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

I. Clinical and Hematologic Observations

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The use of large amounts of radioactive sulfur in the therapy of chondrosarcoma was first considered when it was demonstrated that this tumor selectively retained tracer doses of sulfate-S\textsuperscript{35} administered intravenously (7). This affinity seemed due to the elaboration of chondroitin sulfate in the tumor ground substance, and the uptake generally exceeded that in normal cartilage, presumably because of faster growth. The fixation of S\textsuperscript{35} at the growing edges of the chondrosarcomas (5, 7), the long-term retention of the isotope in cartilaginous tissues (3, 7), and its significant physical half-life (87.1 days) appeared favorable to therapeutic application. On the other hand, its fixation in the hematopoietic bone marrow (2, 7, 15), the uneven distribution in the chondrosarcomas (5, 7), their known radioresistance (12, 13), and the weakness of the beta radiation of S\textsuperscript{35} made it appear doubtful that the isotope could be of therapeutic value. Actual therapeutic trials in man could be considered only after it was initially demonstrated that massive amounts of sulfate-S\textsuperscript{35} (0.2–1 mc/gm body weight) selectively destroyed the growing epiphyseal cartilages of mice, while producing only a temporary leukopenia (10, 11). Slightly smaller amounts (0.1 mc/gm) of S\textsuperscript{35} destroyed the growing epiphyseal cartilages of young rats in our experiments (6, 11) and in those of Rubin et al., who also considered the use of S\textsuperscript{35} in the treatment of chondrosarcomas (16).

In planning the therapeutic trials, the doses of S\textsuperscript{35} that would have a radiobiological action in man could only be inferred from the data on animal toxicity (6, 11), the relative rates of excretion in man (5), rat (2), and mouse (10), and the uptake in various human tissues obtained by biopsy after injection of tracer amounts (7). The proposed plan was approved in April, 1957, by the U.S. Atomic Energy Commission for use at The George Washington University Hospital in cases of chondrosarcoma with fatal prognosis. The plan included a maximum of eight intravenous injections of 250 mc. of sulfate-S\textsuperscript{35} each, to be given at least 1 week apart, with a rest period of 3 weeks after the fourth injection, to permit observation of maximal hematologic effects.

The total amounts that were actually administered to the patients were lower, and the injections were directed by the hematologic response, by the condition of the patients, by the rate of excretion of S\textsuperscript{35} after each injection, and by the concentrations of S\textsuperscript{35} in the tissues obtained by biopsy. Three patients were treated with total amounts of S\textsuperscript{35} ranging from 559 to 926 mc. of sulfate-S\textsuperscript{35}. The patients who received treatment were not chosen because of unusually high uptake after tracer doses, but as they became available. Chondrosarcomas, although one of the more common primary malignant tumors of bone, is only about half as common as osteogenic sarcoma (13).

The observations provided data on the hematologic and clinical effects in man of large doses of S\textsuperscript{35}. The dosimetry calculations based on the tissue analyses will be presented in a subsequent paper (9).

MATERIALS AND METHODS

Radioactive sulfur was obtained from Oak Ridge National Laboratories as carrier free H\textsubscript{2}S\textsuperscript{35}O\textsubscript{4}. Sterile isotonic solutions of sodium sulfate at pH 7 were prepared by adding NaOH, S\textsuperscript{35} that would have a radiobiological action in man could only be inferred from the data on animal toxicity (6, 11), the relative rates of excretion in man (5), rat (2), and mouse (10), and the uptake in various human tissues obtained by biopsy after injection of tracer amounts (7). The proposed plan was approved in April, 1957, by the U.S. Atomic Energy Commission for use at The George Washington University Hospital in cases of chondrosarcoma with fatal prognosis. The plan included a maximum of eight intravenous injections of 250 mc. of sulfate-S\textsuperscript{35} each, to be given at least 1 week apart, with a rest period of 3 weeks after the fourth injection, to permit observation of maximal hematologic effects.

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NaCl, and pyrogen-free H2O and autoclaving. These solutions were assayed for activity and for radiochemical purity by comparison with standardized solutions of S35 supplied by the National Bureau of Standards. The solutions of S35 were used only when they contained less than 0.06 per cent of P32, to avoid cumulative toxicity of the two isotopes. The proportion of P32 decreased with time because of more rapid decay. Previous animal experiments had shown that S34 solutions containing more P32 than the stated limit of 0.1 per cent produced higher mortality in mice.

