Radioactive Phosphorus as a Therapeutic Agent in Malignant Neoplastic Disease*†

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Radioactive phosphorus, or P⁵², as a therapeutic agent in malignant disease, has been studied at the Memorial Hospital since January, 1940. Investigations have been carried on by a large group of workers in several clinical and laboratory departments. Their individual investigations are to be published separately. It seems desirable however, to present a summary of the principal findings in the various problems investigated to bring out the inter-relations of the different aspects of the work, and to indicate further desirable extensions. The author, who has been associated with all parts of the study, was requested to prepare the present paper.

Initially, the investigation followed the original work of Lawrence and associates (2, 4', 7, 8, 9, 11) and was limited to patients with leukemia. It was found, as Lawrence had previously stated, that the leukemic cells and the tissues which were infiltrated with them absorbed greater amounts of radioactive phosphorus than did normal leukocytes or noninfiltrated tissue. The study was then directed toward other types of malignant neoplasms in the hope that a similar selective absorption might be found.

PREPARATION AND GENERAL PROPERTIES OF RADIOACTIVE PHOSPHORUS

Radioactive phosphorus, P⁵², is produced by bombarding red phosphorus with deuterons (H²) in the cyclotron. The following reaction takes place:

\[ ^{31}_{15}P^{31} + H^2 \text{(deuteron)} \rightarrow ^{32}_{15}P^{32} + H^1 \text{(proton)} \]

The radioactive red phosphorus † is converted to disodium acid phosphate, Na₂HPO₄, by suitable chemical means, and in this form it can be administered either orally or parenterally. As used at present, the phosphate is in an aqueous solution containing 15 mgm. of phosphate per cc., with an activity of about 300 microcuries (µc.)² per cc. of solution.

Our average single therapeutic dose for a 70 kg. adult varies between 1.5 and 4.0 mc. Therefore, between 5 and 15 cc. are administered at a time, and the total amount of phosphate in a dose varies between 75 and 225 mgm. It is estimated that about one in ten million of the phosphorus atoms in this solution is radioactive. The actual amount of radioactive phosphorus administered is thus extremely minute, between 0.000005 and 0.0001 mgm. for a single dose.

This isotope, P⁵², has an unstable nucleus whose half-life is 14.3 days and disintegrates according to the following formula:

\[ ^{32}_{15}P^{32} \rightarrow S^{32} + \beta \text{(beta particle)} \]

The beta particles produced by the disintegration have an average energy of 700 kv. and can penetrate several meters of air, or between 2 and 4 mm. of tissue. This particle has about the same average energy as the beta particle ejected in soft tissue by 2,000,000 volt x-rays.

The unit of measurement of the radioactivity of P⁵² is the international millicurie (mc.) which, for any radioactive element, is the quantity in which occur 3.7 x 10⁷ disintegrations per second. Thus, a millicurie of radioactive phosphorus, a milligram of radium per se, or a millicurie of radon per se are identical insofar as the number of atomic disintegrations per second are concerned. They differ vastly, however, in that radium and radon emit alpha particles, and radioactive phosphorus emits only beta particles. Also, in a milligram of radium in equilibrium with its products there is present one millicurie of each of the other members of the series, each disintegrating at the same rate of 3.7 x 10⁷ atoms per second and emitting its own radiation. The beta and gamma radiations attributable to radium and radon come from the radium B and radium C in this equilibrium. It cannot be said, therefore, that one milligram of radium or one millicurie of radon and one millicurie of radioactive phosphorus will produce

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‡ Rockefeller Clinical Research Fellow.

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1 microcurie (µc.) equals 0.001 millicurie.
identical biological effects when used in the same fashion, nor can it be said that they produce identical amounts of radiation.

If the concentration of the radioactive phosphorus in a tissue is known, it is possible to estimate the radiation dose delivered to that tissue by the isotope. Through suitable formulae which take into account the energy of the beta ray, the number of disintegrations per second, and the half-life, this dose can be expressed on an ionization basis to correspond closely to doses delivered with x-rays. For convenience, doses thus determined are expressed in "roentgen equivalents" (10). For example:

1. If 1.1 μc. of P32 remain in a kg. of tissue until it has completely disintegrated, 1 "roentgen equivalent" of radiation will be delivered to that tissue.
2. If 1 μc. of P32 remains in a gm. of tissue for 24 hours, 43 roentgen equivalents will be delivered to that tissue.
3. If 1 mc. is retained for 24 hours by an adult of 70 kg. weight, 0.6 roentgen equivalents of whole body radiation are delivered.

Treatment with radioactive phosphorus is simply another form of radiation therapy. Its single significant difference from x-ray or radium therapy is that it is administered orally or parenterally and distributed throughout the whole body, and the sources of the radiation are all within the tissues where the material is present. Its localization in any tissue is, so far as is known, purely a metabolic phenomenon and takes place in accordance with the metabolic needs of the various tissues for phosphorus. Therapy with radioactive phosphorus is, therefore, systemic irradiation. Hence, in the treatment of any malignant neoplasm, its effectiveness will depend on its distribution within the body. If it should prove to be more effective than conventional radiation therapy, it will be so because of this, and especially if there is a favorable differential absorption by scattered tumor cells.

**TRACER STUDIES**

If a small amount of radioactive material is administered to a living organism, subsequent ionization measurements can show how this substance is distributed among the various tissues (4, 9). Such tracer studies are useful for the investigation of various problems in metabolism; they also furnish a guide to possible therapeutic values, for it is believed that the findings after tracer doses probably indicate the differential absorption that would occur after therapeutic doses provided that the difference between the amount of phosphate in the tracer dose and the therapeutic dose is not large. Hence, if neoplastic tissues absorb amounts sufficiently greater than normal ones, the material should be a useful clinical adjunct. Such studies have been carried out for P32. This work will be reported in detail elsewhere and will only be summarized briefly in this article (6).

In these studies, small amounts of radioactive phosphorus, about 30 per cent of our usual single therapeutic dose, were administered to a group of patients with various malignant neoplasms, at varying times before operation. Patients with the following conditions were selected for this investigation: carcinoma of the breast, osteogenic sarcoma, and lymphosarcoma. Portions of the different tissues in the surgically excised specimens of these patients were weighed, ashed, and their radioactivity measured and corrected for decay to the date of administration of the P32.

In order that an adequate comparison could be made of the absorption by neoplastic tissue with that of normal tissue, whether in the same patient or in different patients, it was necessary to devise a suitable method. This was done by determining in every instance the ratio of μc. of P32 measured per kg. of tissue to the μc. of P32 administered per kg. of body weight.

All the calculations were based upon the amount administered per kg. of body weight. This figure indicates how much of the isotope would be present in any tissue if it were equally distributed throughout the body. If this quantity is divided into the amount actually found to be present in 1 kg. of any tissue, there is established the ratio between the amount of phosphorus actually taken up by that tissue and what it would have contained if the isotope had been equally distributed. This ratio of differential absorption indicates approximately how much of the isotope will reach different tissues after a measured amount of the P32 is administered, provided that the amount of phosphate in the dose is not large. The ratio also shows at once whether a neoplastic tissue absorbs an amount of the isotope sufficiently above the average for the entire body to make it a probably useful method of therapy. If, for example, a neoplastic tissue has a differential absorption ratio of 1, it will receive no more radiation from radioactive phosphorus than will the whole body. On the other hand, if the ratio were 6, it would receive 6 times as much radiation as the average body tissue. In the first instance, P32 would be expected to be of little value, and in the second instance, it could be of significant therapeutic effect.

