
| Sulfur content of fat-free skin | 0.375 g. S/100 g. fat-free skin |

from which data one calculates:

10 grams of sulfur in the whole skeleton of standard man.
0.388 grams of sulfur in the whole skin of standard man.

and therefore the following values which are not in the Handbook:

1230 μg S/gm. bone
3190 ug S/gm. skin.

Data is also available to calculate Handbook values for: muscle, blood, brain, liver, intestines, lungs, heart and spleen.

Based on above data, there is disagreement with the Handbook value (p. 159) of $0.2 = f_2$ for the stable element, since:

$$f_2 = \frac{10 \text{ g. S in bone}}{175 \text{ g. S in whole body}} = 0.0572 \text{ for stable element in bone}$$

The Handbook value was based on the following references (as cited):

Dziewiatkowski, J BIOL CHEM 161, 723-9 (1945)
Shohl, MINERAL METABOLISM, Reinhold Pub. (1939) .

Similarly, there is disagreement with $f_2$ for the stable element in skin:

$$f_2 = \frac{0.388 \text{ g. S in skin}}{175 \text{ g. S in whole body}} = 0.0222 \text{ for stable element in skin}$$

The Handbook value (p.160) of $f_2 = 0.17$ for stable element in skin is based on the Shohl, MINERAL METABOLISM reference.

1026277

Geigy

Organs



# Chemical Composition of the Body and some of its Organs[1]

For further elements, see the tables of the elements, pages 84–96

| Content per 100 g | Per cent of total body weight: Newborn | Per cent of total body weight: Adults | Fats: Total | Fats: Phospholipids | Fats: Steroids | Water (on fat-free basis) | Elements (on fat-free basis): Sodium Na | Potassium K | Calcium Ca | Magnesium Mg | Chlorine Cl | Phosphorus P | Sulphur S | Manganese Mn | Lead Pb | Tin Sn | Aluminium Al | Copper Cu | Silver Ag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Whole body | | | g | g | g | g | g | g | g | g | g | g | g | mg | mg | mg | mg | mg | mg |
| Foetus 3–4 months | .... | .... | 0.5 | — | — | 93 | — | — | 0.34 | 0.018 | 0.27 | 0.214 | — | | | | | | |
| Foetus 5 months | .... | .... | 1.2 | — | — | 91 | 0.230 | 0.20 | 0.50 | 0.021 | 0.25 | 0.300 | 0.148 | | | | | | |
| Foetus 6 months | .... | .... | 2.5 | — | — | 87 | 0.216 | 0.162 | 0.62 | 0.021 | 0.25 | 0.302 | 0.180 | | | | | | |
| Foetus 7 months | .... | .... | 2.5 | — | — | 86 | 0.214 | 0.180 | 0.62 | 0.022 | 0.26 | 0.302 | 0.153 | | | | | | |
| Premature 7th month | .... | .... | 3.0 | — | — | 85 | 0.242 | 0.171 | 0.75 | 0.022 | 0.27 | 0.302 | — | | | | | | |
| Newborn | .... | .... | 12.0 | — | — | 80 | 0.170 | 0.190 | 0.92 | 0.027 | 0.20 | 0.540 | 0.246 | | | | | | |
| Adults | .... | .... | 18.0 | — | — | 72 | 0.109 | 0.265 | 2.01 | 0.036 | 0.156 | 1.16 | 0.196 | | | | | | |
| **Adult organs** | | | | | | | | | | | | | | | | | | | |
| Muscle | 25.1 | 28.7 | 7.5 | 1 | [illegible][4] | 79 | 0.072 | 0.360 | 0.007 | 0.023 | 0.066 | 0.220 | 0.230 | 0.020 | 0.080 | 0.021 | 0.065 | 0.125 | 0.00 |
| Skeleton | 13.7 | 11.6 | 10.0 | 0.3 | — | 44 | 0.18 | 0.061 | 11.0 | 0.105 | 0.19 | 5.05 | 0.137 | [illegible][1] | [illegible][1] | [illegible][1] | [illegible][1] | [illegible][1] | [illegible][1] |
| Blood serum | 6.5 | 2.7 | 0.06 | 0.3 | 0.210 | 92 | 0.335 | 0.020 | 0.011 | 0.003 | 0.370 | 0.015 | 0.001 | 0.09 | 0.55 | — | 0.1 | 0.220 | — |
| Blood corpuscles | | 1.8 | 0.06 | | | 65 | 0.420 | 0.395 | 0.125 | 0.006 | 0.193 | 0.1 | 0.0001 | | | — | | — | — |
| Skin | 19.7[2] | 17.4[2] | 15 | 0.3 | 1.40 | 73 | 0.16 | 0.107 | 0.20 | 0.014 | 0.30 | 0.065 | 0.375 | 0.14 | — | — | — | — | — |
| Brain | 12.3 | 1.4 | 12.6 | [illegible][3] | [illegible][3] | 90 | 0.17 | 0.33 | 0.012 | 0.016 | 0.015 | 0.38 | 0.13 | 0.030 | 0.013 | 0.00 | 0.004 | 0.400 | 0.003 |
| Liver | 4.6 | 1.8 | 21.3 | 2.5 | 0.350 | 79 | 0.19 | 0.215 | 0.012 | 0.022 | 0.16 | 0.21 | 0.19 | 0.205 | 0.130 | 0.060 | 0.160 | 0.710 | 0.005 |
| Intestines | 2.1 | 1.4 | 6.5 | 1 | — | 85 | 0.214 | 0.29 | 0.014 | 0.008 | 0.065 | 0.100 | 0.120 | 0.035 | 0.023 | 0.016 | 0.087 | 0.110 | 0.002 |
| Lungs | 1.8 | 1.0 | 1.7 | 1.5 | 0.375 | 78 | 0.25 | 0.15 | 0.017 | 0.007 | 0.26 | 0.12 | 0.127 | 0.022 | 0.028 | 0.045 | 5.94 | 0.110 | 0.004 |
| Kidneys | 0.8 | 0.3 | 5.2 | 2.5 | 0.430 | 80 | 0.175 | 0.175 | 0.020 | 0.21 | 0.22 | 0.14 | — | 0.060 | 0.027 | 0.020 | 0.042 | 0.166 | 0.00 |
| Heart | 0.8 | 0.3 | 8.3 | 1.5 | — | 77 | 0.185 | 0.250 | 0.010 | 0.017 | 0.135 | 0.270 | 0.200 | 0.032 | 0.038 | 0.022 | 0.056 | 0.190 | 0.00 |
| Spleen | 0.3 | 0.16 | 3.0 | 1 | 0.250 | 77 | — | — | 0.010 | 0.015 | 0.16 | 0.38 | 0.17 | 0.022 | 0.030 | 0.022 | 0.130 | 0.085 | 0.00 |
| Pancreas | 0.1 | 0.1 | 10.5 | 2 | 0.310 | 80 | 0.87 | 0.226 | 0.017 | 0.019 | 0.18 | 0.34 | — | — | — | — | — | — | — |
| Thyroid | — | — | 4.4 | — | — | 75 | — | — | — | 0.10 | 0.18 | 0.34 | — | Iodine 7–180 mg | | | | | — |
| Testes | — | — | 4.5 | 2 | — | — | — | — | 0.009 | 0.010 | 0.24 | — | — | | | | | | |
| Uterus | — | — | — | — | — | — | 0.145 | 0.145 | 0.022 | 0.016 | 0.26 | 0.057 | — | | | | | | |
| Adrenals | — | — | — | 2 | 5.0 | — | — | 0.103 | 0.016 | 0.010 | 0.24 | — | — | | | | | | |

[1]) first value: long bones; second value: [illegible]
[2]) skin and subcutaneous tissue
[3]) first value: grey matter; second value: white matter
[4]) first value: smooth muscles; second value: striated muscles

[1]) After [illegible], A. T., *Mineral Metabolism*, American Chemical Society Monographs, No. 82, New York, 1939; [illegible], *J. Nutr.*, 19, 383, 1940; [illegible], *Pathologische Physiologie*, Berlin, 1950; [illegible], M. K., *Medical Biochemistry*, New York, 1946; [illegible], *Biochem. J.*, 28, 1340, 1934.

The quantity a

From the paro
1.002–1.008; fro
Enzymes: amy
100 ml saliva co
Water ........
Dissolved subst
organic ...
inorganic .
Mucin and epith

Specific gravity
ingestion of foo
Duodenum
Upper jejun
Enzymes: erepsi
100 ml intest
Water .....
Dissolved su
Salts .......
Calcium ....
Phosphorus

Specific gravity 1
1–1½ litres.
Enzymes: trypsin
100 ml pancreatic
Water ..... 98
Dry residue. 2
Ash ....... 0
Sodium ... 13
Calcium ... 0.2
The alkalinity inc

Freezing-point de
1.026–1.032. Da

Water .........
Dry residue .....
Mucin and pigmen
Alkali salts of bile
taurocholates
glycocholates

From DOCUMENTA GEIGY SCIENTIFIC TABLES, p. 282 (1959), Basle, Switzerland

1026278

AUTHOR: J.M. Brown, J.R.Howley, Y. McIntosh, D.Driver and M.B. Dickinson

Termatrex Number _____

TITLE: CONTAMINATION PROBLEMS ASSOCD WITH ADMIN OF MASSIVE DOSES OF S-35 TO PATIENTS

JOURNAL: HEALTH PHYSICS Vol. 10, pp. 557-561 (August 1964)

REPORT No:

FILED:

Abstracted by: C. F. Holoway Date: 31 July 1964

KEY WORDS:

ANIMAL:
- man
- cow
- dog
- goat
- guinea pig
- monkey
- mouse
- pig
- rabbit
- rat
- sheep
- other mammals
- other vertebrates
- Cells and Microorganisms

AGE:
- embryo
- feotus
- infant
- young
- adult
- aged

SEX:
- male
- female

CONDITION:
- pathological
- grossly normal

METHOD:
- single
- multiple
- continuous
- inhalation
- oral
- IV
- IM
- IP
- SC
- IT
- submersion
- surface absorption

ISOTOPE:
- $Sr^{85}$, $Pu^{239}$, etc.
- S-35

ELEMENT:
- Sr, U-nat, etc.

LEVEL:
- tracer
- chronic
- toxic
- high 0.3 to 0.5 curie

CHEMICAL FORM:
- acetate
- carbonate
- citrate
- Halide
- nitrate
- oxide
- phosphate
- sulphate
- thymidine
- organic
- Other form
- carrier free

PHYSICAL FORM:
- aerosol
- gas
- particle data
- solid
- solution (suspension or colloid)

LENGTH OF EXPERIMENT:
- hour; day; week; month; year

SOLUBILITY:
- Soluble - acid; blood; GI tract; Lung; Water
- InSoluble - acid; blood; GI tract; Lung; Water

STANDARD ANIMAL DATA:
- Intake/day: air; food; water
- Elimination/day: air; food; water; elements
- Composition: whole body; body organs
- Mass: whole body, body organs
- Radius: body organs

DIET DATA:
- food; water
- Diet: composition (elements)
- Diet: % water; % solid

OTHER DATA (discussed):
- Chemical toxicity
- Radiotoxicity
- Uptake
- RBE and/or MF
- MPC's
- Power Function
- Exponential
- Variability

OTHER DATA:
- bibliography
- $f_1$ (fraction from GI tract to blood)
- $f_2$ (fraction in organ of reference of that in total body)
- $f_2'$ (fraction from blood to organ of reference)
- $f_a$ (fraction in organ of reference by in halation)
- $f_w$ (fraction in organ of reference by ingestion)
- $T_b$ (biological half-life)
- $T_r$ (radioactive half-life)
- T (effective half-life)
- $f_f$ (fraction in feces)
- $f_u$ (fraction in urine)
- fecal to urine ratio
- blood to urine ratio

OTHER DATA:

Elimination by perspiration (skin)

| WHOLE BODY AND BODY ORGANS | %deposited | %retention | Burden | distribution | Elimination Urine | Elimination Fecal | Time |
|---|---|---|---|---|---|---|---|
| WHOLE BODY | | | ? | | ✓ | | ✓ |
| Adrenal | | | | | | | |
| Aorta | | | | | | | |
| Blood | | | | | | | |
| Bone | | | | | | | |
| Brain | | | | | | | |
| Breast | | | | | | | |
| Gastrointestinal tract | | | | | | | |
| Esophagus | | | | | | | |
| Stomach | | | | | | | |
| Duodenum | | | | | | | |
| Jejunum | | | | | | | |
| Ileum | | | | | | | |
| Cecum | | | | | | | |
| Sigmoid colon | | | | | | | |
| Rectum | | | | | | | |
| Heart | | | | | | | |
| Kidney | | | | | | | |
| Larynx | | | | | | | |
| Liver | | | | | | | |
| Lung | | | | | | | |
| Muscle | | | | | | | |
| Diaphragm | | | | | | | |
| Pectoral | | | | | | | |
| Psoas | | | | | | | |
| Omentum | | | | | | | |
| Ovary | | | | | | | |
| Pancreas | | | | | | | |
| Prostate | | | | | | | |
| Skin | | | | | | | |
| Spleen | | | | | | | |
| Testis | | | | | | | |
| Thymus | | | | | | | |
| Thyroid | | | | | | | |
| Tongue | | | | | | | |
| Trachea | | | | | | | |
| Urinary bladder | | | | | | | |
| Uterus | | | | | | | |
| Vagina | | | | | | | |

June 18, 1964

TX-3514 (6-64)

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COPY

Abstract:

This paper is of value mainly for the fact that it may be the only available human data estimating the small but significant loss of S-35 via perspiration route, which amounts to about 1% of the total administered dose as estimated below.

There appears to be a continued interest in S-35 for treatment of advanced chondrosarcoma, a total of 5,594 mc of S-35 having been used on 10 patients since 1957 at NIH, in the form of $H_2SO_4$.

LAUNDRY DATA:

| Patient | Route | Dose (mc) | Time (days) for 70% excretion of the admind. dose via urine * | Accumulated mc recovered from laundry * | % of admind. dose recovered from laundry |
|---|---|---|---|---|---|
| EP | I.V. | 350 | 13 | 3 - 0.591 = 2.4 | 0.69 |
| HT | I.V. | 488 | 4 | 6 - 0.5 = 5.5 | 1.1 |

* Corrected for decay.