The injections of S35 were administered through the tubing of intravenous drips of 5 per cent glucose in water. The solutions used had concentrations in the range of 20 mc/ml. Biopsies were obtained 64 hours after administration of a tracer dose (2.2-3.8 mc.) to determine the uptake in the tumors and in various normal tissues. After longer delays following the series of injections of large amounts, additional tissue specimens were obtained in two patients by operations, and in one patient at autopsy. Twenty-four-hour urine specimens were collected throughout the periods of hospitalization and were analyzed for radioactivity.

Blood counts were made on either venous or fingertip samples as feasible. The volume of packed red blood cells was determined only on venous blood. Platelets were counted after supravital staining with new methylene blue. The progress of the tumors was recorded by repeated measurements, photographs, and roentgenograms.

RESULTS

CLINICAL OBSERVATIONS

Data on the patients treated and on the radiosulfur injections are summarized in Table 1.

### Table 1: Injections of Sulfate S35 to Chondrosarcoma Patients

| Patient | \(\text{No. injections}^*\) | Interval, first to last inj. (days)* | Total S35 injected (mc.) | Minimum leukocytes/cu mm | Minimum neutrophils in 100 WBC | Minimum platelets/cu mm | Average urinary excretion of S35 in first 24 hours (per cent of inj. amounts)* |
|---------|-----------------|-------------|-----------------|------------------|------------------|------------------|------------------|----------------------------------|
| 1       | 6               | 6           | 559             | 41               | 2150             | 60,700           | 69               |
| 2       | 5               | 2           | 267             | 41               | 1600             | 99,800           | 64               |
| 3       | 3               |             | 368             | 24               | 580              | 5,340            | 48               |

* Excluding initial tracer injection.
† Expired.

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In view of the debilitated condition of the patient, the chronic infection, and the previous radiotherapy, the increments of S35 were kept under the maximum dosage planned for therapy, and the largest single dose administered was 196.8 mc. The leukocyte counts (Chart 1) which initially reflected the inflammatory condition returned to about a normal level prior to the isotope treatment, probably as a result of the use of antibiotics. Moderate leukopenia and thrombocytopenia appeared during the rest period following the fourth injection, and this became somewhat more pronounced after the two ensuing injections. The isotope injections were discontinued after administration of a total of 559 mc. because of the leukopenia.

Numerous measurements of the axillary mass for about 80 days during and after the period of treatment showed no appreciable increase in size. Tissue specimens were obtained from this area on May 21, 22 days after the last injection. The biopsies showed chondrosarcoma with marked inflammatory and fibrous reaction, and neoplastic involvement of the resected bone. The tumor was mainly myxomatous and precartilaginous with infiltrating, degenerating, and inflamed portions. Cells with double or bizarre nuclei were numerous.

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showed a fluctuant cystic mass containing a mucinous fluid with semisolid degenerated tumor particles. The outer layer of neoplastic tissue was extremely thin, less than 3 mm. thick, and supported by a fibrous capsule. At the time of discharge on May 29 the general condition appeared to have improved, and the size and distribution of the foci of neoplastic induration were about the same as prior to the S\textsuperscript{35} injections. The condition remained stationary until the end of June when the small wound, that had drained intermittently, started to enlarge. An ulcerated tumor 6 cm. in diameter developed in this area and required transfusions and emergency excision on July 24 because of bleeding.

The patient was readmitted to The George Washington University Hospital on August 30. She had a fungating neoplastic mass 10 cm. wide on the anterior chest. For the first time there was evidence of metastases to a lower dorsal vertebra and to the right femur. A fluctuant, not ulcerated mass had developed above the clavicle, and mucinous fluid with tumor particles was aspirated from it on September 20. Further studies\textsuperscript{5} were made on this patient as she followed a downhill course.

\textsuperscript{5}R. G. Gottschalk, to be published.