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Footnote: For example: If an adult of 70 kg. is given 1 mc. (1,000 μc.) of P32, 14.3 μc. (1,000/70) per kg. of body weight is the administered dose, corrected for decay to date of administration of the isotope. If, then, in this same adult, a cancer tissue absorbs 28.6 μc. per kg., the 28.6 is divided by 14.3. The resultant figure of 2 is the differential absorption ratio for that cancer tissue.
The ratio has been based on the administered dose rather than on the retained dose because in many instances it was not possible to measure the excretion of the isotope and thus determine the actual value of the latter. This method is satisfactory, since all figures would change proportionately if the retained dose instead of the administered dose were the basis of the ratio. Admittedly, the ratio may be different on different days for the same tissue in the same patient. However, this can be compensated for by making observations on a large group of patients at different intervals after the administration of a tracer dose of $^{32}P$. Such a series of observations will show if the isotope is retained a sufficient length of time to deliver its effective radiation, a matter of 3 weeks.

This ratio can probably be decreased or increased to some extent by varying the total amount of phosphorus administered. In all of the tracer studies, however, it did not exceed 10 per cent of the average patient's daily intake of 1 gm. of phosphorus.

**Carcinoma of the Breast**

This lesion was selected for study primarily because its frequency made available a sufficient number of cases in a relatively short time. A further reason was that the figures obtained from the study of this type of neoplasm should indicate to some degree what absorption of the phosphorus would take place in other types of carcinoma.

Table I shows the results of the analyses of tissue from patients with breast carcinoma. The differential absorption ratio for the primary tumor varied between 0.8 and 1.9. There is, therefore, little reason to expect that radioactive phosphorus could be used for primary therapy in this disease. A dose of 500 μc. per kg. of body weight would administer only between 450 and 1,000 “r” to the primary tumor. This dose of the isotope is about as great as can be safely administered to an adult of 70 kg. weight and would probably provide about 300 “r” whole body radiation during the period of its administration, a matter of about 12 or 14 weeks.

The lymph nodes which contained metastatic foci of breast carcinoma had an absorption ratio of from 1.9 to 4.0. Hence, the dose just discussed would deliver to the nodes between 1,000 and 2,000 “r” tumor dose. The higher absorption by the metastatic areas suggests that the radioactive phosphorus might be a useful therapeutic adjunct in patients who are to be treated by x-ray. This is on the grounds that the administration of the phosphorus might add sufficient supplementary radiation to that delivered by x-ray treatments to inactivate the disease. Because the radioactive phosphorus probably is handled as a normal metabolite, it is to be expected that it would reach all the metastatic foci outside the area treated by x-rays. It is thus possible that a sufficient amount of the isotope might be absorbed by the minute sub-

<table>
<thead>
<tr>
<th>Case number</th>
<th>Tracy administered per kg. of body weight</th>
<th>Days between administr-</th>
<th>Primary tumor</th>
<th>Breast tissue</th>
<th>Metastatic node</th>
<th>Normal node</th>
<th>Muscle</th>
<th>Fat</th>
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<td>0.7</td>
<td>0.2</td>
<td>0.3</td>
<td>0.8</td>
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<td>0.1</td>
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<td>0.1</td>
<td></td>
</tr>
<tr>
<td>59935</td>
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<td>7</td>
<td>1.0</td>
<td>0.2</td>
<td>1.9</td>
<td>1.6</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

**Osteogenic Sarcoma**

Phosphorus is a normal constituent of bone, whose metabolism is in a large degree controlled by an alkaline phosphatase (13). Many osteogenic sarcomas are rich in it (13), a fact which is often reflected by a high serum phosphatase. The phosphatase in the tumor increases the need of that tissue for phosphorus. It seemed quite likely, therefore, that radioactive phosphorus would be absorbed by osteogenic sarcoma in sufficiently large quantities to make it a useful therapeutic agent. It also seemed possible that the minute metastatic foci might absorb sufficient phosphorus to be destroyed. If this last should prove to be true, then radioactive phosphorus would offer a real therapeutic hope in a disease which is fatal in about 90 per cent of the patients within two years from the time of diagnosis.

Table II shows the results of the analyses of tissues from patients with osteogenic sarcoma. The primary
tumor showed a differential absorption ratio that varied from 0.6 to 8.3. Those regions with the lowest absorption ratio were regions in which the tumor was hemorrhagic or had otherwise degenerated. The areas most actively growing were the ones with the highest absorption ratios. If we use the figure 4 as an over-all average absorption ratio for the primary tumor, for a dose of 500 μc. per kg. of body weight, it would receive about 2,000 roentgen equivalents tumor dose, too little to provide a primary method of therapy. However, if the only method of therapy to be used is x-radiation, the administration of 500 μc. per kg. of weight of the isotope would provide the advantage of at least a 30 per cent increase in the usual roentgen tumor dose which, in osteogenic sarcoma, does not usually exceed 6,000 to 7,000 r, and is

**LYMPHOSARCOMA**

The relative radiosensitivity of this type of lymphoma made it seem likely that this disease could be effectively treated with radioactive phosphorus. Table III shows the results of the analyses of lymphosarcoma tissue. Because only local biopsy was done, no normal tissue was available to serve as a control. The differential absorption ratio varied between 1.6 and 2.0, with an average of about 1.5. It is to be noted that there are varying lengths of time between the administration of the isotope and the biopsy, but that the ratio remains as nearly constant as can be expected. This suggests that, once the radioactive phosphorus has been absorbed by the lymph node, it tends to remain in it for at least 2 weeks.

**Table II: Differential Absorption Ratio of Radioactive Phosphorus in Patients with Osteogenic Sarcoma**

<table>
<thead>
<tr>
<th>Case number</th>
<th>μc. P3 administered per kg. of body weight</th>
<th>Days before operation</th>
<th>Differential absorption ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary tumor</td>
</tr>
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<td>7.3</td>
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<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>59044</td>
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<td>5</td>
<td>8.3</td>
</tr>
<tr>
<td>59202</td>
<td>41.0</td>
<td>7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Limited by the tolerance of the skin for radiation. Skin damage is not a factor in therapy with radioactive phosphorus; rather, as will be shown later, the limiting factor is probably damage to bone marrow.

In only one case are measurements of the amount of P32 absorbed by metastatic tumor tissue available. In this instance, the ratio varied from 1 to 5, a fact which indicates that the radioactive phosphorus does reach distant metastases and might provide sufficient irradiation to inactivate them. Minute foci of metastatic disease are probably not too securely established. It is conceivable then that if they were damaged, their destruction might be completed by some bodily defense mechanism. Frequently, metastases appear months or years after the primary tumor has been destroyed. Hence, it may be supposed that they were present before the destruction of the primary tumor. Some force has kept them in the quiescent state for a period and, if to this force further damage could be added, it is not impossible that total destruction might result.

If a total dose of 500 μc. per kg. of body weight were administered to one of these patients, the diseased nodes would, on an average, receive about 1,500 roentgen equivalents tumor dose. This is in excess of the usual x-ray dose and suggests that radioactive phosphorus should be a useful method of therapy in

**Table III: Differential Absorption Ratio of Radioactive Phosphorus in Patients with Lymphosarcoma**

<table>
<thead>
<tr>
<th>Case number</th>
<th>μc. of P3 administered per kg. of body weight</th>
<th>Days between administration of P3 and biopsy</th>
<th>Differential absorption ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lymph node</td>
</tr>
<tr>
<td>SED</td>
<td>1.7</td>
<td>5</td>
<td>4.2</td>
</tr>
<tr>
<td>OBI</td>
<td>9.6</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>ANG</td>
<td>5.5</td>
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<td>ARB</td>
<td>4.7</td>
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</tr>
<tr>
<td>SEA</td>
<td>13.3</td>
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<td>9.2</td>
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<td>NFG</td>
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</table>

on October 3, 2017. © 1942 American Association for Cancer Research.
lymphosarcoma. The isotope would reach all lymph nodes and conceivably could destroy or inactivate all areas of disease.