Control laundry washes showed 85-100% recovery of S-35. Patient HT gave little S-35 recovery from laundry washes after 6th day, but patient EP laundry gave as much as 0.8 mc between 14th day and the 16th day.

URINARY DATA: (Included in above table.)

~~Despite~~ A higher dose (488 mc), patient HT, was excreted in 1/3 rd the time taken by EP to excrete a 350 mc dose. Assuming both should have excreted their respective doses in the same time, percentagewise, individual variability is probably reflected here. Patient HT (488 mc) showed very little excretion after 15 days (85% of total injected dose). Patient EP (350 mc) showed little excretion after 28 days (about 85% of total injected dose).

No fecal data is given, so one cannot tell whether the remaining 14% of total dose (100% - 85% + 1%) contributed a significant body burden or not. Assuming 7% of total dose excreted via feces, a body burden of 7% of total dose migh be assumed.

(Rat data, Dziewiatkowski, JBC 178, 197-202 (1949), gave about 90% total recovery from urine + feces in 100 hrs., about 81% of total I.P. dose via urine and about 8% of total I.P. dose via feces, leaving a body burden of about 11% at 100 hrs (4.2 days).)

1026280

*Health Physics* Pergamon Press 1964. Vol 10, pp. 557–561. Printed in Northern Ireland

# CONTAMINATION PROBLEMS ASSOCIATED WITH THE ADMINISTRATION OF MASSIVE DOSES OF SULFUR-35 TO PATIENTS*

JOSEPH M. BROWN, Jr., JOHN R. HOWLEY, YVONNE McINTOSH, DONALD DRIVER, and MARDALEE B. DICKINSON

U.S. Public Health Service, National Institutes of Health, Bethesda, Md.

(*Received* 31 *July* 1963; *in revised form* 23 *December* 1963)

**Abstract**—Sulfur-35 as $H_2SO_4$ in HCl solution has been used by the National Institutes of Health in the treatment of chondrosarcoma. Therapy doses have ranged from 295 mc to 488 mc with the total amount of $S^{35}$ received by any one patient being 997 mc. Owing to the rapid excretion of $S^{35}$ in all body fluids, the problems of general radioactive contamination of the hospital are many, accentuated by the relative long half-life (87 days). The safety techniques developed for patient-care personnel are presented and contamination monitoring techniques and results are reported for two of the patients.

SULFUR-35, as $H_2S^{35}O_4$ in a solution of HCl and NaCl has been used for several years at the National Institutes of Health in the treatment of chondrosarcoma.[1] The amount of sulfur-35 given per therapy dose has ranged from 295 to 488 mc with a total dose to one patient of 997 mc. A total of 5594 mc of sulfur has been used in patient treatment in ten cases since 1957.

Since sulfur-35 emits only low-energy beta particles (0.167 MeV maximum), external radiation from the patient does not present a problem to patient-care personnel. However, bremsstrahlung is detectable as would be expected from low energy electrons and low Z materials making up the human body. On the other hand, the problems of general radioactive contamination are many because of the rapid excretion, primarily in the urine with small amounts in other excreta, the relatively long half-life (87 days), and the difficulties of monitoring for low energy beta contamination. However, techniques have been developed for controlling contamination levels during the administration of the dose and the subsequent care of the patient.

Two typical cases are presented to illustrate the safety techniques developed by the Radiation Safety Department of the Clinical Center and carried out by patient-care personnel following the administration of the therapy doses. Area monitoring techniques and results are reported.

Patient E. P. was given 350 mc of sulfur-35 intravenously in a regular operating room. This was done in the operating room in order that biopsy could be performed immediately after the dose was administered. Patient H. T. was administered 488 mc of sulfur-35 in a regular patient-care room of the Clinical Center. Each therapy dose was assayed against a $S^{35}$ standard supplied by the National Bureau of Standards, using a liquid scintillator spectrometer. Each dose was given in a 350 ml intravenous drip and no untoward event occurred during either procedure. In each case Radiation Safety Department personnel were present during the administration with equipment for coping with a spill.

In the case of patient E. P. the only deviation from normal operating room procedures were:

(1) Extra precautions were taken to reduce traffic into and out of the operating room.
(2) The shoe covers normally worn by operating room personnel were changed at the operating room door when personnel left the room.

* Presented at the Health Physics Society Meeting, Chicago, Illinois, 11–14 June 1962.



1026281

(3) Instruments and equipment in the operating room remained until after the completion of the surgical procedure and until monitoring and decontamination of the equipment and area were completed.

(4) All operating room laundry including towels placed at strategic places to absorb accidental spills was kept in the room until general decontamination of the area began. It was then placed in a laundry bag for subsequent removal to the isotope laboratory for decontamination.

(5) Operating room personnel were monitored for contamination at the doorway when leaving the area. A thin window (less than 2 mg/cm$^2$) survey meter was used for this survey.

Several of the operating room personnel were found to have contaminated hands caused by touching the patient after the surgical gloves had been removed. This occurred about 2 hr after the dose was given. No detectable hand contamination was found following a prompt and thorough washing of the hands with the usual operating room cleansing agent. The clean-up of the area involved standard techniques of mopping and rinsing. The instruments were decontaminated in the operating room sink by wiping down with detergent solution and rinsing in running water.

Table 1 indicates the results of a smear* or wipe survey of the operating room and adjoining hallway following the procedure and also following the decontamination of the area and equipment. Smears 1, 2 and 3 were taken in the hallway outside the operating room. The remaining smears were taken from the floor and some of the equipment in the room, avoiding obviously contaminated items and areas such as surgical instruments and blood spots on the floor. Hence it emphasizes only the rather general contamination that one might expect in the operating area and on some of the equipment following the administration of the dose and the surgical biopsy procedure. Note the sharp demarcation between the controlled area which was in this case the door to the operating room. It should be pointed out that the operating room team in this case was experienced in the handling of radioisotopes and every effort was made to keep contamination levels to a minimum.

*Table 1. Smears taken before and after decontamination of operating room (Smears 1, 2 and 3 were taken from the hallway floor outside the room)*

| Smear no. | D/min | D/min after decontamination |
|---|---|---|
| 1 | B* | B |
| 2 | B | B |
| 3 | B | 62 |
| 4 | B | B |
| 5 | 386 | 64 |
| 6 | 544 | B |
| 7 | 190 | B |
| 8 | 372 | 74 |
| 9 | 270 | B |
| 10 | 300 | 30 |
| 11 | 86 | B |
| 12 | 258 | B |
| 13 | 550 | B |
| 14 | 56 | B |
| 15 | 364 | B |
| 16 | 1102 | B |
| 17 | 348 | B |
| 18 | 1130 | B |

* Indicates background counts (25–45 cpm).

After surgery, Patient E. P. was removed to one of the Clinical Center nursing units and placed in a room by himself. Patient H. T. was placed in an adjoining room. Each patient was restricted to his room. Air samples were taken 2 hr after these patients were placed in their rooms and again each 24 hr for a period of 8 days. Twenty min samples were taken at a flow rate of 20 l. per minute through a 1-in. circle of Whatman No. 41 filter paper. These were counted on a windowless gas flow system immediately after collection and again following the decay of natural radioactivity. Gaseous samples of room air were measured by bubbling air through a 0.1 N NaOH solution which was, in turn, counted in a liquid scintillation spectrometer. None of the air samples showed a

* Our smear technique uses a 1 in. circle of Whatman No. 41 filter paper which is wiped on the surface to be checked. In the case of large flat surfaces such as floors, an area equivalent to four asphalt tiles, or roughly 324 in.$^2$, is wiped. These smears are then counted in a windowless gas flow counter for a predetermined count. Counting efficiency is assumed to be 50 per cent for all smears counted in this manner.

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significant increase over background attributable to sulfur-35.

The doorway to the patient's room became the radiation control point.

The following procedures were required:

(1) Patient-care personnel entering the room were required to wear rubber gloves, gowns and booties. These were donned and removed at the doorway.

(2) Visitors were permitted to enter the room but were dressed as in (1).

(3) Patients left their rooms only for required medical procedures. When it was necessary for patients to leave their rooms they were dressed in clean gowns, booties and cotton gloves. Where this was impossible or impractical, stretchers and wheelchairs were draped with cotton sheets to prevent contamination.

(4) The patient's food was served in disposable paper containers which were removed by the Radiation Safety Department daily. These were incinerated in the NIH incinerator, after being monitored. Due to the tremendous dilution afforded by the daily charge to this incinerator, the ash was not monitored.

(5) The patient's laundry, separated from the regular patient-care laundry, and including booties worn in the room, was collected daily. Handling of this laundry will be discussed later.

(6) Urine was collected in screw cap bottles and stored in the toilet area. The floor in this area was covered with an absorbent paper which was taped to the floor with masking tape to prevent slippage.

Figure 1 shows the accumulated percentage of the administered dose recovered in the urine per day. Patient H. T. excreted more than 70 per cent of the dose within the first 4 days after the dose was given. Patient E. P. required approximately 13 days to excrete 70 per cent of the administered dose.

The contaminated laundry from these patients was handled under Radiation Safety control. The laundry was washed in a 9-lb home-type washer using a commercially available detergent. Water from the machine was collected

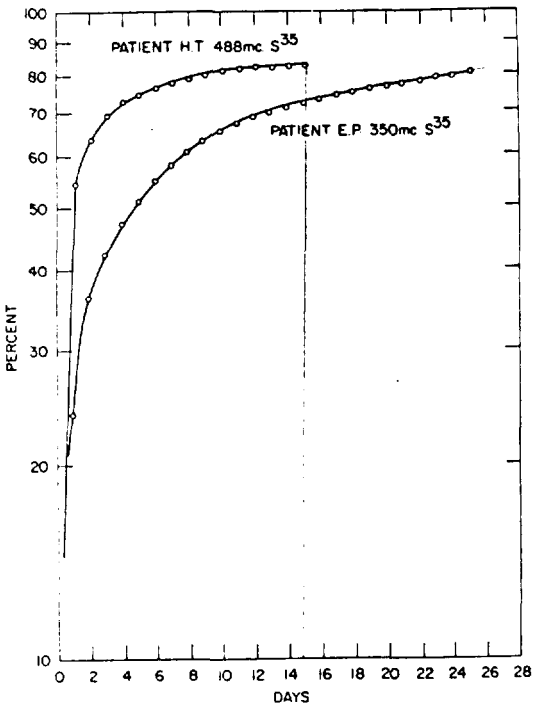


FIG. 1. Accumulated per cent of dose recovered in urine corrected for decay to day of administration.

in 55-gal drums. An aliquot of this wash water was counted in a liquid scintillation spectrometer. Previous studies on a number of deliberately contaminated batches of laundry indicated between 85–100 per cent of the total sulfur-35 contamination present in laundry is removed in a single washing by this method. The wash water from the operating room laundry, in the case of Patient E. P., contained a total of 591 $\mu c$ of sulfur-35. Figure 2 indicates the accumulated amount of $S^{35}$ recovered from each patient's laundry. After the sixth day, the amount of sulfur removed from the laundry of Patient H. T. was rather small, whereas the wash water from the laundry from Patient E. P. contained as much as 800 $\mu c$ between the fourteenth and sixteenth day. As a group, the excretion patterns in these individuals have shown a high variability. Collection of patients' laundry by the Radiation Safety Department was discontinued when the contamination in the wash water was found to be below the MPC

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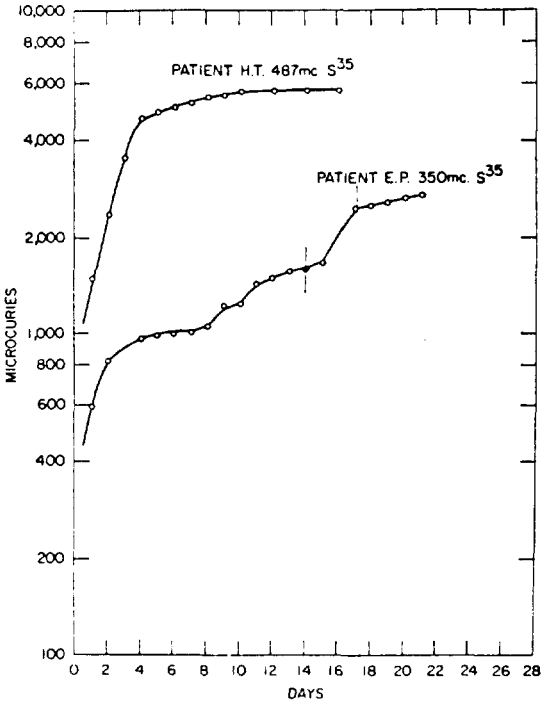


FIG. 2. Accumulated $\mu$c S-25 recovered from patients' laundry corrected for decay to day of administration.

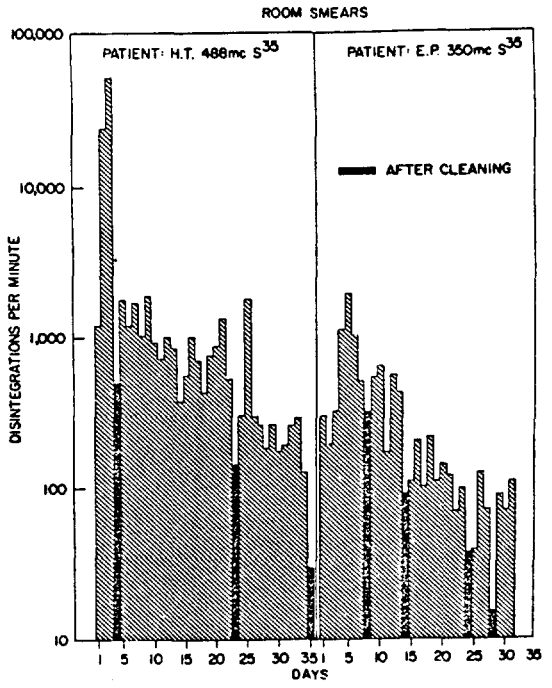


FIG. 3. Average of ten smears taken in the patients' room over an extended period of time.

for water as listed in the Federal Register, Title 10, Part 20. The value for sulfur-35 given in Appendix B, Table 2, is $6 \times 10^{-5}$ uc/ml. The gowns worn by patient-care personnel were collected for one week following the administration of the doses. No significant contamination has been found in the wash water from these gowns and after 1 week the gowns are sent directly to the NIH laundry.