\textbf{Case 2}.—This patient had a large chondrosarcoma encircling the right femur. A swelling of the thigh was first noted in the winter of 1956–57. In March, 1957, the patient was admitted for cholecystectomy to the Grace-New Haven Community Hospital. At that time the leg tumor, which had reached a significant size, was biopsied, and the diagnosis of chondrosarcoma was made. The tumor proved to be transplantable in the anterior eye chamber (Dr. Greene’s laboratory). The patient repeatedly refused radical resection and was followed at the Yale University Tumor Clinic. During the following winter the tumor began to bulge anteriorly and to interfere with the patient’s activity. In March, 1958, the right thigh had increased considerably in size as compared with March, 1957.

The patient was admitted on April 13, 1958, to The George Washington University Hospital, and she again refused radical surgical treatment or even attempt at local resection of the tumor. On examination the thigh was distended by a huge tumor mass and measured 80 cm. in maximum circumference. On roentgenograms (Fig. 1) the tumor showed a typical pattern of chondrosarcoma with calcified areas in the center and multilobulated, less calcified portions. There were no demonstrable osteophytes or signs of destruction of the femur. The

\begin{figure}
    \centering
    \includegraphics[width=\textwidth]{chart1.png}
    \caption{Blood counts of Case 1. Red blood cells in millions per cu. mm. Hemoglobin in gm. per cent. Volume of packed cells in per cent. White blood cells, neutrophils, and lymphocytes in thousands per cu. mm. Platelets in hundred thousands per cu. mm. Columns indicate the amounts of \textsuperscript{35}S sulfur in millicuries. The blood counts plotted on the days of \textsuperscript{35}S injection were made on blood samples taken before the injection. T indicates the day a transfusion was given and X the day when tissues were obtained for analysis. Time scale reduced \frac{1}{2} after May 31.}
\end{figure}
chondrosarcoma may have developed in soft tissues (13, 17), or from tendinous insertions (4), or possibly from an osteophyte and have been of the "peripheral" type (18).

Following intravenous injection of a tracer dose of S\textsuperscript{35}, biopsies were obtained on April 21 from the ninth costal cartilage, the iliac crest, the adjacent skin and muscle, and the thigh tumor. The latter was encapsulated under the stretched muscles and showed well differentiated cartilaginous chondrosarcoma nodules. The neoplastic cells varied in size and often had double, bizarre, or giant nuclei. They were scattered in lacunae in the abundant ground substance. There were foci of calcification and incomplete ossification. The stroma contained neoplastic mesenchymatous portions as well as fibrous and adipose tissue.

During and after a series of five injections of S\textsuperscript{35} totaling 923 mc. moderate leukopenia and slight thrombocytopenia developed (Chart 2). Biopsy specimens at varied depths in the tumor mass were obtained on June 27, 16 days after the last injection.

The circumference of the thigh was regularly measured at five different levels. During and immediately after the period of injections there was no detectable increase of the average or of the maximum circumference. The very tense induration of the anterior aspect of the thigh decreased moderately as indicated by palpation, by measurements of its vertical extent (reduced from 23 to 12 cm.) and by the statements of the patient. She volunteered the information that the cutaneous sensitivity had improved in the area and that flexion of the thigh was easier. After discharge on July 13, she was followed in New Haven and returned to Washington for check-up in November, 1958, and in March, 1959. The circumference of the thigh had increased slightly. The extent of the induration was still less than before the injections.

Over-all comparison of the roentgenograms taken in March, 1957, and March, 1958, in New Haven and of the numerous films taken in Washington since April, 1958 (Fig. 1), indicated that the tumor had grown rapidly from March, 1957, to April, 1958, and that it had not grown from beginning of treatment to the first discharge. The radiologist considered that in November, 1958, the tumor was still about the same size as before.
the injections, but later it grew more rapidly. Measurements on antero-posterior and lateral roentgenograms of the different diameters of the tumor and of its calcified portions all indicated an arrest or a marked reduction of the rate of growth after the injections (Chart 3). Roentgenograms of the lungs showed no metastases in March, 1959.