**Normal Tissues**

Sufficient data have not yet been collected from patients coming to autopsy to permit accurate estimation of the amount of the isotope that will be absorbed by normal liver, spleen, lymph nodes, or kidney.

The relative radiosensitivity of the various normal organs as contrasted with malignant neoplastic tissue is also of importance. Normal liver and kidney are not radiosensitive, but are actually radioresistant. If their ratio does not exceed 1.0 to 1.5, they would probably be able to absorb the amount of radiation they would receive during a therapeutic trial of the isotope in such a disease as osteogenic sarcoma without, in all probability, showing radiation damage.

**Therapeutic Studies**

The proper method for the therapeutic administration of radioactive phosphorus is still unsettled. Originally, large single doses were administered with the amount only roughly related to the weight of the patient. These doses were repeated at approximately weekly intervals until, in leukemia, satisfactory reduction of the leukocyte count occurred. More recently, dosage has been related directly to body weight. The disease to be treated, the stage of the disease, and the patient's general condition are then carefully evaluated and become the deciding factors in the control of initial dosage. Patients in good general condition and...
whose bone marrow show good erythropoietic tissue, receive an initial course of from 70 to 100 μc. per kg. of body weight. For patients with poor erythropoiesis, or those who are in the subacute phase of leukemia, the initial dose is reduced to 20 to 30 μc. per kg. of body weight, and may be even smaller for patients who are in the acute phase of leukemia. At the present time, it is not possible to decide upon a definite dose for each condition to be treated. Cases must be treated individually until more is known about the use of the isotope. The controlling factors should be the blood count, the marrow count, and the patient's general condition.

The present policy is to divide each course of therapy into 5 to 7 doses. This is based upon metabolic considerations. The phosphorus is, presumably, distributed as a normal metabolite, and its localization in any tissue will depend on that tissue's need for it. Apparently, leukemic and lymphosarcomatous tissue have a higher ratio of absorption than the average normal tissue. If, therefore, the total phosphate is given in small amounts repeatedly, rather than in one large amount, diseased tissues may absorb more of the radioactive phosphorus.

Limited experimental evidence appears to bear out this view. Two female patients with chronic myelogenous leukemia were treated by two technics. The first patient (Fig. 7) was given 10.2 mc. in a period of 10 days in 4 doses varying in size from 2.0 to 2.9 mc. The amount of phosphate administered at one time varied between 300 and 555 mgm. and totalled 1,768 gm. The peak activity of the leukocytes, 25 μc. per 100 cc., was reached 24 hours after the administration of the last dose of P⁢³⁵. The second patient (Fig. 8) was given 8.1 mc. in a period of 10 days in 8 doses varying in size from 0.7 to 1.4 mc. The amount of phosphate administered each time was 60 mgm. and the total was 480 mgm. The peak activity of the leukocytes, 55 μc. per 100 cc., was reached 24 hours after the administration of the last dose of P⁢³⁵. This peak was more than twice that seen in the first case. The time of administration in each case was the same, but the total amount of P⁢³⁵ administered to the second patient was less than that given to the first.

At the time of the peak value in the leukocytes for the first patient, the amount of retained P⁢³⁵ was 4.2 mc. In the second case, for the same point the retained dose was 4.9 mc. This difference in retained dose is not great enough in itself to account for the difference in the leukocyte values of radioactivity. It suggests that when small amounts of phosphate are administered repeatedly there is a higher absorption of the P⁢³⁵ by the leukemic tissue than when a single large dose is given. Whether this increase is due to the subdivision of the therapy or to the small amounts of total PO₃ administered, has not as yet been established. The retention of a greater percentage of the administered dose by the second patient than by the first also shows the importance of the administration of small amounts of phosphate in preventing undue loss due to excretion. This is discussed in detail below.

Careful measurements of the amounts of P⁢³⁵ excreted in the feces and urine have been made on a number of patients. These patients have received different amounts of phosphate at different intervals between doses. It has been consistently noted that, if the total phosphate administered in a single dose is less than 100 mgm., the total excretion during the next 96 hours is less than 20 per cent of the administered dose. This holds true when daily doses are given for 5 or 6 days. When the total phosphate administered in a single dose is 200 mgm. or more the excretion is usually above 30 per cent and may reach 50 per cent. The difference is in the amount excreted in the feces. Usually between 7 and 15 per cent of the administered dose, average 10 per cent, is excreted in the urine in the first 96 hours. This fraction increases somewhat as the amount of administered phosphorus increases. The per cent excreted in the feces rises abruptly as the amount of phosphate is increased. With small doses it varies from 3 to 7 per cent; with amounts in excess of 150 mgm. of phosphate, it varies from 20 to 40 per cent. The daily fecal excretion of the P⁢³⁵ after the initial 96-hour period is very small, less than 0.3 per cent of the retained body dose. The urinary excretion after the initial 96-hour period varies from 0.4 to 0.6 per cent of the retained dose each day. Excretion measurements have also been made on patients who received the P⁢³⁵ by the intravenous route. The urinary excretion in these patients for the same amount of phosphate was comparable to that seen after oral administration. The fecal excretion was less than 1 per cent.

Succeeding courses of therapy are usually, though not necessarily, smaller than the initial course. Here the response of the individual patient is the deciding factor. Usually 7 to 10 days elapse between the completion of one course of therapy and the commence- ment of another. The optimum total amount to be administered is not as yet determined, but it would seem probable that it will be in the neighborhood of 500 μc. per kg. of weight. Here again more experience is needed before this point can be determined. The effect of the time factor, which is still poorly understood in x-ray therapy, is totally unknown in radioactive phosphorus therapy.

**Myelogenous Leukemia**

Eight patients with myelogenous leukemia, of whom 4 are living and 4 are dead, have been treated with
radioactive phosphorus. Six were in the chronic phase of the disease, one was in the subacute, and one in the acute phase.

One patient in the acute phase of the disease died one week after the administration of 1.5 mc. of \( {\text{P}}^{32} \). He had a platelet count of about 30,000, widespread purpura, and 95 per cent myeloblasts in his bone marrow.

One patient in the subacute phase of the disease died 6 weeks after the commencement of therapy. Aspiration biopsy of the bone marrow before therapy showed poor erythropoietic tissue and beginning aplasia. The terminal picture was one of complete marrow aplasia. He received 3 doses of 0.8 mc., each at weekly intervals. The relationship of badly damaged marrow to failure of therapy is discussed later.

One patient with chronic myelogenous leukemia died 4 months after the start of therapy. There had been excellent hematological response to the isotope (Fig. 1) and the patient’s general condition at his last clinic visit was good. He died suddenly at home and the story, as given by his family doctor, suggested a splenic and a pulmonary infarct. He had received 29 mc. (490 mc. per kg.) in 3 months’ time.

The history and course of the fourth patient who died is as follows:

**Case No. 61153.** (Fig. 2.) A 24-year-old, white female, admitted on October 21, 1940. No contributory data were obtained from the past history or family history.