The wash water from the laundry and the urine from the patients, excluding that urine collected over the first 6 days, was added to the Isotope Laboratory's 10,000-gal storage tank and metered into the sanitary sewer system over an extended period of time. The urines collected for the first 6 days were disposed of as long half-life waste.

Daily wipe smears were used as an index of the contamination present in the patients' rooms and the adjoining corridor. Figure 3 gives the average of ten smears taken in the patient's room over an extended period of time. In the case of Patient H. T., the highest smear readings were made on the third day, the average of the ten smears yielding approximately 50,000 disintegrations per min. The highest smear readings in Patient E. P.'s room occurred on the fifth day when 1900 disintegrations/min were recorded as the average of ten smears. Decontamination of these rooms was effected on the indicated days by housekeeping personnel under Radiation Safety Department supervision and assistance. The normal procedures of cleaning a hospital room were used, with all personnel wearing gloves, gowns and booties. No area outside the rooms showed signs of contamination throughout the period of restriction of the patients, which was 35 days for Patient H. T. and 31 days for Patient E. P. Following the removal of restrictions, the patients were treated as routine tracer studies by hospital personnel.

## SUMMARY

(1) Patients receiving massive doses of sulfur-35 can present a serious and general contamination problem to the hospital and should be

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isolated. Areas of rather high level general contamination will go undetected unless appropriate survey measures are used to monitor for this low-energy beta emitter.

(2) Under the regimen instituted, air borne contamination did not present a problem.

(3) The main contamination problem resulted primarily from small spills of highly contaminated urine and from other body fluids.

(4) Control of contamination can be easily established at the doorway to patients' rooms, thereby preventing the general spread of contamination throughout the hospital.

(5) Sulfur-35 contamination in laundry is easily removed by normal washing procedures using commercially available detergents.

(6) Decontamination of rooms and areas lends itself well to normal hospital cleaning procedures.

## REFERENCE

1. J. ROBERT ANDREWS, *et al.*, The Effects of One Curie of Sulfur-35 Administered Intravenously as Sulfate to a Man With Advanced Chondrosarcoma, *Amer. J. Roentgenol.* **83,** No. 1, January (1960).

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AUTHOR: A. R. Maass, T. L. Flanagan, D. Blackbur and M. Smyth (Smith, Kline and French Labs, Phila) Termatrex Number

TITLE: ACCIDENTAL PERSONNEL EXPOSURE TO ELEMENTAL S-35

JOURNAL: HEALTH PHYSICS 9, 731-740 (1963)

REPORT No:

FILED:

Abstracted by: C. F. Holoway & S.R Bernard Date: 22 June 1964

KEY WORDS:

ANIMAL:
- man
- cow
- dog
- goat
- guinea pig
- monkey
- mouse
- pig
- rabbit
- rat
- sheep
- other mammals
- other vertebrates
- Cells and Microorganisms

AGE:
- embryo
- feotus
- infant
- young
- adult
- aged

SEX:
- male
- female

CONDITION:
- pathological
- grossly normal

METHOD:
- single
- multiple
- continuous
- inhalation
- ? oral - 13 μc ?
- IV
- IM
- IP
- SC
- IT
- submersion
- surface absorption

Accidental intake

ISOTOPE: $Sr^{85}$, $Pu^{239}$, etc.

S-35

ELEMENT: Sr, U-nat, etc.

LEVEL:
- tracer - 26 μc
- chronic
- toxic
- high 1.2 curie, exposure - ext. and int.

CHEMICAL FORM:
- acetate
- carbonate
- citrate
- halide
- nitrate
- oxide
- phosphate
- sulphate
- thymidine
- organic
- Other form
- carrier free
- elemental

PHYSICAL FORM:
- aerosol
- gas
- particle data
- solid
- solution (suspension or colloid)

LENGTH OF EXPERIMENT: hour; day; week; month; year

SOLUBILITY:
- Soluble - acid; blood; GI tract; Lung; Water
- InSoluble - acid; blood; GI tract; Lung; Water

STANDARD ANIMAL DATA:
- Intake/day: air; food; water
- Elimination/day: air; food; water; elements
- Composition: whole body; body organs
- Mass: whole body, body organs
- Radius: body organs

DIET DATA:
- food; water
- Diet: composition (elements)
- Diet: % water; % solid

OTHER DATA (discussed):
- Chemical toxicity
- Radiotoxicity
- Uptake
- RBE and/or MF
- MPC's
- Power Function
- Exponential
- Variability

OTHER DATA:
- bibliography
- $f_1$ (fraction from GI tract to blood)
- $f_2$ (fraction in organ of reference of that in total body)
- $f_2'$ (fraction from blood to organ of reference)
- $f_a$ (fraction in organ of reference by in halation)
- $f_w$ (fraction in organ of reference by ingestion)
- $T_b$ (biological half-life) - plasma
- $T_r$ (radioactive half-life)
- T (effective half-life)
- $f_f$ (fraction in feces)
- $f_u$ (fraction in urine)
- fecal to urine ratio
- blood to urine ratio

| WHOLE BODY AND BODY ORGANS | %deposited | %retention | Burden | distribution | Elimination Urine | Elimination Fecal | Time | $T_b$ |
|---|---|---|---|---|---|---|---|---|
| WHOLE BODY | | | 13-26 μc. | | | 9 μc | | |
| Adrenal | | | | | | | | |
| Aorta | | | | | | | | |
| Blood | | | | | | | 60 hrs | 19 hrs |
| Bone | | | | | | | | |
| Brain | | | | | | | | |
| Breast | | | | | | | | |
| Gastrointestinal tract | | | | | | | | |
| Esophagus | | | | | | | | |
| Stomach | | | | | | | | |
| Duodenum | | | | | | | | |
| Jejunum | | | | | | | | |
| Ileum | | | | | | | | |
| Cecum | | | | | | | | |
| Sigmoid colon | | | | | | | | |
| Rectum | | | | | | | | |
| Heart | | | | | | | | |
| Kidney | | | | | | | | |
| Larynx | | | | | | | | |
| Liver | | | | | | | | |
| Lung | | | | | | | | |
| Muscle | | | | | | | | |
| Diaphragm | | | | | | | | |
| Pectoral | | | | | | | | |
| Psoas | | | | | | | | |
| Omentum | | | | | | | | |
| Ovary | | | | | | | | |
| Pancreas | | | | | | | | |
| Prostate | | | | | | | | |
| Skin | | | | | | | | |
| Spleen | | | | | | | | |
| Testis | | | | | | | | |
| Thymus | | | | | | | | |
| Thyroid | | | | | | | | |
| Tongue | | | | | | | | |
| Trachea | | | | | | | | |
| Urinary bladder | | | | | | | | |
| Uterus | | | | | | | | |
| Vagina | | | | | | | | |
| Bone marrow | | | | | | | 36 hrs | |
| Urine | | | | | | | | 120 hrs |
| Feces | | | | | | | | 60 hrs |

OTHER DATA:

Analytical methods discussed.

No visible after-effects in 3 years from 13-26 μc body burden.

June 18, 1964

TT-3514 (6-64)

Abstract: (by C. F. Holoway) 22 June 1964

1.27 curies of elemental S-35 dissolved in 15 ml of benzene in a sealed ampoule exploded, contaminating an organic chemist externally and internally. Using various forms of sulfur, the major load of deteatable S was cleared from the body within 5 days, biol. half-life of plasma radioactivity being about 19 hrs., approx. 85% of urinary and 90% of fecal radioactivity excreted within 24 hrs of accident, in agreement with the classical concept that only a small portion of S introduced in non-organic form is retained by the body. Observations in this unusual case are discussed in the light of available lit. on S-35.

Mode of entry: minor cuts on hands and face, and probably inhalation of S-35 aerosol, as well as through skin absorption, since in latter, activity not removable, mechanically, slowly disappeared.

Analyses: (1) plasma, (2) $CCl_4$ plasma proteins, (3) urine, (4) feces, (5) hair, (6) sternal puncture bone marrow, (7) skin surfaces.

Results: (1) plasma content dropped from 0.68 μc to background in 4 days.
(2) $CCl_4$ plasma proteins contained no detectable radioactivity at any time.
(2a) RBC's contained small but sig. activity, ranging from 1/6 to 1/2 plasma activity.
Semilog plot of plasma data suggested rate of disappearance of S-35 from plasma was exponential, with a half-life of approx. 19 hrs, suggesting maximal plasma concn. following the accident of 0.61 μc, assuming plasma vol. of 5% of body wt., or 4.65 l.
(3) Approx. 0.9 or 90% of the urinary S-35 accounted for as sulfate, and probably more. [redacted] S-35 excreted in urine, when plotted against time, as a semilog function, was fitte to

$$y = a(1 - e^{-kt})$$

The observations have been plotted about a line generated u a = 4.29 μc and k = 0.076.
(4) Extremely erratic nature of fecal S-35 excretion did not justify a cumulative plot, but the data suggest that a max. of 9 μc of S-35 might be reasonably anticipated. Since only 0.002 μc S-35 could be extd. from the total fecal radioacti with benzene as elemental S-35, it seemed likely that the total activity was present as sulfate.
(5) A sample of hair 2 months after the accident contained appr 2-14 c/m above background, in accord with lit. that inorgar S may be incopporated into cysteine in human.
(6) Bone marrow contained no activity above background.
(7) Skin c/m ranged from 200 c/m at back of right knee to a count beyond range of instrument over left forearm.

Authors believe that the total body burden of 13-26 μc did not constitute a significant internal radiation hazard. Based on a fecal content of 9 μc, a total body burden of 18 μc might be estimated. Assuming that all of the S-35 appearing in the urine was absorbed from the GI tract rather than from lungs, one might exp that 13 μc had been swallowed, giving an estimated body burden of 26 μc, ignoring entrance into bloodstream of any radioactivity via cuts from flying glass or by skin absorption.

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Abstract: (by S. R. Bernard) 3 August 1964

The authors report on urinary excretion, fecal excretion, disappearance from plasma, and a sternal bone marrow sample with respect to S-35 taken in accidently by an organic chemist while manipulating an ampoule containing elemental S-35 in benzene which exploded. The man received minor cuts and hands and face, his clothing and skin being contaminated, he could have inhaled, ingested, and/or been administered via puncture wound the S-35.

The authors give fecal measurements out to 60 hours following intake, and they estimate 9 μc in the fecal excretions. (I estimate a half-life of 6 days and a total amount of 17 μc excreted in the urine.) They present a table and graph of urinary excretion (designating on the abscissa units of μc and not μc per hour, day or liter). This graph needs to be checked. They also present a plot of cumulative μc excreted, fitting it with a one-exponential equation, and a half-life of 9.1 hours is found. They estimate 4.3 μc to have been excreted in the urine. Maass et al indicate that they corrected all data for radiological decay. A sample of bone marrow taken 36 hours after intake showed no significant activity. A plot of S-35 in plasma is shown, with a half-life of 19 hours. They estimate from feces and urine that 13-26 μc were taken in. The subject was administered large quantities of elemental S as sulfur and molasses, and $MgSO_4$ to accelerate excretion. (Thus, parameters may not be applicable for Internal Dose Estimation) They also discuss the analytical methods and hospital procedure. Does $HClO_4$-$HNO_3$ volatilize sulfur from oxidation of feces?

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# ACCIDENTAL PERSONNEL EXPOSURE TO ELEMENTAL $S^{35}$

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(*Received* 23 *March* 1962; *in revised form* 4 *March* 1963)

**Abstract**—While an organic chemist was attempting to open a glass ampule containing 1.27 c of elemental $S^{35}$ dissolved in 15 ml of benzene, the vial exploded, and the operator was contaminated internally and externally with the radioactive material. It is extremely difficult to measure the effectiveness of therapy employed to encourage the removal of absorbed radioactivity, or to assess with assurance the validity of our estimation of total body radioactive burden. However, utilizing the techniques of dilution of the absorbed radioactive material with non-radioactive sulfur in several of its many utilized forms, as well as the administration of agents which seem likely to increase the rate of excretion of $S^{35}$, the major load of detectable $S^{35}$ was cleared from the body within 5 days. The biological half-life of plasma radioactivity was about 19 hr. Approximately 85 per cent of the urinary and 90 per cent of the fecal radioactivity were excreted within 24 hr of the accident. This is in agreement with the classical concept that only a small portion of sulfur introduced in a non-organic form is retained by the body. The observations in this unusual case are discussed in the light of available literature on $S^{35}$.

The body burden has been estimated to have been 13–26 $\mu$c. There is ample evidence in the literature to suggest that these quantities of radioactive sulfur are unlikely to cause any radiation damage and, indeed, no adverse effects have been noted during the 3 years since exposure.

## INTRODUCTION

ELEMENTAL $S^{35}$ in benzene in amounts varying from 200 mc to 1.5 c had been utilized for the synthesis of several radioactively labeled phenothiazines. The $S^{35}$ was generally received in a heat sealed all-glass ampule, since on one previous occasion the packing material in a shipment of $S^{35}$ in a screw-capped container was found to be contaminated.

On this occasion, as on previous occasions, the ampule was chilled in an ice bath prior to opening. After chilling, the ampule was placed inside two concentric containers. The ampule was scored with a carborundum chip but could not be snapped open. Before it could be scored again it exploded, shattering both containing vessels and severely contaminating the operator.

The operator, an organic chemist, Ph.D., received minor cuts on his hands from glass that penetrated his rubber gloves. There were also superficial cuts on his face around, but not within, the area protected by his safety glasses. His uniform and the exposed areas of his face were highly contaminated. He discarded his uniform, changed to clean clothes, and left his laboratory, which was thereupon sealed. When monitoring indicated that the $S^{35}$ had contaminated even areas protected by several layers of clothing, he then began decontamination of all body surfaces. Within 1 hr after the accident, blood and urine samples were obtained which contained radioactivity indicating internal contamination. This paper presents the method of his treatment and methods used to estimate his total body burden of $S^{35}$.