Case 3.—This patient had a bulky chondrosarcoma involving the left chest. The tumor arose in the posterior part of left seventh rib. It was biopsied in October, 1957, about 10 months after the initial symptoms, and was considered inoperable because of pulmonary involvement and of massive bloody hydrothorax on the left. Local radiotherapy was administered from December 3 to January 4 (two portals, 3850 r each, 200 kv). On admission to the Roswell Park Memorial Institute, Buffalo, in April, 1958, the patient was pale and dyspneic. The left chest was bulging, and a tumor mass protruded from the posterior wall. Thick bloody fluid of high viscosity was obtained by thoracentesis.

The life expectancy appeared very short when the patient was admitted to the Veterans Administration Center, Martinsburg, on May 6, 1958. The left chest was expanded in all diameters and the left shoulder was held higher than the right. Roentgenograms showed that the left lung field was obliterated by tumor which contained a fluid level. The mediastinum and heart were considerably shifted to the right. A Horner’s syndrome appeared during the hospitalization. The liver edge was irregular and extended 5 cm. below the costal margin. The volume of urinary output was small. Following injection of a tracer dose of radiosulfur, biopsy specimens were obtained on May 12 from the tumor mass under the left scapula. The chondrosarcoma was mainly precartilaginous, with cartilaginous and myxomatous areas and minimal calcification. The ground substance contained numerous neoplastic cells, often with bizarre nuclei.

The patient was admitted to The George Washington University Hospital on May 28, 1958. The maximum impulse of the heart was in the right anterior axillary line. Because of dyspnea the patient remained propped up with the feet hanging down. Pedal edema became more pronounced after June 1. There was no albuminuria. In view of the almost terminal condition, large amounts of radiosulfur, totaling 684 mc., were given in a relatively short period of time from May 29 to June 13. The rate of urinary excretion of $^{35}$S following the injection of large doses was slower than that in the other patients (Table 1), and the blood levels of isotope were correspondingly higher. Leukopenia and thrombocytopenia developed and became severe 2 weeks after the last injection (Chart 4). On July 3 scattered petechiae appeared on the trunk and limbs with a few small ecchymotic areas. The purpura did not increase thereafter. Capillary blood coagulation time and bleeding time were within normal limits on July 4. Partial recovery of the leukocyte level started about July 13. The platelet counts remained around 7000 per cu. mm. There were no signs of gastrointestinal hemorrhage or of complications of agranulocytosis. No transfusions were given. During and after the radiosulfur injections the chest deformity, dysphagia, dysphonia, and signs of cardiac impairment continued to increase. Mercurial diuretics were administered. The mass on the posterior chest bulged somewhat higher. The emaciation and dyspnea became very severe, and the patient expired on July 22.

Necropsy showed that death was due to the widespread neoplastic involvement. The left pleural cavity was obliterated by semi-liquid chondrosarcoma tissue containing residual areas of old hemorrhage. The tumor extended directly into the chest from the primary endosteal chondrosarcoma of the rib. The completely collapsed left lung, the pericardial cavity and the mediastinum were invaded by tumor that extended, anterior to the right lung, up to 4 cm. from the right chest wall. There were metastases in the liver, mesentery and skin, and in a vertebra. The bone marrow was hypoplastic with foci of regeneration including young cells of the myeloid, erythroid, and megakaryocytic series.
HEMATOLOGIC OBSERVATIONS

In the three patients (Table 1 and Charts 1, 2, and 4) the fractionated isotope injections had a cumulative effect and the maximum leukopenia was generally observed after the last injection. The delay from injection to maximum response was longest (25 days) and the leukopenia was most severe in patient 3, who had received large doses at relatively short intervals. There was some suggestion in this patient of a temporary increase of neutrophils soon after the injections of radiosulfur. The lymphocytes fell moderately and progressively. A subsequent more severe fall of neutrophils than of lymphocytes resulted in all cases in relative lymphocytosis at the time of the maximum leukopenia. An increasing proportion of the neutrophils showed toxic granulations as the leukopenia became marked. At the onset of the severe neutropenia of patient 3 only hypersegmented forms were found in the blood. Recovery of myelopoiesis was heralded by the reappearance of stab cells. The degree of platelet depression generally paralleled that of the white blood cells.