One year before admission, the patient discovered a mass in upper half of the left side of her abdomen which gradually increased in size. There were no other symptoms.

The findings on admission were as follows: The spleen extended 3 cm. to the right of the midline and to within 5 cm. of the symphysis pubis. The liver extended 3 cm. below the costal margin. Hemoglobin, 50 per cent; red corpuscles, 2,600,000; leukocytes, 3,072,000. Differential blood count: myelocytes, 55 per cent; myelocytes, 2 per cent. Material from sternal marrow aspiration showed: myelocytes, 55 per cent; myeloblasts, 20 per cent.

Course and treatment: From 11/6/40 to 11/15/40 the patient received four doses of \( {\text{P}}^{32} \) totalling 10.2 mc. From 11/12/40 to 12/14/40 she received, at weekly intervals, four doses that totalled 8.7 mc. There was excellent reduction of the leukocyte count by 12/14/40, and the spleen had regressed to within 1 cm. of the costal margin. On 2/1/41, the white count had risen to 31,000 and the spleen had enlarged and filled the left upper abdominal quadrant; 2.9 mc. of \( {\text{P}}^{32} \) were administered. On 3/8/41, the white count was 56,000 and the spleen slightly larger. The patient was admitted to the hospital. X-ray therapy was instituted 3/10/41, with 250 kv., 70 cm. T.S.D.: 15 r (air) were administered daily over the spleen for 3 days. On 3/15/41, the white count was 44,000, and the spleen filled over two-thirds of the abdomen. She was then given 500 mgm. hours daily with the radium element pack at 15 cm. from 3/15 to 3/18. There was no improvement and the patient died 3/19/41. Autopsy was not permitted.

This case clearly illustrates that a patient may pass into the rapidly progressive phase of leukemia just at the time when apparently the therapy has been highly efficacious. It is to be noted that partial continuation of the therapy did not arrest the progress of the disease. The change to external radiation was made to increase the rate of local radiation therapy.

Four patients who were in the chronic phase of the disease are living, 16, 7, 5, and 4 months respectively, after the commencement of therapy. There has been marked improvement in the general condition of these patients. In each case the enlarged spleen has regressed, and in only one case is it, at present, more than barely palpable.

The patient who was first treated 5 months previously (Fig. 4) received 25 mc. (420 mc. per kg.) in that time. His white count became normal, but a number of myelocytes were observed in the blood smears. Further therapy is to be administered. His spleen is not palpable.

The patient who was first treated 4 months before the writing of this report (Fig. 5) has received 26 mc. (480 mc. per kg.) during that period. The reduction of the leukocyte count and the regression of the spleen have been slower than in the other patients. The spleen is about 2 cm. below the costal margin.

The history and course of the first patient to be treated is as follows:

**Case No. 58868.** (Fig. 6.) A 41-year-old, white male, admitted on January 27, 1940.

The patient’s mother died of leukemia at 72.

The present illness began about 5 years ago with profuse bleeding after extraction of teeth, and a marked tendency to ecchymosis after trivial injuries. There had been vague abdominal discomfort for several months. Six weeks before admission he had a tooth extracted. This was followed by severe bleeding for 8 days, and admission to a hospital was necessary. A diagnosis of myelogenous leukemia was made at that time.

The findings on admission were: the spleen extended 4 cm. to right of the midline and to the crest of the ilium. The liver was not palpable. Hemoglobin was 65 per cent; red blood corpuscles, 3,400,000; white corpuscles, 31,000. The differential count: myelocytes, 27 per cent; polymorphonuclear leukocytes, 47 per cent; mast cells, 3 per cent; monocytes, 20 per cent; lymphocytes, 2 per cent.

Course and treatment: From 2/26/40 to 3/27/40, at intervals of from 2 to 14 days, the patient was given 7 doses of \( {\text{P}}^{32} \) totalling 21.8 mc. Three additional doses at intervals of about 6 weeks were then given, raising the total dose to 28.8 mc. This reduced the white count to normal levels and decreased the size of the spleen to about 1 cm. below the costal margin.
A marrow aspiration on 10/10/40 showed 60 per cent myelocytes. Between 10/10/40 and 12/14/40, at 7- to 14-day intervals, the patient was given 6 doses of $^{32}$P totalling 8 mc. This reduced the myelocytes in the marrow to 20 per cent. The white count remained normal and the spleen nonpalpable until 3/5/41. At that time the count rose to about 30,000 with 35 per cent myelocytes and the spleen was palpable 3 cm.

Earlier in this paper several factors were given which permitted an estimation of the tissue dose of radiation in roentgen equivalents as administered by radioactive phosphorus. Figs. 7 and 8 show the radioactivity in the blood of two of the patients treated. At the level of 20 u.c. per 100 cc. of leukocytes, assuming that 1 cc. of leukocytes weighs 1 gm., the white cells received between 8 and 9 "roentgens" daily. Analysis of Fig. 7 shows that in the period between November 9th and December 21st, the patient's leukocytes received about 180 "roentgens." Another comparison with x-ray therapy is possible on the basis of whole body radiation per mc. retained in the body (of a 70 kg. adult) for 24 hours. If decay and excretion are taken

Fig. 5.—Regression of the leukocyte count with concurrent rise in the red corpuscle count in a case of myelogenous leukemia treated with $^{32}$P.

Fig. 6.—Regression of the leukocyte count and concurrent rise in the red corpuscle count in a case of myelogenous leukemia (Case No. 58868) treated with $^{32}$P. Note the absence of myelocytes during a period of 6 months, September to February, and that an exacerbation of the disease responded to additional therapy.

Fig. 7.—The radioactivity of the leukocytes, red corpuscles, and plasma secured by centrifuging oxalated blood, in a case of myelogenous leukemia treated with $^{32}$P, is shown in u.c. per 100 cc. of each blood fraction. Values from the middle of November on are for fractions of blood drawn just before administration of $^{32}$P and one week after the last dose of $^{32}$P. Note the marked differences between the radioactivity of leukocytes and red corpuscles.

Fig. 8.—Radioactivity in u.c. per 100 cc. of leukocytes, red corpuscles, and plasma from blood of a patient with myelogenous leukemia treated with $^{32}$P. Values after April 1 are from blood taken just before administration of $^{32}$P, and one week after the last dose of $^{32}$P. The marked differences between the radioactivity of leukocytes and red corpuscles are clearly shown.

This patient had an excellent initial response to therapy. A recurrence has been well controlled by additional therapy.
into account, it is possible to derive an approximate whole body radiation dose in terms of "roentgens." For the patient of Fig. 7 this would amount to 240 "roentgens" for the period between November 6th and January 18th. It is to be remembered, however, that the radioactive phosphorus is not distributed evenly throughout the body. Therefore, the estimation of whole body therapy due to radiation from radioactive phosphorus is not exactly comparable to that from whole body x-irradiation. If x-radiation is used, all tissues at the same depth receive equal doses. When radioactive phosphorus is the source of whole body radiation, the tissues are irradiated unevenly, and for leukemia, the involved tissues receive a larger dose than do normal tissues.

Table IV shows the unequal distribution of phosphorus in leukemia. It contains the measurements made on tissues from patients who died after therapy and were autopsied. The difference between identical tissues with different degrees of leukemic infiltration is, in some instances, striking and is best illustrated by comparing the values for kidney and testis of cases or gain due to absorption, during this period, is unknown. The figures do suggest, however, that absorption is rapid and early, and that the absorbed amount is largely retained for at least 8 days. This is also borne out by tissue measurements in patients with diseases other than leukemia, in whom biopsy or surgical specimens were removed at varying periods after administration of the radioactive phosphorus. If this is true, it is of greatest importance, because the largest and most significant part of the radiation from this isotope is administered during the first 3 weeks after any given dose (10).