## METHODS

### A. *Immediate post-accident medical care*

The immediate treatment was directed toward three goals:

(1) Decontamination of radioactive skin areas.

(2) Establishing as nearly as possible "base line" values for blood and urine radioactivity.

(3) Elimination of whatever $S^{35}$ might have been absorbed or ingested.

The patient was placed immediately in a shower, given a brush, and told to scrub vigorously with soap those skin areas exposed to



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the explosion and found to be contaminated. Within 1 hr Phisohex was substituted for soap in the belief that it might cleanse more thoroughly; contaminated body hair was removed by shaving.

Blood and urine samples were obtained for "base line" values. At this time magnesium sulfate (15 g, p.o.) was given as a stimulant to sulfur excretion and large amounts of coffee were administered orally to encourage diuresis.

Four hours after the accident, when no further reduction in skin radioactivity could be achieved by washing, the remaining contaminated areas were covered with bandages and the patient was transferred to a hospital where the staff had been alerted to receive him for observation and treatment.

B. *Hospital care*

Blood was drawn for hematological study and the patient was placed on the following regimen (abstracted from his hospital records):

(1) Ambulatory within the room.
(2) Regular hospital diet-force fluids.
(3) Save all stools and urine in special plastic container. Label time of excretion of each.
(4) Lanolin and Aquaphor to face.
(5) Methionine 0.5 g, Tryptophan 1.0 g } p.o. every 4 hr starting 1800 hours.
(6) Sulfur and molasses, 1 tbs. (15 ml) 1900 hours
(7) I.V. 1000 ml $H_2O$ containing 9.8 mg of sodium sulfate (140 mEq $SO_4$).
(8) Saturated solution of magnesium sulfate 30 ml at bed time.
(9) Rounded tsp. of DL-tyrosine in glass of fruit juice at 2000 hours.

Starting the second day, the following orders were added:

(1) Methionine 0.5 g, Tryptophan 0.5 g, Tyrosine 0.5 g } every 4 hr p.o.
(2) Collect all stools in 24-hr samples. Collect all urines in fractional periods ending at 0600, 1200, 1800, 2400.
(3) Collect 10 ml citrated blood at 1200, 1800, 2400 and 0600 hours.

That same day, tests were done for liver function, serum creatinine and BUN, blood glucose, and serology, and a bone marrow biopsy was obtained. On the third day, 15 grains of aspirin p.o., q. 6 hr was added to the regimen. On the fifth day a repeat I.V. infusion of sodium sulfate (containing 56 mEq of $SO_4$) was administered. Daily skin counts were made to follow the level of radioactivity of the contaminated areas. The patient was discharged on the seventh hospital day to be followed as an outpatient for 2 months with weekly blood counts.

With the exception of tiny cuts on his fingers and the reddening of his skin due to scrubbing, no abnormal clinical signs or symptoms were exhibited which could be in any way related to his exposure to radioactivity.

The patient was carefully surveyed on admission to the hospital with an end window geiger tube attached to a radiation monitor (Nuclear Chicago Laboratories, Model 1619). No calibration was available on this instrument for $S^{35}$; hence, there was no way of determining or even estimating the actual amount of radioactive sulfur present on the skin at any of the sites where activity was found. The counter was calibrated for consistency, however, with a radium source. The fact that erythema did not at any time develop in any area where radioactivity was found suggests that the quantity present was not sufficient to produce skin injury.

C. *Analytical methods*

All determinations of radioactivity in the samples obtained were corrected for background, quenching, absorption and decay by appropriate techniques.

1. *Blood analysis for radioactivity.* One-half ml aliquots of heparinized plasma were pipetted in duplicate and counted in 20 ml of a Cab-O-Sil aqueous phosphor solution on a Tri-Carb Liquid Scintillation Spectrometer.

Plasma proteins from 1 ml of plasma were precipitated by the addition of 2 ml 10% trichloroacetic acid. The precipitate was washed 3 times with 5% trichloroacetic acid, suspended in 10 ml thixin-toluene phosphor, and counted. Four-tenths ml of the trichloroacetic acid filtrate was pipetted into 10 ml aqueous phosphor and analyzed for $S^{35}$.

2. *Urine analysis.* Five-tenths ml of each urine sample was pipetted, in duplicate, into 20 ml aqueous phosphor solution. To determine the amount of radioactive sulfate in urine, 1 and

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10 ml aliquots of the urine were adjusted to approximately pH 3 with HCl. The urine was heated on a hot water bath for approximately 20 min, after which 10 ml barium chloride solution (10% solution) was added and the heating continued for at least an additional hour. The samples were allowed to stand overnight and then the $BaS^{35}O_4$ was filtered off on the tared filter disc. The precipitate was washed, dried, weighed and counted in the Gas Flow Counter.

3. *Fecal analysis.* Fecal samples were suspended in concentrated nitric acid. The total volumes were recorded and a 10 ml aliquot removed and heated with concentrated nitric acid until no solid matter was visible in the oxidation flask. Perchloric–nitric acid oxidation mixture was added to the sample and heated until a clear solution was obtained. Heating was continued for approximately 2 hr to insure complete oxidation of the sample. The sample was quantitatively transferred and made up to a known volume with distilled water. Aliquots of 0.4 ml were removed, in duplicate, and counted in 20 ml aqueous phosphor solutions. In an attempt to estimate the amount of elemental $S^{35}$ in the feces, a 200 ml aliquot of the combined fecal–nitric acid suspension was extracted with 100 ml benzene. The benzene was centrifuged and a 0.4 ml aliquot was counted in 10 ml of aqueous phosphor.

4. *Hair analysis.* A sample of hair, 1.56 g was oxidized with the perchloric–nitric mixture as described for feces. An aliquot was pipetted, in duplicate, into 10 ml aqueous phosphor solution and counted.

5. *Sternal sample.* On the second day of his hospital stay (about 36 hr after the accidental exposure) a sternal bone marrow specimen was obtained. The sample was oxidized with perchloric–nitric acid mixture as described above and an aliquot counted in aqueous phosphor.

6. *Skin.* On admission to the hospital, the patient had ten areas of radioactive contamination on his skin. These included the forehead, right upper lip, left upper chest, left forearm, right forefinger, front and back of right thigh, front and back of right knee and front of right calf. Counts (above background) in these areas ranged from 200 counts/min at the back of the right knee to a count beyond the range of the instrument used over the left forearm.

Daily counts of these skin areas indicated steadily and rapidly decreasing numbers of active sites and activity. On the day of discharge from the hospital (7 days post-accident), only two skin areas remained radioactive; the left forearm counted 500 counts/min and the anterior surface of the right knee counted 200 counts/min.

All clinical laboratory studies were within normal limits throughout the hospital course and have remained normal throughout the 3-year period since the accident. Cellular studies of the bone marrow biopsy indicated no abnormalities.

## RESULTS

The results of the determination of radioactivity in plasma, urine and feces have been recorded in Tables 1, 2 and 3, respectively.

Plasma samples were obtained and counted for 4 days after the accident, at which point activity approached background. Plasma proteins precipitated with trichloroacetic acid did

*Table 1. Radioactivity in plasma*

| Date | Sample time | Hours elapsed | Plasma cpm/ml | dpm/ml | Plasma content* ($\mu$c) |
|---|---|---|---|---|---|
| 3/28 | 1130 | 1.75 | 186 | 320 | 0.68 |
| | 1415 | 4.50 | 134 | 231 | 0.48 |
| 3/29 | 0545 | 20.00 | 84 | 145 | 0.31 |
| | 1200 | 26.25 | 54 | 93 | 0.20 |
| | 1415 | 28.50 | 48 | 83 | 0.17 |
| 3/30 | 0015 | 50.50 | 40 | 69 | 0.14 |
| | 0600 | 56.25 | 18 | 31 | 0.06 |

* Assuming a plasma volume of 5 per cent body weight, 4.65 l.

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*Table 2. Radioactivity in urine*

| Date | Time | Volume ml. | Total μc excreted/interval | | | | | Cumulative | % of Total |
|---|---|---|---|---|---|---|---|---|---|
| | | | A | B | C* | D* | Average | | |
| 3/28 | 1100 | 37 | 0.07 | — | 0.072 | 0.067 | 0.070 | 0.070 | 1.6 |
| | 1223 | 106 | 0.51 | 0.35 | — | 0.539 | 0.466 | 0.536 | 12.3 |
| | 1745 | 790 | 1.49 | 1.14 | 1.52 | 1.57 | 1.430 | 1.966 | 45.6 |
| | 2045 | 500 | 0.56 | — | 0.64 | 0.60 | 0.60 | 2.566 | 59.0 |
| 3/29 | 0030 | 690 | 0.59 | — | 0.66 | 0.664 | 0.638 | 3.204 | 73.7 |
| | 0430 | 360 | 0.40 | — | 0.44 | 0.268 | 0.369 | 3.573 | 82.1 |
| | 1200 | 335 | 0.27 | — | 0.32 | 0.138 | 0.243 | 3.816 | 87.7 |
| | 1800 | 360 | 0.15 | 0.13 | 0.10 | 0.066 | 0.111 | 3.927 | 90.3 |
| | 2400 | 1000 | 0.10 | 0.09 | 0.12 | 0.073 | 0.096 | 4.023 | 92.5 |
| 3/30 | 0600 | 195 | 0.05 | 0.04 | 0.039 | 0.016 | 0.036 | 4.059 | 93.3 |
| | 1200 | 790 | 0.06 | 0.06 | 0.048 | 0.042 | 0.053 | 4.112 | 94.5 |
| | 1800 | 422 | 0.02 | 0.01 | 0.014 | 0.014 | 0.015 | 4.117 | 94.6 |
| | 2400 | 1230 | 0.04 | 0.04 | 0.066 | 0.027 | 0.043 | 4.170 | 95.9 |
| 3/31 | 0600 | 572 | 0.02 | 0.02 | 0.019 | 0.011 | 0.017 | 4.187 | 96.3 |
| | 1200 | 760 | — | 0.02 | 0.028 | 0.020 | 0.023 | 4.210 | |
| | 1800 | 932 | 0.02 | 0.02 | 0.033 | 0.013 | 0.022 | 4.232 | |
| | 2400 | 952 | 0.02 | 0.01 | 0.019 | 0.010 | 0.015 | 4.247 | |
| 4/1 | 0600 | 742 | 0.02 | 0.02 | 0.019 | 0.014 | 0.018 | 4.265 | |
| | 1200 | 312 | 0.01 | 0.01 | 0.010 | 0.008 | 0.010 | 4.275 | |
| | 1800 | 402 | 0.02 | 0.01 | 0.014 | 0.003 | 0.017 | 4.292 | |
| | 2400 | 255 | 0.01 | — | 0.010 | 0.001 | 0.007 | 4.299 | |
| 4/2 | 0600 | 390 | 0.01 | — | 0.011 | 0.003 | 0.007 | 4.306 | |
| | 1200 | 168 | 0.008 | — | 0.005 | 0.002 | 0.005 | 4.311 | |
| | 1800 | 272 | 0.006 | — | 0.006 | 0.002 | 0.005 | 4.316 | |
| | 2400 | 365 | 0.01 | — | 0.009 | 0.003 | 0.007 | 4.323 | |
| 4/3 | 0600 | 230 | 0.007 | — | 0.007 | 0.002 | 0.006 | 4.329 | |
| | 1200 | 325 | 0.01 | — | 0.005 | 0.004 | 0.006 | 4.335 | |
| | 1800 | 195 | 0.006 | — | 0.005 | 0.001 | 0.004 | 4.339 | |
| | 2400 | 720 | 0.009 | — | 0.006 | 0.001 | 0.005 | 4.344 | |
| 4/4 | 0600 | 530 | 0.008 | — | 0.007 | 0.006 | 0.007 | 4.351 | |
| | 1200 | 382 | 0.008 | — | 0.006 | 0.003 | 0.006 | 4.357 | |
| 4/5 | 1630† | 490 | 0.01 | — | 0.006 | 0.005 | 0.021‡ | 4.378 | |
| 4/6 | 1700† | 440 | 0.005 | — | 0.005 | 0.004 | 0.017‡ | 4.395 | |
| 4/7 | 1700† | 260 | 0.005 | — | 0.004 | 0.002 | 0.017‡ | 4.412 | |
| 4/8 | 1700† | 378 | Background | | 0.005 | 0.002 | 0.012‡ | 4.424 | |

* Radioactivity collected as $BaS^{35}O_4$ by filtration.
† Note 6-hr collection, representative of 24-hr urinary excretion.
‡ Based on 1500 ml as 24 hr collection.

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*Table 3. Radioactivity in feces*

| Date | Time | Elapsed time hr | μc/collection | Cumulative μc | % of Total |
|---|---|---|---|---|---|
| 3/29 | 0030 | 14.45 | 4.74 | 4.74 | 55.4 |
| | 0815 | 22.5 | 1.96 | 6.70 | 78.0 |
| | ? | | 1.28 | 7.98 | 93.2 |
| | 1445 | 29 | 0.43 | 8.41 | 97.4 |
| | 1800 | 32.25 | 0.10 | 8.51 | 99.0 |
| 4/1 | — | | 0.04 | 8.55 | |
| | — | | 0.008 | 8.58 | |

not contain any detectable radioactivity at any time. The red blood cells were found to contain a small but significant amount of radioactivity, ranging from $\frac{1}{6}$ to $\frac{1}{2}$ the activity present in plasma. All radioactivity detected in the blood was present as water-soluble material, including that in the plasma. It seems likely that all of the radioactivity in the blood was present as sulfate, which would be anticipated based on reports in the literature that the oxidative mechanism of the body can readily convert elemental sulfur to water-soluble sulfate.[1–3]

A semi-logarithmic plot (Fig. 1) of the plasma data suggested that the rate of disappearance of $S^{35}$ from the plasma was exponential, with a half-life of approximately 19 hr. The solid line represents the equation $y = ae^{-kt}$ fitted to the observed data by the method of least squares. These data suggest a maximal plasma concentration following the accident, of 0.61 μc, assuming a plasma volume of 5 per cent body weight, or 4.65 l.