The injection of large amounts of S\textsuperscript{35} was followed by a distinct fall in the erythrocyte values only in patient 3. Interpretation of moderate changes in red blood cell values was made difficult by the anemia due to the operations and to the

![Chart 4](chart4.png)

*Chart 4.*—Blood counts of Case 3. Abbreviations same as Chart 1
neoplasms and by the long life span of the erythrocytes.

The hematologic changes observed were generally similar to those elicited in man by a large dose of total-body irradiation (1); they developed more slowly than in mice given radiosulfur injections (11).

### Systemic Effects

There was no radiation-type sickness, diarrhea, or gastric upset following the administration of S\textsuperscript{35}. Petechiae were observed only in patient 3. There were no articular pains, despite the fixation of S\textsuperscript{35} in cartilage. Some complaints of patient 1 were referable to the development of metastases and pressure on nerve roots. No signs of radiation damage to the skin were noted.

### Blood and Serum Analyses of Patients before and after Injections of Large Amounts of Sulfate-S\textsuperscript{35}

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>During</td>
<td>After</td>
</tr>
<tr>
<td>Total protein, gm%</td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Albumin-globulin ratio</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Thymol turbidity units</td>
<td>6.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Bilirubin, direct, mg%</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Bilirubin, total, mg%</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Urea nitrogen, mg%</td>
<td>6.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Calcium, mg%</td>
<td>9.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Phosphorus, mg%</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Alk. phosphatase†</td>
<td>3.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

† Bodansky units.

Table 2 lists the average blood chemistry values before, during, and after the injections. The changes in blood constituents, if any, seemed related to the clinical condition of patients with advanced neoplasms and not to the injections of radiosulfur per se. There were no demonstrable changes of the clinical laboratory tests of patient 2 up to 9 months after the injections.

### DISCUSSION AND CONCLUSION

When this study was undertaken the largest amounts of radioactive sulfur which had been used in man were approximately 7 mc. (7). The observations following the administration of amounts up to 926 mc. of sulfate-S\textsuperscript{35} demonstrated that in man as in animals (10, 16) the limiting factor was the injury to the radiosensitive hematopoietic tissues, and especially the bone marrow, and not the injury to the skin. The "Handbook on Maximum Permissible Amounts of Radioisotopes . . ." (18) considers that the site of main toxicity of S\textsuperscript{35} is the skin, but this is based on metabolic data for labeled amino acid sulfur and not for oxidized sulfur.

The most severe blood changes were observed in patient 3 who, without receiving the maximum total dosage, received relatively large amounts at short intervals. A slower rate of renal excretion of S\textsuperscript{35} in this patient also contributed to higher blood levels and to larger doses of radiation delivered in a short period to blood (9). The size and frequency of the injections as well as the rate of excretion of radiosulfur appeared to influence the severity of the leukopenic and thrombocytopenic effects. The delay occurring between the admin-
lymphoma but rare in FL. The viral leukemia of Gross is indistinguishable from spontaneous thymic lymphoma. Whether the thymic lymphomas in Swiss mice are related to a virus, as in Ak mice, remains to be established. The transplantable tumor variants of FL described here are characterized by mono- and multinucleated giant cells, not encountered in transplantable lymphomas or myeloid leukemias of mice.

The leukemia produced by cellular graft of the transplantable tumor variant of FL here described (best done by intravenous injection of tumor cells) is somewhat different from that induced by FV. Leukemia produced by cell graft has a rapid onset and course and is often advanced after 30 days, whereas the characteristic leukemia following virus infection usually occurs after about 3 months and is seldom seen in less than 30 days.

The most characteristic gross anatomic feature of FD is splenomegaly in which the spleen is soft and red with rounded edges, often with frank hemorrhagic areas. In contrast, the splenomegaly induced by cell grafts is indistinguishable from other autonomous leukemias, the organ being gray or gray-red and firm with more sharp (less rounded) edges.

Earlier work called attention to extensive erythrogenic hyperplasia appearing early in FD before any manifestation of anemia (4). This may be due to a stimulation of erythrogenic cells by virus, suggesting that this was unrelated to the proliferation of reticulum cells. The bone marrow, the usual site of erythrogenesis, is involved infrequently and only at the late stage of the disease, whereas the reticulum cells of the spleen proliferate within a few days after virus infection. In contrast, leukemia produced by cellular grafts is characterized by monomorphous proliferation of large reticulum cells without erythroblastosis or anemia. In many animals the tumors remained localized at the site of graft (Fig. 1), in others they spread by continuity (Fig. 2). It is possible that virus was contained in the cells and, if slowly released, produced immunity which prevented later development of lesions characteristic of the viral disease. In the morphogenesis of viral leukemia, antibody production may play a prominent, hitherto poorly explored, role.