Table IV: Leukemia: Radioactivity of Tissues in Patients Autopsied

<table>
<thead>
<tr>
<th>Case number</th>
<th>Diagnosis</th>
<th>Age and sex</th>
<th>Amount of (^{32}P) administered in mc, and date</th>
<th>Tissue</th>
<th>mc, per kg</th>
<th>L.I.</th>
<th>(\mu c), per kg</th>
<th>L.I.</th>
<th>mc, per kg</th>
<th>L.I.</th>
<th>(\mu c), per kg</th>
<th>L.I.</th>
<th>mc, per kg</th>
<th>L.I.</th>
<th>(\mu c), per kg</th>
<th>L.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>59290</td>
<td>Lymphatic leukemia</td>
<td>3 yrs., M.</td>
<td>8/2 0.4 11/9 0.6 8/20 0.6 8/30 0.8 9/4 0.6 9/13 0.6</td>
<td>Liver</td>
<td>120</td>
<td>3</td>
<td>137</td>
<td>3</td>
<td>138</td>
<td>3</td>
<td>112</td>
<td>0</td>
<td>162</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spleen</td>
<td>107</td>
<td>3</td>
<td>145</td>
<td>3</td>
<td>112</td>
<td>3</td>
<td>98</td>
<td>1</td>
<td>69</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymph Node</td>
<td>131</td>
<td>3</td>
<td>117</td>
<td>3</td>
<td>82</td>
<td>3</td>
<td>101</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marrow</td>
<td>147</td>
<td>3</td>
<td>112</td>
<td>1</td>
<td>285</td>
<td>4</td>
<td>53</td>
<td>3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vertebral</td>
<td>102</td>
<td>3</td>
<td>113</td>
<td>3</td>
<td>93</td>
<td>2</td>
<td>285</td>
<td>2</td>
<td>53</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61134</td>
<td>Lymphatic leukemia</td>
<td>13 yrs., F.</td>
<td>10/31 1.0 11/9 1.0 11/12 1.2</td>
<td>Kidney</td>
<td>112</td>
<td>3</td>
<td>143</td>
<td>3</td>
<td>68</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>85</td>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Muscle</td>
<td>45</td>
<td>3</td>
<td>27</td>
<td>3</td>
<td>34</td>
<td>2</td>
<td>60</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart</td>
<td>65</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>34</td>
<td>2</td>
<td>60</td>
<td>2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>64</td>
<td>0</td>
<td>56</td>
<td>2</td>
<td>46</td>
<td>2</td>
<td>47</td>
<td>0</td>
<td>35</td>
<td>2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Pancreas</td>
<td>85</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>49</td>
<td>1</td>
<td>64</td>
<td>2</td>
<td>35</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intestine</td>
<td>89</td>
<td>0</td>
<td>54</td>
<td>0</td>
<td>34</td>
<td>2</td>
<td>60</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stomach</td>
<td>64</td>
<td>1</td>
<td>39</td>
<td>1</td>
<td>26</td>
<td>1</td>
<td>76</td>
<td>0</td>
<td>35</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60554</td>
<td>Lymphatic leukemia</td>
<td>61 yrs., M.</td>
<td>8/20 2.8 8/24 3.4 8/28 3.2</td>
<td>Testis</td>
<td>132</td>
<td>0</td>
<td>57</td>
<td>0</td>
<td>57</td>
<td>1</td>
<td>76</td>
<td>0</td>
<td>35</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61435</td>
<td>Lymphatic leukemia</td>
<td>6 yrs., F.</td>
<td>11/30 1.1 incl.</td>
<td>Ovary</td>
<td>132</td>
<td>3</td>
<td>80</td>
<td>3</td>
<td>80</td>
<td>3</td>
<td>80</td>
<td>3</td>
<td>80</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62061</td>
<td>Myelogenous leukemia</td>
<td>19 yrs., M.</td>
<td>12/16 0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| No. 59290 and No. 60554, or by comparing values in case No. 61134 for two pieces of kidney, one of which had marked, and the other no, leukemic infiltration. The amount of radiation, in roentgen equivalents, administered to these tissues can be estimated from these measurements. The estimations probably would not be accurate to more than plus or minus 15 per cent, because the values for the days preceding death can only be calculated by allowing for the decay in radioactivity. Loss in these tissues due to excretion...
A careful study of the patients with chronic myelogenous leukemia has led to the conclusion that radioactive phosphorus is an effective therapeutic agent in this disease because: 1. It reduces the white count to normal, or nearly normal (6 of 6 patients). 2. Enlarged spleens regress (6 of 6 patients). 3. Erythropoiesis is not disturbed, and the hemoglobin and erythrocyte count rise during therapy (6 of 6 patients). 4. It reduces the percentage of myeloblasts and myelocytes in the marrow (see section on Bone Marrow). 5. There is no radiation sickness during P\textsuperscript{32} therapy (6 of 6 patients).

The failure of P\textsuperscript{32} to influence the course of the disease in the patients in the subacute and acute phases may mean that the isotope would be of no more value in these phases than any other form of radiation.

**Lymphatic Leukemia of Childhood**

This is usually an acute type of leukemia which is notorious for its early and fatal outcome. Radiation therapy of any type has been uniformly unsuccessful in the treatment of these patients. Eight children with acute or subacute lymphatic leukemia have been treated with radioactive phosphorus. Seven are dead, all except one within 4 weeks from the time treatment began. The one patient still living was only partially treated before he was removed from the hospital. The therapeutic effect of the isotope in this patient has led to the following conclusions: 1. It should be considered therapy; i.e., had no value at all.

**Lymphatic Leukemia in Adults**

Eight patients have been treated with radioactive phosphorus. Four are dead, 6, 6, 6, and 4 months, respectively, after the commencement of therapy. The patient whose first treatment was administered 4 months before this report was written (Fig. 9) had just finished a full course of x-ray therapy, but without complete control of his disease. He has received 16.1 mc of P\textsuperscript{32} in 120 days with a reduction of the leukocyte count from 20,000 to 7,000. There are no palpably enlarged lymph nodes and the spleen is only barely palpable. There has been some recent improvement in the differential count. Two of the 3 patients who have been under treatment for the past 6 months have long histories and have had a moderate amount of x-ray therapy. The disease in one patient was well controlled, in the other patient only partially controlled, and it was necessary to administer x-ray therapy to a group of enlarged lymph nodes. The history of the fourth patient follows:

**Case No. 61374.** (Fig. 10.) A 58-year-old, white male, admitted 11/15/41. There were no contributory factors found in the family history. The patient was a chronic alcoholic with a mild addiction to barbiturates. Progressive weakness and fatigability had existed for 3 years. Enlarged lymph nodes in neck and axillary had been present for 3 years. The patient had frequent attacks of lower abdominal pain radiating to both flanks during 18 months. In June, 1940, chronic lymphatic leukemia was diagnosed, but no therapy was prescribed.

The findings on admission were: Generalized enlargement of lymph nodes in the neck, axillary, and groin, none of which exceeded 1.5 cm. in size. The liver was palpable 1 cm. below the costal margin and the spleen palpable 2 cm. below costal margin. Hemoglobin, 82 per cent; red corpuscles, 4,100,000; white corpuscles, 17,200.