Microcuries of $S^{35}$ excreted in the urine have been plotted (Fig. 2) as a semi-logarithmic function against time. Since the data appeared to be an exponential function, the equation $y = a\ (1 - e^{-kt})$ was fitted to the data of an accumulation plot (Fig. 3) of urinary radioactivity. The observations have been plotted about the line generated using $a = 4.29$ μc and the rate function $k = 0.076$.

A comparison of the data in columns C and D (Table 2), radioactivity precipitable as barium sulfate, and columns A and B, total urinary radioactivity, indicates that approximately 90 per cent of the urinary $S^{35}$ can be accounted for as sulfate. Considering experimental error, it seems probable that all or almost all the radioactivity in these urine samples was present as sulfate-$S^{35}$.

The extremely erratic nature of the excretion of fecal $S^{35}$ does not justify a cumulative plot, but the data suggest that a maximum of 9 μc of $S^{35}$ might reasonably be anticipated; since only 0.002 μc $S^{35}$ could be extracted from the total fecal radioactivity with benzene as elemental $S^{35}$, it seemed likely that the total activity was present as sulfate.

The rapid drop in radioactivity detectable in plasma, urine and feces indicates a rapid and steady clearance of residual $S^{35}$ from the body. Bone marrow did not contain any radioactivity above normal background. A sample of hair

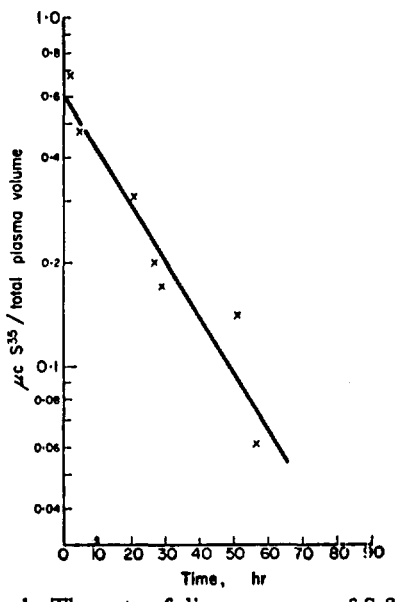


FIG. 1. The rate of disappearance of S-35 from plasma.

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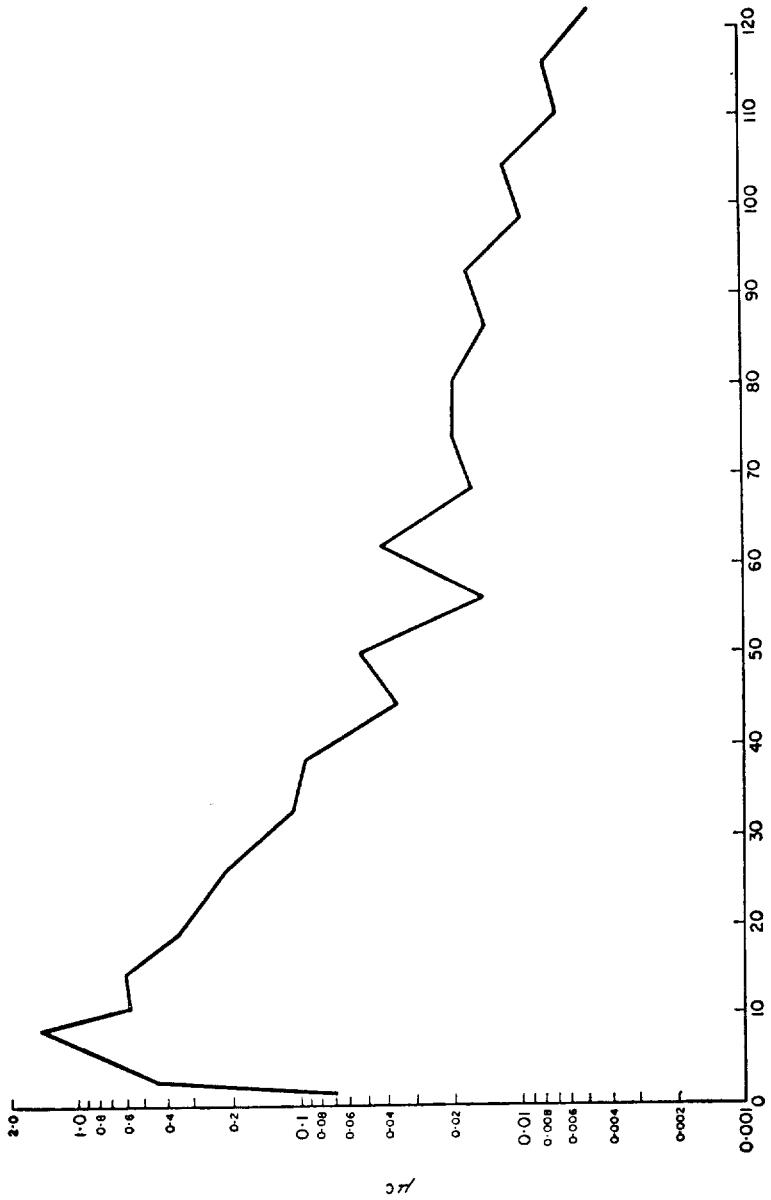


FIG. 2. The rate of urinary excretion of S-35.

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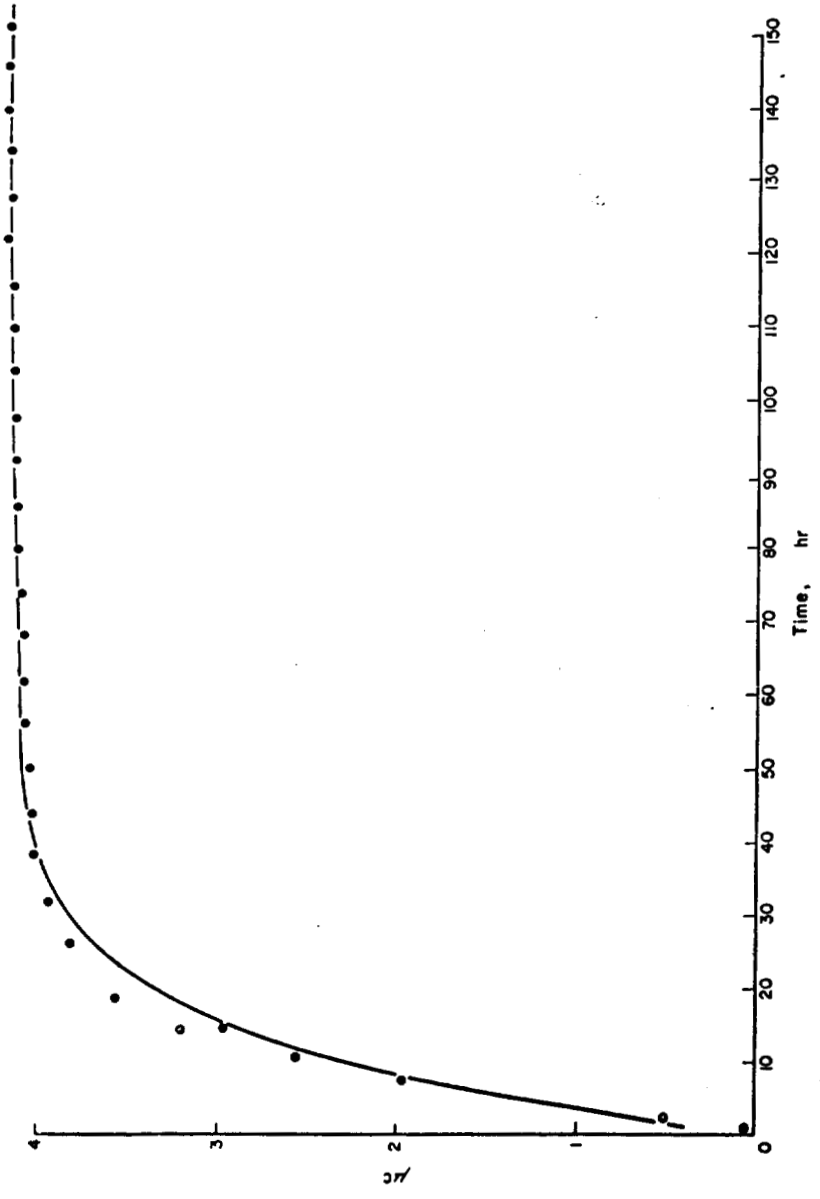


FIG. 3. An accumulation plot of the urinary excretion of S-35.

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obtained 2 months after the accident contained approximately 2–14 counts/min above background, in the duplicate samples (utilizing two slightly different methods). This observation is in accord with the statements of SMYTHE and HALLIDAY,[4] SINGHER and MARINELLI[5] and DZIEWIATKOWSKI[1,6] that inorganic sulfur may be incorporated into cysteine in the human, possibly through the reversible action of desulfurase.

## DISCUSSION

Internal contamination could have occurred by direct absorption through superficial cuts on the face and hands, or by absorption through the skin, or could have been acquired through inhalation or swallowing of contaminated air. All are equally difficult to evaluate as sources, and the extent of contamination from any single avenue is impossible to quantitate.

Data in the literature[7–10] indicate that elemental sulfur may be absorbed percutaneously. As ROTHMAN has pointed out[10] this absorption would be enhanced by simultaneous exposure of the skin to benzene. These reports coincide with the observation that although the incident radioactivity could not be removed completely from the skin by a variety of treatments, it disappeared within a few days, presumably due to absorption into the body.

Since the maximum blood level of radioactivity found occurred within 2 hr after exposure it seems most likely that the major amount of radioactivity in the blood was due to rapid absorption of $S^{35}$ from the lung. Material swallowed would be absorbed from the GI tract and might appear later in the blood. It is possible that the benzene was volatilized by the explosion and formed an aerosol of the elemental $S^{35}$. Studies with radioactive aerosols indicate that they follow the mechanical movements of inspired air; hence, some of the material inhaled was probably also exhaled. It is likely that the constant draft of the hood (125–250 $ft^3$/min) also helped to reduce this source of exposure.

In an attempt to prevent utilization of $S^{35}$ in ordinary metabolic pathways sulfur was administered to the patient in a variety of forms. Sodium sulfate was infused shortly after the patient entered the hospital and again on the fifth day, to dilute any radioactive sulfate in the blood, as well as to function as an osmotic diuretic. Sulfur and molasses administered after admission was followed by a second oral dose of magnesium sulfate. Methionine was given to provide a readily usable source of organic sulfur.

Data in the literature indicate that colloidal sulfur is readily absorbed from the intestinal tract of rats[1,3,11] and humans,[12] and only a small quantity of $S^{35}$ is excreted via the gastrointestinal tract. Thus the high fecal excretion (65 per cent of total $S^{35}$ recovered) of 9 $\mu$c was unexpected. Therefore, it seems likely that the prompt administration of magnesium sulfate approximately 1 hr and 5 hr after the accident with subsequent administration of sulfur and molasses and other forms of utilizable sulfur may have prevented more extensive absorption of the $S^{35}$.

Tyrosine was administered to aid sulfate excretion via urinary etheral sulfate. DZIEWIATKOWSKI[1,5] has shown that sulfate sulfur can be utilized in the synthesis of urinary ethereal sulfate for excretion with phenol, and according to TALLOW *et al.*[13] about half of the bound tyrosine excreted daily by man is ethereal sulfate.

Aspirin was administered in hopes of increasing the excretion of ethereal sulfate, but this procedure is not clearly justified by reports in the literature[14,15] which indicate that acetylsalicylic acid, unlike salicylamide, is not conjugated with sulfate, at least *in vitro*.

To estimate total body burden we have accepted the assumptions stated in the National Bureau of Standards Handbook No. 52.[16] Following inhalation of an insoluble radioisotope, 12 per cent is retained in the lower respiratory tract and the remainder is eliminated by swallowing or exhalation. If we ignore any elimination by exhalation and assume that the total amount eliminated by the feces, approximately 9 $\mu$c, represents 88 per cent of the dose received, the total body burden may be estimated as approximately 10 $\mu$c.

Since the 12 per cent retained by the lower respiratory tract goes to blood, we might expect 1.2 $\mu$c in blood based on this partition; since the maximum concentration estimated for total plasma volume was 0.61 $\mu$c, this is a reasonable estimate. However, the observations of

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WALSER[17] indicate that sulfate-$S^{35}$, administered intravenously to humans, becomes distributed, within 15–20 min, in a reproducible space which is 16 per cent of the body weight. Based on this figure the circulating $S^{35}$ might be expected to be 2.5 $\mu$c, which exceeds by at least a factor of 2 the estimated blood value. Moreover, the total urinary and fecal radioactivity recovered was approximately 13 $\mu$c, which exceeds the body burden of $S^{35}$ estimated on the assumptions above.

Since the body can readily convert insoluble elemental $S^{35}$ to a soluble form,[1,2] it may have been distributed accordingly. Soluble isotopes are assumed to be partitioned:[16] 50 per cent swallowed, 25 per cent exhaled and 25 per cent retained in the lower respiratory tract, from which they go to the blood and are ultimately excreted in the urine. Based on a fecal content of 9 $\mu$c, a total body burden of approximately 18 $\mu$c might be estimated, 4.5 $\mu$c ultimately being excreted in the urine. This estimation is at least in accord with our observations.

Assuming further that all of the $S^{35}$ appearing in the urine was absorbed from the intestinal tract, rather than coming from the lungs, we might expect that 13 $\mu$c had been swallowed, giving an estimated body burden of approximately 26 $\mu$c. This estimate would also ignore the entrance of any radioactivity into the blood stream via cuts from the flying glass of the explosion or by absorption through the skin from surface contamination. Hence it would appear, without attempting to justify any of the above reasoning, that a total body burden of 13, minimum, to 26 $\mu$c, maximum, is a reasonable range.