The occurrence of "leukemic" thrombi in the lung is characteristic, but the interpretation of its pathogenesis is conjectural. It may be the consequence of some antibody formation against the grafted cells. This may explain why these lesions are common in transplanted leukemias and relatively rare in spontaneous leukemias. The development of such lesions in spontaneous (including virus-induced) leukemias may be due to autoantibody production or perhaps to mere blocking of the circulation by clumps of tumor cells which have entered the pulmonary arteries.

A word of caution on the designation of the transplantable tumor cells described here as "autonomous": the failure of two tumors, from animals with no gross or microscopic evidence of FD, to yield tumors (or the generalized viral disease) on subpassage suggests the possibility that the presence of virus is a prerequisite for tumor growth. On the other hand, the change in character of the tumor cells, notably in their nuclei, is also suggestive of transformation of virus-driven normal cells to autonomous, virus-independent cells. However, resident virus can conceivably alter the nuclear pattern, and reliance on the latter in determining whether a cell is autonomous should not be dogmatic. Thus, even cells with abnormal nuclear (chromosomal) morphology can be dependent on a "masked" resident virus.

Further work is needed (a) to define the cytogenetic change, suggested by chromosomal abnormalities associated with acquisition of transplantability, (b) on the association of virus with leukemic cells or the conceivable loss of virus in the araplastic tumor cells, and (c) on the presumed existence of a dual type of leukemic cell population:

All sections are from tissues fixed with Zenker-formol and stained with hematoxylin and eosin.

FIG. 1.—Large tumor, localized to graft site (right thigh), without metastasis to regional lymph nodes and without splenomegaly and hepatomegaly.

FIG. 2.—Small tumor at graft site (right thigh), with extensive abdominal metastases but without splenomegaly and hepatomegaly.

FIG. 3.—Small tumor at graft site (right thigh), with metastasis to regional lymph nodes, splenomegaly, and hepatomegaly. Hemorrhagic "leukemic" infarcts in lungs.

FIG. 4.—Generalized leukemia and splenomegaly and hepatomegaly following intravenous injection of tumor cells.
ment in this matter is difficult. The patient expired 54 days after onset of the treatment. Analyses indicated that about 60 per cent of the possible irradiation dose had been delivered at that time to the chondrosarcoma (9).

In patient 1 there was little or no progress of the tumors for about 100 days from the start of the injections until June when the tumor started to grow rapidly. The beneficial effects of the external irradiation administered about 3 months before the isotope injections cannot be excluded.

In patient 2, who had not been previously treated, the leg tumor did not increase in size during and immediately after the period of treatment. The induration around it decreased. The rate of growth remained much slower than before treatment for about 6 months and later increased.

The observations on patient 2 are suggestive of a temporary inhibition of the chondrosarcoma by the isotope. Since it is recognized that a regular or logarithmic rate of growth cannot be expected in large tumors, any such variation in the rate of progress of neoplasms short of clear-cut regression must be interpreted with great caution in individual patients, although dosimetric considerations demonstrated favorable ratios between the doses of radiation delivered by radiosulfur to the chondrosarcomas and to the normal tissues of these patients (8, 9).

SUMMARY

Large amounts of radioactive sulfur (Na$_2$$^{35}$SO$_4$) were administered to three patients with advanced chondrosarcomas because of the preferential fixation of the isotope in this tumor. Total amounts of 559–926 mc. were given in divided intravenous injections. They produced leukopenia with relative neutropenia and thrombocytopenia. The radiotoxic hematologic effects appeared reversible, but they are the limiting factor in the use of large amounts of radiosulfur and require caution in therapeutic trials. No radiation sickness occurred as a result of the injections. In two patients, the rate of progress of the chondrosarcomas appeared reduced for several months after the $^{35}$S injections, but no marked tumor regression was observed.

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