The differential count showed: polymorphonuclear leukocytes, 14 per cent; eosinophiles, 2 per cent; monocytes, 3 per cent; lymphocytes, 80 per cent.

Marrow aspiration on 11/15/41 showed: lymphoblasts, 18 per cent; lymphocytes, 40 per cent; erythroblasts, 6 per cent; normoblasts, 10 per cent; myelocytes, 11 per cent; polymorphonuclears, 6 per cent; metamyelocytes, 5 per cent; eosinophiles, 4 per cent.

Course and treatment: The patient received 7 doses, totalling 9.1 mc, at 7 to 14 day intervals between 11/19/41 and 1/20/41. During this time there was no significant change in the white count. There was some regression in the size of the lymph nodes and spleen. On 1/27/41, the patient complained of acute left upper quadrant pain of 4 days' duration. A diagnosis of splenic infarct was made. Recovery was complete after 7 days' bed rest. From 3/4/41 to 4/16/41 the patient received, at weekly intervals, 6 doses totalling 11.2 mc. There was still no significant change in the white count. On 4/16/41, there were no enlarged lymph nodes and the spleen was only slightly palpable. The patient's general condition was excellent.

Radioactive phosphorus therapy has not altered this patient's white count. It has caused a regression in size of the enlarged lymph nodes and spleen. Symptomatically, the patient has improved markedly.

Analysis of the group of 8 patients with chronic lymphatic leukemia who have been treated with P\textsuperscript{32} has led to the following conclusions: 1. It should be
administered cautiously to patients with aplastic or infiltrated bone marrow. It has not been effective in cases that have become radiation-fast. It reduced the enlarged lymph nodes in 4 patients and reduced the enlarged spleens in 3 patients. The leukocyte count was decreased in 1 of 8 patients. The proportion of lymphocytes in the differential count was altered in 1 of 8 patients. Symptomatically, 5 of the 8 patients were improved. There is no radiation sickness.

LYMPHOSARCOMA

A group of 12 patients with a biopsy diagnosis of lymphosarcoma have been treated with radioactive phosphorus (5), and of these, 7 have been observed for a sufficient period of time to permit some evaluation of the benefits of the therapy in their cases. There has been good regression of the enlarged nodes in all of these cases except one. In 5 of the cases, this regression has been complete. In 1 patient there has been complete regression of enlarged neck nodes and about 50 per cent regression of enlarged axillary nodes. The patient whose disease did not regress actually showed enlargement of his nodes while therapy was being administered.

During therapy, some of the patients have shown moderate depression of the blood count, particularly the leukocyte count. In only one has there been a serious depression, and in this instance the marrow showed marked lymphocytic infiltration before therapy was started. Shortly after therapy was complete, the blood count began to fall and marrow biopsy showed aplastic tissue. Repeated transfusions have kept the patient in good condition, and a recent marrow aspiration has shown beginning regeneration.

The method of therapy in these patients has varied, but recently a more stable procedure has been outlined, to provide between 60 and 90 mc per kg, as an initial course of therapy. This dose is divided into 5 to 7 portions administered on successive days. After a week or ten days, the course is repeated, though usually the second total dose is somewhat smaller. Successive courses follow at 10-day to 2-week intervals until about 300 mc per kg. of weight have been administered. The plan of therapy depends on the patient's blood count, bone marrow, and responses to treatment. Each patient must be handled as an individual problem.

While all these patients have been treated only with radioactive phosphorus, it is believed that the greatest use for this isotope will be as an adjunct to x-ray therapy. The isotope has been used alone in these cases in order that some estimation might be made of its effect on lymphosarcoma. It is probable that the best method would be to treat the enlarged node masses with x-rays in the usual manner and then also to administer radioactive phosphorus either during or after the x-ray therapy. This method would destroy rapidly the obviously diseased tissue and might lead to destruction or inactivation of the small foci of disease in nonenlarged nodes. If therapy with radioactive phosphorus is combined with x-irradiation, it should be administered slowly and the blood count should be watched carefully.

Only 7 months have elapsed since the first patient was treated. Hence, no estimation of the end results is possible at this time. A careful study of these cases does permit, however, the following conclusions: 1. Lymphosarcoma nodes apparently will completely regress under radioactive phosphorus therapy (6 of 7

![Fig. 9. Regression of leukocyte count and partial regression of the per cent of lymphocytes in a case of lymphatic leukemia (Case No. 62314) treated with P32.](image)

![Fig. 10. A case of lymphatic leukemia treated with P32 with virtually no change in either the leukocyte count or the per cent of lymphocytes.](image)
patients). 2. There is some depression of the blood count during therapy, but, when the marrow has been normal at the outset, the damage has not been serious. 3. Radioactive phosphorus should prove to be a valuable adjunct to x-ray therapy in the treatment of lymphosarcoma.

**Osteogenic Sarcoma**

Eight patients with osteogenic sarcoma are receiving radioactive phosphorus therapy. In all but one patient this has been administered prophylactically with the hope that it will be absorbed sufficiently by the probably present, though clinically nonevident, metastases to damage them enough to prevent their growth.

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**Table V: Osteogenic Sarcoma: Tissue Absorption After Therapeutic Amounts of Radioactive Phosphorus**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Amount of Pa2 and time</th>
<th>Interval from first dose to operation of body at operation</th>
<th>Remaining P2 in body at operation after decay &amp; subtracted from administered dose</th>
<th>Ratio</th>
<th>Estimated dose in mc.</th>
<th>Differential absorption ratio and estimated roentgen dosage from P32</th>
<th>X-ray therapy tumor dose in r units</th>
</tr>
</thead>
<tbody>
<tr>
<td>61863</td>
<td>5 doses in 34 days totalling 4.5 mc.</td>
<td>61 days</td>
<td>9.6 mc.</td>
<td>218</td>
<td>29</td>
<td>3.6</td>
<td>600</td>
</tr>
<tr>
<td>60931</td>
<td>4 doses in 29 days totalling 10.96 mc.</td>
<td>34 days</td>
<td>2.5 mc.</td>
<td>233</td>
<td>53</td>
<td>3.8</td>
<td>400</td>
</tr>
<tr>
<td>61944</td>
<td>7 doses in 24 days totalling 10.71 mc.</td>
<td>28 days</td>
<td>3.3 mc.</td>
<td>195</td>
<td>60</td>
<td>4.3</td>
<td>400</td>
</tr>
<tr>
<td>61059</td>
<td>12 doses in 115 days totalling 20.8 mc.</td>
<td>123 days</td>
<td>2.1 mc.</td>
<td>320</td>
<td>33</td>
<td>2.4</td>
<td>400</td>
</tr>
</tbody>
</table>

All but one of these patients are still being treated, and no estimation of end results of this therapy is possible. One patient who had refused amputation and whose primary tumor had received a 9,100 "r" tumor dose of 1,000 kv. x-ray at 70 cm. T.S.D., was given 20 mc. over a period of 3 months. Treatment was discontinued because of the growth of extensive metastases during the period of phosphorus administration.