The hazard from internal deposition of radioisotopes is always of concern. However, $S^{35}$ with an average energy ($E_\beta$) of 0.049 MeV[18] may be of relatively little concern, for 0.1 mc uniformly distributed in the body of 90 kg man would produce approximately 0.003 rad/day[19] or, with decay, approximately 0.019 rad/week. The AEC regulations[20] limit body burden, on a continuous 50-year basis, to a dose calculated to deliver not more than 0.1 rem/week to the gonads or total body and somewhat more to other specified organs. Even had this estimated dosage equaled the permissible dosage, tissue damage would not be anticipated because the permissible dosages have not been chosen as a result of positive evidence of damage. Moreover, $S^{35}$, with a half-life of 86.35 $\pm$ 0.17 days,[21] has been estimated to have a biologically effective half-life of 26.1 $\pm$ 41.8 days,[18] which markedly reduces the possible time of exposure.

The only indication in the literature concerning tissue damage caused by $S^{35}$ is that of GOTTSCHALK *et al.*[22] who injected 559–926 mc for treatment of cancer; at these doses significant hematological effects were observed. These observations have been confirmed by ANDREWS *et al.*[23] who administered 1.0–8.8 mc sodium sulfate-$S^{35}$ intravenously as tracer doses, and ultimately approximately 1 c, in three increments, to chondrosarcoma patients. Severe, but reversible, depression of hematopoiesis occurred after administration of 1 c of $S^{35}$. GOTTSCHALK's patients required transfusions.

It is generally agreed that inorganic sulfur compounds, regardless of the route of administration, are rapidly excreted from the body[2,11,23–27] and are thus not likely to be damaging. Methionine-$S^{35}$ and cystine-$S^{35}$, however, are recycled in body proteins and in this manner $S^{35}$ is retained in the body. Doses of 0.1–5 mc of methionine-$S^{35}$ have, nevertheless, been administered to humans, without observable detrimental effects.[28–30]

We believe, therefore, that the total body burden in this case of 13–26 $\mu$c did not constitute a significant internal radiation hazard.

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AUTHOR: R. G. Gottshalk, L. K. Alpert and P. O. Miller (V.A. Center, Martinsburg, W.Va.)

Termatrex Number _____

TITLE: USE OF LARGE AMOUNTS OF RADIOACTIVE SULFUR IN PATIENTS WITH ADVANCED CHONDROSARCOMA. II. Distribution and Tissue Irradiation

JOURNAL:

REPORT No:

FILED:

Abstracted by: S.R/Bernard and C.F.H. Date: 3 August 1964

KEY WORDS:

ANIMAL: ✓man, cow, dog, goat, guinea pig, monkey, mouse, pig, rabbit, rat, sheep, other mammals, other vertebrates, Cells and Microorganisms

AGE: embryo, feotus, infant, young, ✓adult, aged

SEX: male, ✓female

CONDITION: ✓pathological, grossly normal

METHOD: single, ✓multiple, continuous, inhalation, oral, ✓IV, IM, IP, SC, IT, submersion, surface absorption

ISOTOPE: $Sr^{85}$, $Pu^{239}$, etc.

S-35

ELEMENT: Sr, U-nat, etc.

LEVEL: tracer, chronic, toxic, ✓high 0.5-0.9 c.

CHEMICAL FORM: acetate, carbonate, citrate, halide, nitrate, oxide, phosphate, ✓sulphate, thymidine, organic, Other form, ✓carrier free

PHYSICAL FORM: aerosol, gas, particle data, solid, ✓solution (suspension or colloid)

LENGTH OF EXPERIMENT: hour; day; week; ✓month; year

SOLUBILITY:
Soluble - acid; blood; GI tract; Lung; Water
InSoluble - acid; blood; GI tract; Lung; Water

STANDARD ANIMAL DATA:
Intake/day: air; food; water
Elimination/day: air; food; water; elements
Composition: whole body; body organs
Mass: whole body, body organs
Radius: body organs

DIET DATA:
food; water
Diet: composition (elements)
Diet: % water; % solid

OTHER DATA (discussed):
Chemical toxicity
Radiotoxicity
Uptake
RBE and/or MF
MPC's
Power Function
Exponential
✓Variability

OTHER DATA:
bibliography
$f_1$ (fraction from GI tract to blood)
$f_2$ (fraction in organ of reference of that in total body)
✓$f_2'$ (fraction from blood to organ of reference)
$f_a$ (fraction in organ of reference by in halation)
$f_w$ (fraction in organ of reference by ingestion)
✓$T_b$ (biological half-life)
$T_r$ (radioactive half-life)
T (effective half-life)
$f_f$ (fraction in feces)
$f_u$ (fraction in urine)
fecal to urine ratio
blood to urine ratio

| WHOLE BODY AND BODY ORGANS | %deposited | %retention | Burden | distribution | Elimination Urine | Elimination Fecal | Time |
|---|---|---|---|---|---|---|---|
| WHOLE BODY | | | | | | | |
| Adrenal | | | | | | | |
| Aorta | | | | | | | |
| Blood | | | ✓ | | | | |
| Bone | | | ✓ | | | | |
| Brain | | | | | | | |
| Breast | | | | | | | |
| Gastrointestinal tract | | | | | | | |
| Esophagus | | | | | | | |
| Stomach | | | | | | | |
| Duodenum | | | | | | | |
| Jejunum | | | | | | | |
| Ileum | | | | | | | |
| Cecum | | | | | | | |
| Sigmoid colon | | | | | | | |
| Rectum | | | | | | | |
| Heart | | | | | | | |
| Kidney | | | | | | | |
| Larynx | | | | | | | |
| Liver | | | | | | | |
| Lung | | | | | | | |
| Muscle | | | ✓ | | | | |
| Diaphragm | | | | | | | |
| Pectoral | | | | | | | |
| Psoas | | | | | | | |
| Omentum | | | | | | | |
| Ovary | | | | | | | |
| Pancreas | | | | | | | |
| Prostate | | | | | | | |
| Skin | | | ✓ | | | | |
| Spleen | | | | | | | |
| Testis | | | | | | | |
| Thymus | | | | | | | |
| Thyroid | | | | | | | |
| Tongue | | | | | | | |
| Trachea | | | | | | | |
| Urinary bladder | | | | | | | |
| Uterus | | | | | | | |
| Vagina | | | | | | | |
| Fat | | | ✓ | | | | |
| Cartilage | | | ✓ | | | | |
| Bone marrow | | | ✓ | | | | |
| Blood serum | | | ✓ | | | | |
| Tumor | | | ✓ | | | | |

OTHER DATA:

Tissue doses estimated.
Analytical procedure given.

June 18, 1964

TX-3514 (6-64)

Abstract: (by S. R. Bernard) and C. F. Holoway

Three patients with chondrosarcoma were given multiple injections (3, 5 and 6, respectively) of S-35, in the range of 100-200 mc/injection, for total doses of 0.5 to 0.9 curie, depending on patient condition, in an attempt at (palliative) therapy.

S-35 concentrations in those organs (under burden) checked for key word-indexing, on reverse side, were measured at various times after I.V. injection.

The authors give a $T_b$ for skin of 9.7 days (and also of 26.1 days based upon a different time period) for 1 patient, and 165 days for a 2nd patient, and of 20.5 days for a 3rd patient.

In addition, a $T_b$ is given for the chondrosarcoma.

The authors show a plot of μc/gm. wet tissue versus time in days for the chondrosarcoma and for blood. These data should be analyzed in terms of a multiple exposure intake to check on their $T_b$ values and to obtain an estimate of $f_2'$ for those organs checked for key-word index.

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# The Use of Large Amounts of Radioactive Sulfur in Patients with Advanced Chondrosarcomas

## II. Distribution and Tissue Irradiation*

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A previous paper (12) described the clinical observations of three patients with advanced chondrosarcomas following the administration of 559 to 926 mc. of radioactive sodium sulfate in divided intravenous injections. The plan of treatment (12) was based on the fixation of tracer doses of radiosulfur by human chondrosarcomas (11) and on the toxic effects of large amounts of radiosulfate for growing epiphysial cartilage in experimental animals (10, 14). Large injections of radiosulfur were administered to these patients after initial studies showed that their tumors retained significant amounts of $S^{35}$ 64 hours after the injection of tracer doses. A total of three to six large increments of $S^{35}$ was administered until there was evidence of leukopenia and thrombocytopenic effects (12). Analyses of tissues obtained after the series of injections provided data on the long-term retention of the isotope and permitted an estimation of the doses of radiation internally delivered to the chondrosarcomas and to other tissues.

## MATERIALS AND METHODS

Tissue specimens obtained at surgery or, in one case, at necropsy (12) were analyzed in duplicate for the total content of radiosulfur by the Denis method (2). Weighed samples were hydrolyzed with sodium hydroxide and oxidized by ashing with Denis reagent in the presence of carrier sodium sulfate. The residue was dissolved in hydrochloric acid, and the pH was adjusted to 2.5. The solution was heated to near boiling, and barium chloride was added dropwise. The sulfate precipitate was allowed to age and was collected on discs of Whatman 42 or Schleicher and Schuell 589 filter paper with the use of lucite filtering assemblies and 20 cm. mercury of differential pressure. The filter paper discs were mounted on planchets, dried, weighed, and counted in the Geiger-Müller range with a Micromil-window Nuclear gas-flow counter, automatic sample changer, and scaler. At least 6,000 disintegrations were counted, and the values were corrected for coincidence and for self-absorption. With each group of samples aliquots of the last injected $S^{35}$ solution were processed in the same fashion or were added before the precipitation to processed blank solutions. The recovery of $S^{35}$ varied from 90 to 104 per cent and averaged 97 per cent.

Duplicate analyses of normal tissues generally agreed within $\pm 5$ per cent. Because of the tissue variations of neoplasms, duplicate analyses were done on each of three to six specimens obtained from different portions of the chondrosarcomas.

The samples taken in duplicate for analysis were supplemented by a third one that was fixed in formalin and sectioned for control of the histological structure. Radioautographs were prepared from these "chemical control" blocks and also from larger sections used for histological study. The radioautographs were prepared by holding strips of Kodak Contrast Ortho Process film against microscopic sections of tissue specimens fixed in formalin and embedded in paraffin. These radioautographs demonstrated the localization of radiosulfur incorporated in tissue structures (sulfated mucoproteins, etc.) except for the compounds soluble in water or formalin. The dialyzable or formalin-soluble $S^{35}$-labeled compounds decrease rapidly with time in the cartilage and bone of experimental animals (6, 18).

The samples of blood obtained at the same time as the surgical specimens (Table 1) were analyzed by the same chemical method. In addition, the rate of disappearance of $S^{35}$ was followed by direct measurements of the radioactivity of numerous blood and serum samples obtained after each isotope injection. Aliquots of dilution in water of blood or serum samples were dried on stainless steel planchets with and without addition of $S^{35}$ standard solution for reference and for self-absorption correction.

## RESULTS

*Concentration of radiosulfur in tissues.*—Because of the weakness of the beta radiation of $S^{35}$ the uptake of this isotope in deep tissues can be measured only by chemical analyses and specimen counting, and not by external monitoring. The energy of the beta radiation from $S^{35}$ is too low for measurable Bremsstrahlung to be produced.

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† Mailing address: Veterans Administration Center, Martinsburg, West Virginia.

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Table 1 gives the $S^{35}$ content of the tissue samples on the day of the operations. They were calculated in μc/gm wet weight. To facilitate the comparison of the degree of uptake after injection of various amounts and after different intervals, the tissue concentrations are given in the table in per cent of the cumulative average amounts injected (mc/kg or μc/gm). This is the concentration of $S^{35}$ that would have been produced if each amount of $S^{35}$ injected had been evenly distributed in the entire body and not excreted, and if it had undergone physical decay to the day of the operation. These per cent values correspond to the "differential absorption ratio" of Marinelli, Quimby, and Hine (20). They reflect the degree of biological uptake and the biological turnover of the isotope in the different tissues of each patient.

The results showed the high uptake and the long retention of $S^{35}$ in the chondrosarcomas. The average concentration of $S^{35}$ in the tumors was consistently higher than in any other tissue obtained at the same operation. There was considerable variation between different tumor samples since they included, whenever possible, deep and superficial portions, or areas of varying differentiation or viability, or different proportions of fibrous stroma. Even duplicate analyses of adjacent tumor samples were more variable than those of normal tissues. This could be correlated with the uneven fixation of $S^{35}$ in the tumor samples, which was demonstrated by the corresponding radioautographs (see Figs. 1–6A). Chemical analyses of the different specimens obtained after tracer injection or at the first operation after the series of large injections showed that the samples from the growing edges of the tumor or from the chondroid or myxomatous portions had high uptakes and that necrotic or calcified samples had low uptakes. A lower average isotope concentration was found in the tumor of patient 1 on July 24 than on Septem-

TABLE 1

CONCENTRATION OF ISOTOPE IN TISSUES AND BODY FLUIDS FOLLOWING $S^{35}$ INJECTIONS μc/gm wet tissue

| | Final injection: 29 April (57 days) = 0 Patient #1 559 mc days | | | | Patient #2 913 mc | | Patient #3 684 mc | |
|---|---|---|---|---|---|---|---|---|
| Date tissues obtained | Feb. 21 | May 21 | July 24 | Sept. 20 | Apr. 21 | June 27 | May 12 | July 22 |
| Interval since last inj. 2.67 days | 64 hr. | 22 days | 86 days | 144 days | 64 hr. | 16 days | 64 hr. | 39 days |
| Total mc. previously inj. | 3.8 | 559 | 559 | 559 | 3.1 | 926 | 2.2 | 686 |
| Cumul. av. amount (μc/gm)* | 0.084 | 8.06 | 4.84 | 3.05 | 0.036 | 8.48 | 0.030 | 6.30 |
| $S^{35}$ conc. in tissues (% of cumul. aver. amount)* | | | | | | | | |
| Skin | 38.3 | 2.7 | 0.48 | | 10.8 | 9.4 | 25.9 | 5.9 |
| Adipose tissue | 14.4 | 0.17 | 0.03 | | 1.70 | 0.61 | 8.5 | 2.1 |
| Muscle | | 0.41 | | | 2.75 | 0.49 | | 1.2 |
| Tumor Av. | 168.5† | 96.6§ | 2.5** | 10.0§§ | 102.3## | 79.0## | 294.0††† | 180.5‡‡‡ |
| Max. | 197.1 | 315.2# | 12.9†† | 11.3 | 217.5‖‖ | 190.1‖‖ | 335.4 | 281.0 |
| Min. | 98.5 | 7.1‖ | 0.4 | 8.6 | 26.2*** | 13.6*** | 209.0 | 84.0 |
| (No. samples) | (7) | (8) | (12) | (5) | (8) | (12) | (8) | (12) |
| Cartilage | | | | | 27.7 | | | 50.2 |
| Bone | 121.7‡ | | 0.4‡‡ | | 30.2 | | | 1.8 |
| Bone Marrow | | | | | 69.3 | | | 5.8 |
| Blood | | 0.066 | | 0.0028 | 3.4 | 0.25 | 5.2 | 0.28 |
| Serum | 14.3 | 0.068 | | 0.0032 | 5.7 | 0.30 | 7.1 | 0.48 |

* Total amount of $S^{35}$ injected in mc/kg body weight or in μc/gm, adjusted for the physical decay of $S^{35}$ from injection to operation.