Four of the remaining 7 patients were operated upon after they had received a portion of their isotope therapy. Table V presents a résumé of their therapy and the measurements of radioactivity in the surgical specimens. It is to be noted that all of these patients had received large doses of x-ray therapy before operation. Included in the table is an estimation of the roentgen equivalents delivered to the tumor by the phosphorus. This "roentgen" dose is not encouraging. There may be a partial explanation for these low values in that the tumor had been largely inactivated by the x-ray therapy. As was mentioned earlier, deposition of radioactive phosphorus in these tumors is largely a function of their alkaline phosphatase content (12). This phosphatase activity is largely inactivated by the preoperative x-radiation (13). It is not at all unlikely, therefore, that the tumor accumulation and tumor roentgen equivalent dose shown in this table do not represent what the irradiation may be in the distant metastases. In this respect, it is to be remembered, however, that distant metastases do not always have the same phosphatase activity as the primary tumor. Another year must elapse, and more patients must be treated, before any evaluation of radioactive phosphorus therapy in osteogenic sarcoma can be made.

**Miscellaneous Cases**

This group is made up of 5 patients, each with a different type of malignant neoplasm, as follows: metastasizing hemangioma; lymphoepithelioma of the tonsil with widespread metastasis; melanoma with numerous cutaneous metastases; extensive mycosis fungoides; widespread multiple myeloma.

The patient with the metastasizing hemangioma received a total dose of 150 mc. per kg. of body weight in 18 days. This was divided into small daily doses in order to maintain the blood concentration of the isotope at as high a level as possible. It was hoped that by so doing sufficient irradiation would be administered to the walls of the blood vessels which comprise the lesions to cause some regression. No regression was observed during life, nor were any changes noted in the tumors at autopsy, 20 days after the commencement of therapy, that could be attributed to the P32.
Three hundred and fifty μc. per kg. of body weight were administered in divided doses in 34 days to the patient with metastasis from a lymphoepithelioma of the tonsil. No regression of these lesions was noted at any time.

The patient with cutaneous metastasis from a melanoma received 350 μc. per kg. of body weight in divided doses in 40 days. There was a steady growth of all of the lesions during and after the administration of the isotope. Measurements of radioactivity of a lesion removed at the close of therapy showed good concentration of the P\textsuperscript{32}.

The patient with mycosis fungoides received 200 μc. per kg. of body weight in 19 days. There was some regression of the disease. Unfortunately he left the hospital before therapy was considered complete and his course since that time is not known. Because some regression of disease was noted in this case, it might be advisable to consider P\textsuperscript{32} therapy when it is proposed to treat a patient with mycosis fungoides.

The patient with multiple myeloma received 250 μc. per kg. of weight in 4 months’ time. This therapy was divided into several courses and administered at irregular intervals. It was observed that during the first 3 months there was marked diminution in the amount of pain, and improvement in the patient’s general condition. There was no regression of the lesions as determined by x-ray pictures. The patient died in an exacerbation of his disease 7 months after the institution of the therapy. The results noted in this case indicate that P\textsuperscript{32} may be a useful palliative method of therapy in patients with multiple myeloma, particularly if the disease is widespread.

**Bone Marrow**

Careful study of the bone marrow, as secured by aspiration, has been made in most of the cases treated by radioactive phosphorus. This has been of importance because in the cases of leukemia it has provided some index of the success of the therapy, and in the cases of lymphosarcoma and osteogenic sarcoma it has given information as to how the blood-forming organs tolerate therapy.

All of the patients with chronic myelogenous leukemia have shown a decrease in the percentage of myelocytic and myeloblastic elements in the marrow. In most of these cases, there has been a corresponding increase in the erythropoietic tissue and in the more mature forms in the myelocytic series. Patients with a high initial percentage of myeloblastic elements and with a low erythropoietic percentage have not tolerated treatment with the radioactive phosphorus.

In chronic lymphatic leukemia, there has been very little change seen in the bone marrow during the therapy. There has been some decrease in the lymphocytic and lymphoblastic elements, but this has not been marked.

The marrow taken from patients with lymphosarcoma or osteogenic sarcoma has shown some suppression of the myelocytic elements during the course of therapy. In general, this has not been serious.

It has been consistently noted that patients with damaged bone marrow, in the sense that there is heavy infiltration with abnormal cells, or beginning aplasia, do not tolerate therapy with radioactive phosphorus. Patients with this type of marrow tissue should be treated cautiously or not at all.

Measurements of the radioactivity of the bone marrow, as secured by sternal aspiration, have been made on many of the patients receiving P\textsuperscript{32}. Table VI presents the essential data on this group of patients, and also contrasts the radioactivity of the marrow with that of whole blood. It is appreciated that marrow secured by aspiration is diluted to some extent by blood and that, therefore, the values for marrow in the table are somewhat lower than their true value. This dilution was reduced to the minimum by limiting the aspiration to 0.5 to 0.7 cc. of marrow. In myelogenous leukemia the activity of the marrow is 3 to 5 times that of whole blood. This is significant because it means that one of the primary sites of infiltration in myelogenous leukemia absorbs adequate amounts of the isotope.

In only a few of the patients with diseases other than leukemia was the activity of the marrow as much as twice that of whole blood. In many of these patients, marrow and whole blood radioactivity were about equal, and in several of the patients, the activity of the blood was greater than that of marrow. Cases No. M8049 and No. N9268 are of especial interest because they had received large amounts of P\textsuperscript{32} only a few days before their marrow biopsy. In these two patients there was less radioactivity in the marrow than in the blood.

**Cyto logical Studies**

Histological examinations were made of tissues from patients who had received radioactive phosphorus for various diseases. The material studied consisted of lymph node tissue removed at biopsy and tissues obtained at necropsy. In several cases, lymph nodes excised before treatment was begun were available for comparison with excised nodes that had shown clinical regression under therapy.

No cyto logical changes in the nodes were found that could be definitely attributed to the action of the radioactive isotope. In one node, partial hyalinization of the germinal centers was present, together with some fibrin deposit, but as these changes were ob-
served in nodes from other untreated cases, their origin is obscure.

Careful examination of organ tissues and bone marrow secured at autopsy from cases of leukemia failed to reveal cellular necrosis or other changes ascribable to the action of P"\(^{32}\), except in one case. In this case, of acute lymphatic leukemia, the terminal bone marrow picture was one of extreme aplasia with multiple hemorrhages. The marrow changes were more severe than those ever seen in this institution in terminal leukemia not treated with P"\(^{32}\). Furthermore, they simulated closely the changes produced in the marrow of normal mice by massive doses of P"\(^{32}\).

While the above changes are suggestive, we have not seen enough well-controlled material from patients receiving appreciable quantities of P"\(^{32}\) to come to any definite conclusions as to the histological alterations produced by this substance.

ALTERATIONS IN THE PHOSPHORUS METABOLISM IN LEUKEMIA AFTER P\(^{32}\)

During the course of an investigation of phosphorus metabolism in leukemia (1), it was noted that the administration of a small amount of P"\(^{32}\) altered the values of chemically determined organic acid-soluble phosphorus in the leukocytes and erythrocytes by 50 to 100 per cent. Four patients with leukemia were put on controlled diets and after a period of time, 450 mgm. of nonradioactive phosphorus were administered. No significant alterations of the organic acid-soluble phosphorus levels in the blood cells were observed. Each of these patients was then given about 1.5 mc. of P"\(^{32}\) in the same amount of phosphate as was administered in the nonradioactive dose. In each instance, this produced a marked increase or decrease in the organic acid-soluble phosphorus level in the leukocytes and usually in the erythrocytes. There was usually a marked agitation of the values over a period of 3 to 10 days. Fig. 11 shows the effect of the P"\(^{32}\) on these compounds in one of the patients studied. All measurements are in mgm. of phosphorus per 100 cc. of cells. The method of Fiske and Subbarrow (3) was used in these determinations.