† Chondrosarcoma (¼ to ½) in inflamed fibrous stroma.

‡ Rib invaded by tumor (1/10).

§ Cystic tumor with semiliquid degenerated chondrosarcoma.

\# Inner part of cyst wall, about ¾ fibrous tissue, ¼ chondrosarcoma. The outer part of the wall was made of fibrosed muscle, and the uptake of this sample was 4.7 per cent of the cumulative injected amount.

‖ Tumor fluid filtered through gauze.

** Ulcerated tumor with inflammation.

†† Necrotic tumor fragments.

‡‡ Necrotic rib with about 1/10 tumor.

§§ Semiliquid content of cystic chondrosarcoma.

\#\# Well differentiated chondrosarcoma, ¼ to ¾ stroma.

‖‖ Peripheral portion of tumor, cartilage-like.

*** Calcified and degenerated deep portion of tumor.

††† Chondrosarcoma of back, about ¼ stroma.

‡‡‡ Six samples of tumor of back, two of primary endosteal tumor in rib, two of intrathoracic tumor, two of tumor fluid inside chest.

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ber 20, but the former tumor was ulcerated with abundant inflamed stroma, since it had to be resected as an emergency measure.

The uptake in the costal cartilage samples stripped of perichondrium was one third to one fourth of the average uptake in the corresponding chondrosarcoma samples and close to their minimum values.

The slow rate of turnover in the chondrosarcomas contrasted with the fast rate of disappearance from the blood so that the ratios of $S^{35}$ content in tumor and blood after the injections of large amounts varied from 310 to 3570.

The uptake in muscle and adipose tissue fell rapidly to relatively low levels. The $S^{35}$ concentrations were higher in the wasted adipose tissue of patients 1 and 3 than in the fat-laden adipose tissue of patient 2.

Specimens of iliac bone marrow obtained early after injection of a tracer dose to patient 2 contained more $S^{35}$ than did normal cartilage. Animal studies have demonstrated a high uptake in hematopoietic marrow but a faster release than from cartilage (4, 5). The concentration of $S^{35}$ in six samples of costal and vertebral bone marrow obtained at the necropsy of patient 3 was quite variable and may have been misleadingly low, since the bone marrow had a high proportion of adipose tissue with foci of hematopoietic regeneration. The hematopoietic cells which have a relatively high $S^{35}$ uptake (22) had probably been removed following the leukopenic and thrombocytopenic effects of large doses of $S^{35}$ (12).

The high $S^{35}$ content of the bone specimens of patient 1 was a reflection of the neoplastic invasion of these portions of ribs. The specimens of bone of patients 2 and 3 were made up of thin cortical bone from the iliac crest and from the femoral condyle, respectively. Adherent red bone marrow was responsible for most of the uptake in the sample of patient 2 as indicated by the corresponding radioautograph.

The skin (dermis and epidermis) had a moderate uptake and a relatively long retention of $S^{35}$. Counts measured against the surface of the skin vary in different areas even early after injection by a factor of about 2 (9), so that the analyses of the skin samples obtained from the hip (April 21) and from the thigh (June 27) of patient 2 may indicate too slow a rate of turnover or may be taken as indication of the ability of the skin to concentrate $S^{35}$ from a metabolic pool as postulated by Denko and Stoughton (3).

There was little evidence to indicate that chondrosarcomas could actively concentrate $S^{35}$ late after injections from such a metabolic pool despite the significant amounts of isotope found in tumors that became prominent only late after the injections (samples of July 24 and September 20, Patient 1). Radioautographs of these tumors showed a high uptake in some necrotic areas, probably remainders of the original tumor, and none in other necrotic portions or in recently formed tumor foci. The pattern of translocation of the isotope in the chondrosarcomas was most suggestive of local fixation for extremely long periods of time.

*Doses of radiation delivered.*—The doses of radiation internally delivered by radiosulfur were calculated from the results of the sample analyses. The results are summarized in Table 2.

The radiation dose-rate $R$ delivered to a tissue containing C $\mu$c $S^{35}$/gm is given by

$$R = 51.2 \times C\ \bar{E}_\beta \text{ rad/day} \quad (19)$$

$$= 2.51 \times C \text{ rad/day},$$

where $\bar{E}_\beta$ is the average energy of the beta radiation in MEV, which for $S^{35}$ is 0.049.[1]

In view of the short distance traveled by the soft beta radiation, variations in radiation dose closely follow variations in concentration.

Only for the *blood* was it possible to obtain a number of samples at intervals after each isotope injection, so that no theoretical consideration of "half-life" had to be introduced in the calculations. Following each injection there was a high initial peak of concentration followed by a rapid disappearance, as observed after tracer amounts (9, 11) (Chart 1). The smoothest possible curves were fitted to the experimental values of $S^{35}$ in the blood ($\mu$c/gm) plotted on semi-logarithmic graphs.

The concentration produced immediately after each $S^{35}$ injection was derived from the property of sulfate-$S^{35}$ to be initially distributed evenly in the extracellular fluid and plasma (25). With 0.16 used as the ratio of the extracellular fluid volume to the body weight $W$ (kg.) and $H$ as the hematocrit value (per cent volume of packed cells), the initial concentration of $S^{35}$ in the blood after the injection of an amount $A$ (mc.) was:

$$C_o = \frac{A \times (100 - H)}{W \times 0.16 \times 100}\ \mu\text{c/gm}.$$

A factor of 0.18 or 0.20 was substituted when edema developed in patient 3. The amount of $S^{35}$ remaining in the blood from one injection to the next one could be ignored, since it amounted to less than 2 per cent of the calculated initial concentration.

[1] The corresponding values in rep quoted in the abstract (13) were obtained by using the formula $R = 60 \times C \times \bar{E}_\beta$ rep/day and the older value of $\bar{E}_\beta = 0.055$ MEV (7).

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Gottschalk et al II. Cancer Res. 19, 1078-85 (1959)



TABLE 2

IRRADIATION DELIVERED TO TISSUES BY RADIOSULFUR

| Patient | Period | Days | Blood | Chondrosarcoma | | | | Skin | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | rad | T½biol* (days) | T½eff* (days) | rad (av.) | rad (max.) | T½biol* (days) | T½eff* (days) | rad |
| #1 | Feb. 18–May 21 | 92 | 39 | 58.0 | 34.8 | 1734 | 2029 | 9.7 | 8.7 | 184.30 |
| | May 21–Sept. 20 | 122 | 0.32 | 37.4 | 26.1 | 707 | 2306 | 26.1† | 20.1† | 1.58 |
| | Sept. 20–Total decay | | 0.007 | " | " | 29 | 33 | " | " | 0.02 |
| | Total | | 40.14 | | | 2470 | 4368 | | | 185.90 |
| #2 | Apr. 18–June 27 | 70 | 54.19 | 80.5 | 41.8 | 761 | 1617 | 165 | 57.0 | 104.8 |
| | June 27–Mar. 3 | 249 | 7.55 | " | " | 995 | 2395 | " | " | 157.0 |
| | Mar. 3–Total decay | | 0.001 | " | " | 16 | 40 | " | " | 8.0 |
| | Total | | 61.74 | | | 1772 | 4052 | | | 269.8 |
| #3 | May 9–July 22 | 74 | 66.50 | 62.5 | 36.4 | 2197 | 2503 | 20.5 | 16.6 | 134.9 |
| | July 22–Total decay | | 1.22 | " | " | 1464 | 2277 | " | " | 22.5 |
| | Total | | 67.72 | | | 3661 | 4780 | | | 157.4 |

* Ditto signs indicate that the extrapolated value of half-life was used in the calculations and not an identical experimental value.

† Based on period May 21–July 24.

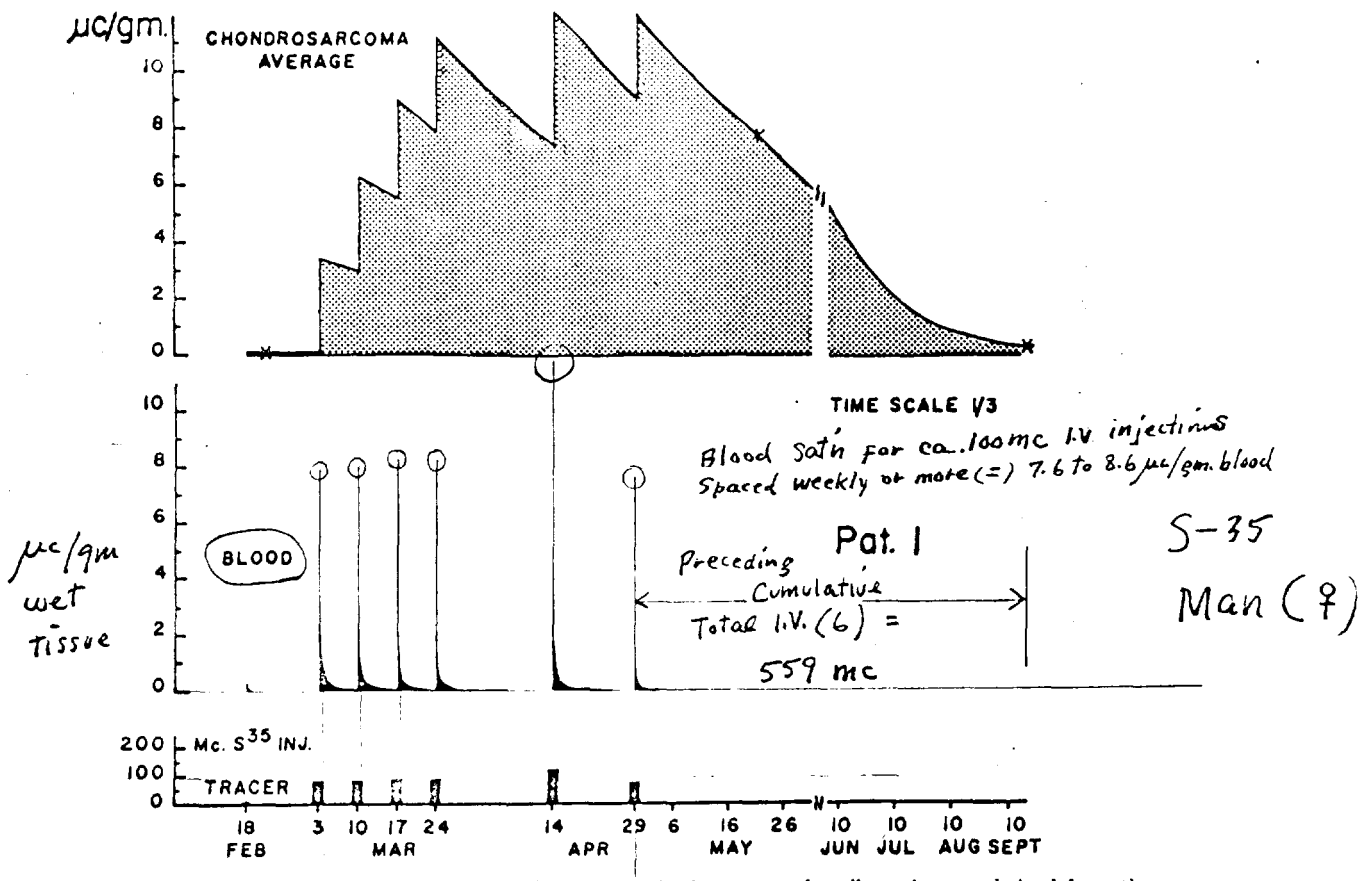


CHART 1.—Concentration of radiosulfur in the blood and in the chondrosarcoma of patient 1 at varied intervals after isotope injections (indicated by columns). The base line of the blood concentration is not indicated when the concentration fell under 0.02 µc/gm. The concentration in the chondrosarcoma is the average for all portions as derived from the specimens obtained at operations (indicated by X, see text). The surfaces under the curves are proportional to the irradiation received.

0 7 17 24 45 60

Days

Δ = 7 10 7 21 15

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Chart 1 shows the changes of concentration of $S^{35}$ in the blood of patient 1 plotted on an arithmetic scale; the areas under the curves are proportional to the irradiation delivered. The total doses delivered to the blood of the different patients during the periods of observation varied from 40.1 to 66.5 rad. Only small additional values were obtained by extrapolating the curves to total decay (Table 2).

Since tissue samples could be obtained only by a limited number of surgical procedures, the radiation doses delivered to the tissues were estimated by calculation.

Since experience with radioautographs of *chondrosarcomas* showed that radiosulfur was fixed for long periods and not homogeneously distributed, it appeared preferable to base the calculated half-life values on the average concentrations of $S^{35}$ realized in all tumor samples rather than only on the samples having the highest uptake.

There was little difficulty in calculating the half-life of $S^{35}$ and the irradiation delivered to the tumor of patient 1 for the period of May 21 to September 20, since no radiosulfur was injected during the interval. The values were based on simple exponential decrease between these 2 days.[2]

To calculate the irradiation dose delivered during and after the period of divided amounts administered, the following hypotheses were accepted:

*a*) The concentration of isotope produced in a tissue at a given time after the injection was proportional to the amount injected.

*b*) The rate of disappearance from the tissue was a decreasing exponential function.

These assumptions are obvious simplifications, but they are generally used in isotope studies. They do not take into account many factors such as the possible interference with metabolism at "toxic" levels, nor the variations in the physiological condition of the patients, or dynamics involving several "compartments" (21). They helped, however, to visualize the rate of turnover in tissues and to obtain a crude estimate of the radiation doses, since the divided injections were necessary in first attempts in patients.

The concentrations produced in a tissue shortly (64 hr.)[3] after an injection decreased exponentially until the next injection when the new increment of isotope concentration was added, the sum following again the same rate of turnover (Chart 1). That divided doses had to produce such cumulative increases of concentration of isotope in tissues having a slow rate of turnover can be seen by noting how high a percentage of the "cumulative average amount" was retained in the chondrosarcoma specimens obtained at the first operation following the series of injections, as compared with the uptake after tracer doses (Table 1).

The rate of turnover can be approximated as follows:

Let us call

$C$ the average concentration of isotope ($\mu$c/gm) in the tissue at the time of the biopsy;

$C_1$, $C_2$, $C_3$, etc., the concentrations resulting from each separate injection of amounts $A_1$, $A_2$, $A_3$, etc. (mc.), made $T_1$, $T_2$, $T_3$, etc. (days) before the biopsy to a patient weighing $W_1$, $W_2$, $W_3$, etc. (kg.);

$F$, the fraction of the amount injected per kg. that was found in the same tissue 64 hours (2.7 days) after the tracer injection;[4] and

$T_e$, the effective half-life,

Then $C = C_1 + C_2 + C_3 + \text{etc.}$

$$= F\frac{A_1}{W_1}2^{-(T_1-2.7)/T_e} + F\frac{A_2}{W_2}2^{-(T_2-2.7)/T_e} + F\frac{A_3}{W_3}2^{-(T_3-2.7)/T_e} + \text{etc.}$$

The value of the effective half-life was obtained from this equation and from the experimental values of $S^{35}$ concentration.

The biological half-life ($T_b$) was obtained by

$$\frac{1}{T_e} = \frac{1}{87.1} + \frac{1}{T_b}$$

It was also verified by direct but somewhat longer calculations from the fractions of the injected amounts corrected for physical decay that were retained in the tissues (Table 1).

The calculated values of half-life were in the same range for the chondrosarcomas of the different patients and indicated a long retention in the

[2] The values of July 24 were not used in the calculation, since this tumor was ulcerated and the average isotope concentration (but not the maximum) was below that found at the next biopsy.

[3] The 64-hour interval was chosen arbitrarily for the tracer biopsy to reflect the early high uptake. In rats the maximum uptake in cartilage occurs after 24 hours and decreases slowly thereafter (1,4). The time of maximum uptake in man is not accurately known because of the difficulty of serial biopsies. Recent serial analyses of mucinous material escaping from a chondrosarcoma showed uptakes close to the maximum values from the 1st to the 15th day after injection of radiosulfate and of human growth hormone.

[4] This fraction $F$ differs from the corresponding value of per cent of the cumulative average amount given in Table 1 by the physical decay for 2.7 days. For instance, $F$ is 1.685/1.024 = 1.645 for the average concentration in the tumor of patient 1 on Feb. 21 instead of 168.5 per cent.

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tumors. The calculated biological half-life varied from 37.4 to 80.5 days and the effective half-life from 26.1 to 41.8 days.[5] Boström (1) found that the biological half-life of $S^{35}$ in chondroitin sulfate of rat cartilage was 16 days; the rate of disappearance from the blood is also faster in rat than in man.[6]

The fractional radiation doses delivered to the tumors following each injection were calculated by the formula:

$$D_{total} = \int_{t_1}^{t_2} R dt = 1.44 T_e (R_1 - R_2)$$

where $D_{total}$ equals the total irradiation dose (rad) delivered in the time interval $(t_1 - t_2)$, $T_e$ is the effective half-life, and $R_1$ and $R_2$ are the initial and final dosage rates (rad/day) calculated from the isotope concentrations. For simplicity it was assumed that the greatest concentration was produced at once after injection. The dose that could be delivered by total decay was calculated by using the same rate of turnover as in the preceding period. The total irradiation was the same that would have been delivered by a single injection of the same total amount of $S^{35}$ having the same effective half-life. Chart 1 gives an image of the time distribution of the irradiation of the tumor and of the blood (patient 1). The average radiation dose delivered to all parts of the chondrosarcomas during the periods of observation was calculated to vary from 1756 to 2441 rad and, if extended to total decay, from 1772 to 3661 rad.

Higher doses were received by the growing areas of the tumors which had higher than average uptakes at the two first operations in each patient. The values of "rad max" given in Table 2 are the radiation doses calculated by multiplying the average dose by the ratio of maximum to average uptake at the beginning of the corresponding period. Such calculations showed that the tumor specimens with maximum uptake came from areas receiving cumulative doses to total decay of about 4000 rad.

Radioautographs of the "chemical control" slides (Figs. 1–6A) showed that even in the samples with the highest uptake the microscopic distribution of the isotope was not homogeneous. In the specimens of the two first biopsies $S^{35}$ was fixed mainly close to growing tumor cells and near the edges of the neoplasm, and only smaller amounts were present in the stroma. Since the maximum range of the radiation of $S^{35}$ is only 0.3 mm. (indicated by lines on Figs. 1–6A), the differentiated neoplastic cells which were proliferating at the time of the isotope injections generally received doses of radiation larger than the maximum values calculated from the analyses of the entire samples while other portions received smaller doses.

The irradiation of the *skin* was calculated by the same method as for the tumors. Duplicate skin samples were in close agreement. The changes of concentration of $S^{35}$ in samples of skin obtained at different times have been discussed above. Despite the marked variation of the calculated half-lives, similar radiation doses delivered to the skin (157–270 rad) were obtained for the different patients on the basis of all the samples analyzed.

The values of concentration of $S^{35}$ indicated that smaller radiation doses were delivered to the *adipose tissue* and to *muscle*, which have lower uptakes and more rapid rates of turnover. Cumulative doses of 11.5 and 12.3 rad, respectively, were calculated for these tissues in the case of patient 2. A small additional dose of radiation was probably contributed by the initial concentration of $S^{35}$ in the extracellular fluid.

Not enough samples of normal *bone marrow* could be obtained in these patients for calculation of the irradiation received, but the radiation dosage was obviously much higher than in the blood, and probably higher than in the skin.

## DISCUSSION AND CONCLUSION

The high uptake and the long retention of radiosulfur in chondrosarcomas reflect both the metabolic pattern of normal cartilage and the increased metabolic activity of neoplastic tissues.

The average cumulative irradiation received by all parts of the chondrosarcomas was 29–61 times as high as the cumulative blood dose for the different patients. A factor of similar magnitude (34 to 1) had been anticipated in the initial planning on the basis of tracer studies. This ratio appeared favorable enough to warrant therapeutic attempts with large doses of $S^{35}$-sulfate in advanced cases of chondrosarcoma.

The distribution of the irradiation in the chondrosarcomas must be considered on an almost microscopic scale because of the short range of the beta radiation of $S^{35}$. Differentiated neoplastic cells that were proliferating during the period of isotope injections generally received radiation doses well in excess of 4000 rad. Calcified or degenerated areas received smaller doses.

Although radiosulfur reaches neoplastic chon-

[5] A still longer effective half-life would have been calculated for the chondrosarcoma of patient 3 by using only the analyses of the superficial tumor of the back at the necropsy ($T_e$ = 47.8 days).

[6] R. G. Gottschalk, unpublished data.

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drosarcoma foci in any part of the body and independently of the limitations imposed by the skin in external irradiation, it is unlikely that radiation doses of such magnitude could permanently destroy all tumor cells, inasmuch as the uptake varies with their degree of differentiation. The growth of epiphysial cartilage of young animals can be permanently arrested by leukopenic doses of radiosulfate (14, 15, 24). A major factor in the clinical response of the chondrosarcomas to the doses of radiation delivered by radiosulfur is their radiosensitivity to the beta radiation, inasmuch as the radiosensitive marrow retains significant amounts of isotope. Chondrosarcomas, contrary to epiphysial cartilage, are generally considered resistant to external irradiation (8, 17), although radiotherapy is given for palliation (8).

Carcinomas of the thyroid treated with radioactive iodine are generally submitted to higher equivalent amounts of internal radiation. Signs of destruction of the thyroid gland by $I^{131}$ appear when about 25,000 rad have been delivered to the gland, and larger doses are used for treatment of carcinoma of the thyroid than for hyperthyroidism (23). Nevertheless, some differentiated thyroid tumors with high uptake show little response to isotope treatment, while some anaplastic radiosensitive thyroid tumors of very low uptake may have a clear response (23). Even in carcinomas of the thyroid therapeutic success with isotope is the exception and not the rule.

The clinical observations on the use of radiosulfur in advanced chondrosarcoma (12) were suggestive of a temporary inhibition of the tumors in two of the three cases, but no final conclusion could be drawn in the absence of clear-cut tumor regression. Studies on additional cases of chondrosarcomas, which may have different degrees of radiosensitivity or of isotope uptake, would be necessary to decide whether radiosulfur can produce with some regularity a significant degree of palliation in some cases. In fact, a minimal degree of inhibition would be expected in a radiosensitive tumor following the administration of large doses of radiosulfur independently of its local fixation, since large doses of radiosulfate inhibited transplanted mouse tumors devoid of specific uptake about to the same degree as did sublethal doses of external total-body irradiation. A malignant transplanted mast-cell tumor with a high uptake of radiosulfur was inhibited to a greater degree (16).

## SUMMARY

In the course of attempts of treatment of advanced cases of chondrosarcoma by injections of large amounts of radiosulfate, tissue samples were obtained at intervals and analyzed for isotope content. The average concentration of $S^{35}$ was greater in the chondrosarcomas than in any other tissue analyzed. The results demonstrated the long retention of $S^{35}$ in the tumors. A method was developed for calculation of the irradiation doses after multiple injections of $S^{35}$. The effective half-life of $S^{35}$ in the chondrosarcomas was estimated to vary between 26.1 and 41.8 days. The average cumulative irradiation delivered to all parts of the tumors was calculated to be 1772–3661 rad. The portions of the neoplasms that were growing during the periods of isotope injections had higher than average uptake and received cumulative doses in excess of 4000 rad. Normal tissues received smaller doses of radiation. The blood received cumulative doses of 40 to 68 rad. The significance of these relatively favorable differential ratios of irradiation for the treatment of advanced chondrosarcomas was discussed.

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Figs. 1 and 1A.—Patient 1, tracer, Feb. 21. Myxomatous chondrosarcoma areas (light staining) on the surface of or attached to inflamed or hemorrhagic stroma (30-μ section, hematoxylin and eosin stain).—Uptake greater at edge of tumor than in degenerated areas, important uptake in inflamed stroma. (Corresponding radioautograph, exposure 15 days.) These and the following microphotographs are low-power views of the "chemical control" sections of the tumor samples showing the highest uptake by analysis. (The bars represent 0.3 mm.)

Figs. 2 and 2A.—Patient 1, therapy, May 21. Thin layer of chondrosarcoma and fibrous wall bordering degenerated cystic tumor (7-μ section).—High uptake in tumor. (Exposure, 4 days.)

Figs. 3 and 3A.—Patient 2, tracer, April 21. Cartilage-like chondrosarcoma (7-μ section).—Uptake near cells, little in stroma. (Exposure, 93 days.)

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drosarcoma foci in any part of the body and independently of the limitations imposed by the skin in external irradiation, it is unlikely that radiation doses of such magnitude could permanently destroy all tumor cells, inasmuch as the uptake varies with their degree of differentiation. The growth of epiphysial cartilage of young animals can be permanently arrested by leukopenic doses of radiosulfate (14, 15, 24). A major factor in the clinical response of the chondrosarcomas to the doses of radiation delivered by radiosulfur is their radiosensitivity to the beta radiation, inasmuch as the radiosensitive marrow retains significant amounts of isotope. Chondrosarcomas, contrary to epiphysial cartilage, are generally considered resistant to external irradiation (8, 17), although radiotherapy is given for palliation (8).

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In the course of attempts of treatment of advanced cases of chondrosarcoma by injections of large amounts of radiosulfate, tissue samples were obtained at intervals and analyzed for isotope content. The average concentration of $S^{35}$ was greater in the chondrosarcomas than in any other tissue analyzed. The results demonstrated the long retention of $S^{35}$ in the tumors. A method was developed for calculation of the irradiation doses after multiple injections of $S^{35}$. The effective half-life of $S^{35}$ in the chondrosarcomas was estimated to vary between 26.1 and 41.8 days. The average cumulative irradiation delivered to all parts of the tumors was calculated to be 1772–3661 rad. The portions of the neoplasms that were growing during the periods of isotope injections had higher than average uptake and received cumulative doses in excess of 4000 rad. Normal tissues received smaller doses of radiation. The blood received cumulative doses of 40 to 68 rad. The significance of these relatively favorable differential ratios of irradiation for the treatment of advanced chondrosarcomas was discussed.

### ACKNOWLEDGMENTS

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Figs. 1 and 1A.—Patient 1, tracer, Feb. 21. Myxomatous chondrosarcoma areas (light staining) on the surface of or attached to inflamed or hemorrhagic stroma (30-μ section, hematoxylin and eosin stain).—Uptake greater at edge of tumor than in degenerated areas, important uptake in inflamed stroma. (Corresponding radioautograph, exposure 15 days.) These and the following microphotographs are low-power views of the "chemical control" sections of the tumor samples showing the highest uptake by analysis. (The bars represent 0.3 mm.)

Figs. 2 and 2A.—Patient 1, therapy, May 21. Thin layer of chondrosarcoma and fibrous wall bordering degenerated cystic tumor (7-μ section).—High uptake in tumor. (Exposure, 4 days.)

Figs. 3 and 3A.—Patient 2, tracer, April 21. Cartilage-like chondrosarcoma (7-μ section).—Uptake near cells, little in stroma. (Exposure, 93 days.)

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