The belief that these alterations of phosphorus metabolism were due to the radiation delivered to the leukocytes and erythrocytes by the P"\(^{32}\) was con-

Table VI: Radioactivity of Bone Marrow

<table>
<thead>
<tr>
<th>Case number</th>
<th>Diagnosis</th>
<th>Degree of marrow infiltration</th>
<th>P&quot;(^{32}) dose and time</th>
<th>Last dose of P&quot;(^{32}) and date</th>
<th>Radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6093</td>
<td>Myelogenous leukemia</td>
<td>Moderate</td>
<td>4.7, 7</td>
<td>2.7, 5</td>
<td>48.4, 15.0, 3.2</td>
</tr>
<tr>
<td>61491</td>
<td>Myelogenous leukemia</td>
<td>Moderate</td>
<td>4.7, 7</td>
<td>2.7, 24</td>
<td>19.0, 4.0, 4.8</td>
</tr>
<tr>
<td>N4954</td>
<td>Lymphosarcoma</td>
<td>Slight</td>
<td>10.7, 21</td>
<td>10.0, 7</td>
<td>3.8</td>
</tr>
<tr>
<td>L5444</td>
<td>Lymphosarcoma</td>
<td>Slight</td>
<td>19.4, 140</td>
<td>18.5, 14</td>
<td>20.6, 6.2, 3.5</td>
</tr>
<tr>
<td>N9268</td>
<td>Lymphosarcoma</td>
<td>None</td>
<td>4.1, 11</td>
<td>0.4, 1</td>
<td>18.4, 10.8, 1.7</td>
</tr>
<tr>
<td>M8049</td>
<td>Lymphosarcoma</td>
<td>None</td>
<td>6.9, 77</td>
<td>1.0, 7</td>
<td>7.3, 5.6, 1.3</td>
</tr>
<tr>
<td>N9268</td>
<td>Lymphosarcoma</td>
<td>None</td>
<td>13.5, 119</td>
<td>1.3, 7</td>
<td>11.3, 11.8, 1.0</td>
</tr>
</tbody>
</table>

These values were determined by the usual technic of measuring blood phosphorus. They are all chemical measurements and were not determined by measuring radioactivity.

4

fully evaluated to be certain that the results represent physiological and not radiation metabolism.

The amount of isotope administered to these patients is the equivalent, on a weight basis, of about 1 μc., in a 30 gm. mouse. From 1 to 5 μc. is the usual tracer dose, for mice, in experimental investigations. Therefore, the amount of P thirty-two, 1.5 mc., administered to these patients should be strictly comparable to the amount of isotope that is usually used in tracer work in mice.

SUMMARY AND CONCLUSIONS

A review has been presented of an 18 months' investigation by a group of workers at The Memorial Hospital on radioactive phosphorus as a therapeutic agent in malignant neoplastic disease. Its physical characteristics and the estimation of the radiation it delivers in tissue have been discussed.

A differential absorption ratio has been devised by means of which it is possible to estimate the relative absorption of the P thirty-two by various tissues after administration of the isotope. It is based on the amount of the isotope administered per kilogram of weight as related to the amount absorbed by a kilogram of a given tissue.

Subtherapeutic amounts ("tracer doses") of radioactive phosphorus have been administered to patients with carcinoma of the breast, osteogenic sarcoma, and lymphosarcoma. Measurements of radioactivity were made on portions of the various tissues removed from these patients at operation. The ratio described above was then calculated in each instance. From the results obtained in this manner, it was learned that radioactive phosphorus was preferentially absorbed by the tissue of osteogenic sarcoma and of lymphosarcoma, and less so by carcinoma of the breast.

The method of the treatment of leukemia with radioactive phosphorus has been discussed. Six patients with chronic myelogenous leukemia (of whom 4 are still living) have been treated with P thirty-two, and the isotope found to be a good and reliable therapeutic agent in this disease, because, in each case, a) it reduced the leukocyte count to nearly normal, b) the enlarged spleen was markedly reduced in size, c) the percentage of myelocytes and myeloblasts in the bone marrow was decreased, d) erythropoiesis was not seriously disturbed, and e) there was no radiation sickness.

P thirty-two therapy has been used on 8 patients with chronic lymphatic leukemia, 4 of whom are still living. Five of the 8 patients improved symptomatically during treatment. Three patients had enlarged spleens, and 4 patients had enlarged lymph nodes. In each instance, these were reduced in size to normal, or nearly normal. The leukocyte count and differential count were not appreciably altered except in one instance. It would appear that P thirty-two will be a useful therapeutic agent in this disease.

Ten patients in the acute, or subacute, phase of leukemia (2 myelogenous and 8 lymphatic) have been treated with P thirty-two. All but one of these patients are dead, and in no case was there any improvement which could be attributed to the isotope. It is believed that radioactive phosphorus is not a useful method of therapy in this type of disorder.

Twelve patients with lymphosarcoma have been treated with radioactive phosphorus. Seven patients have been observed for a sufficient period of time to permit a preliminary evaluation of the results of the therapy. Five patients have had complete regression of the disease, plus freedom from recurrence for periods of 1 to 8 months. One patient has had partial regression of his disease. One patient did not respond to P thirty-two therapy. There has been some depression of the blood count during therapy in all patients, but this was serious in only one instance. It is believed that the isotope will be a useful therapeutic agent in this disease, because it brings about regression of lymphosarcoma tissue and because it is distributed to all the areas in which such tissue is present.

Eight patients with osteogenic sarcoma have been treated prophylactically with P thirty-two, with the hope that the probably present, though clinically nonevident, metastases would absorb a sufficient amount of the isotope to be inactivated by its radiation. Seven patients are still living, but sufficient time has not elapsed to justify even a preliminary evaluation of
results. One patient is dead. In this case, extensive metastases appeared during the period of administration of the isotope.

The cytologic studies made on tissue removed from patients treated with radioactive isotopes are briefly presented. No alterations of cellular characteristics were noted that could be definitely ascribed to $^{32}P$.

Careful studies have been made on the bone marrow of most of the patients treated with radioactive phosphorus. Marrows infiltrated with neoplastic tissue tend to absorb more of the isotope than noninfiltrated ones.

A change in the phosphorus metabolism of blood cells in patients with leukemia after the administration of subtherapeutic amounts of $^{32}P$ has been described.

As stated at the beginning of this paper, the material presented is a summary of cooperative research.

Dr. Jules C. Abels developed and supervised the investigation of the alterations of the organic acid-soluble phosphorus compounds in leukocytes and red corpuscles in leukemia after radiation.

Dr. Lloyd F. Craver, of the Department of Medicine, contributed much to the success of the clinical application of $^{32}P$. His experience in radiation therapy of leukemia and lymphosarcoma has been a valuable asset.

Mr. L. D. Marinelli, of the Department of Physics, was in charge of all measurements of radioactivity. He has developed the methods used by us for estimating tissue doses of radiations from absorbed $^{32}P$.

Dr. Levin Waters, of the Department of Pathology, under the supervision of Dr. Fred Stewart, examined the tissues secured at operation or autopsy from patients receiving therapeutic amounts of radioactive phosphorus.

Dr. Helen Q. Woodard, of the Department of Chemistry, supervised or performed all the phosphatase measurements on blood and in tissue secured at operation or autopsy from patients with bone tumors who had received $^{32}P$.

The author is deeply indebted to Dr. Edith Quimby and Dr. G. Failla, of the Department of Physics, and to Dr. C. P. Rhoads, Director of the Memorial Hospital, for their many valuable suggestions during the preparation of the paper.

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