The Gross Electrolyte Composition of Certain Human Malignant Tissues*

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Certain unexpected relationships between the nitrogen and phosphorus balances in patients with neoplasms led us to suspect that the ratio of nitrogen to phosphorus might be altered in human malignant tissue. Previous studies on patients with rapidly growing tumors have shown a proportionately greater retention of phosphorus and potassium, as related to nitrogen, than is usually seen in the repletion of normal body tissue (5). This stimulated our interest in the gross composition of human neoplastic tissue.

A review of the recent literature revealed that in experimental tumors particular biochemical systems have received the most attention (6). When total analyses have been reported, these tumors have consistently been relatively rich in water and poor in nitrogen, compared with the related normal tissues. Some studies have demonstrated an increased concentration of phosphorus and potassium (13, 15). The data on human tumors are more fragmentary and suffer from the fact that the analytical values have been compared with a variety of standards. The total content of specific substances present in tumor tissue can be most easily related to the weight of the specimen used. However, for this to be meaningful, certain corrections are necessary to indicate the quantity of malignant protoplasm actually present. Those corrections that can be readily applied provide for the variable moisture, fat, and collagen content of tumor tissue. Corrections for the presence of variable amounts of supporting structures other than collagen and for the small amounts of necrotic and mucinous material which may be interspersed with the living tumor cells are much more difficult. With full recognition of the problems involved, we believe we have accumulated satisfactory data on 42 biopsy specimens of malignant tissue from human tumors. The purpose of this paper is to report on the values for their water, nitrogen, and electrolyte content. The results are consistent along certain lines and allow for certain deductions and interpretations.

MATERIALS AND METHODS

The samples of malignant tissue were obtained for the most part from patients who were undergoing study on the metabolism ward, and the biopsies were done solely for analytical purposes. For this reason peripheral tissues were most frequently obtained, and the procedure was done under local anesthesia. The major exception to this occurred in the patients with carcinoma of the bowel, where the specimens were obtained during the course of an operative procedure. Two autopsy specimens which were obtained soon after the patient died are included; it was felt that these results were valid with the exception of the potassium and sodium concentrations, which are known to change rapidly at the time of death. Several patients had repeated biopsies over considerable periods of time to determine whether results were consistent for a particular tumor. The white blood cells in the leukemic patients were obtained and treated as described previously (5).

Immediately after each sample was obtained, it was wiped free of any blood, and any fat or necrotic material was removed. It was then divided into three portions, one for microscopic section, one for nitrogen determinations, and one for ashing in preparation for the electrolyte determinations. For the latter, between 1 and 3 gm. were usually used, and the electrolyte analyses were carried out on the ashed sample by the methods described in a previous publication (5). In some specimens from which good duplicate analyses for phosphorus could not be obtained from the nitric acid ashes, separate samples were ashed in sulfuric acid specif-

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ically for the phosphorus determinations. Total nitrogen values were determined by the standard micro-Kjeldahl technic either on whole tissue or on aliquots of homogenized tissue. When homogenates were used, they were prepared in a glass mechanical homogenizer, and the homogenate was allowed to stand overnight with 0.1 N NaOH and then centrifuged. The sediment, containing the collagenous nitrogen, was analyzed, as was the supernatant, the latter containing the noncollagenous nitrogen (10).

RESULTS

Analyses of normal source tissue.—Although the direct comparison of the composition of malignant tissue with the normal source tissue is frequently misleading, it does offer a rough framework of values. Table 1 shows the variation of water and electrolyte content of some normal human tissues. Some of the data for muscle and lymph node were obtained from samples secured and analyzed by us, while the values for other organs are based on data from the literature (2–4, 7, 12, 16, 17).

Malignant tissues from patients with lymphoma and leukemia.—Table 2 shows the water, nitrogen, and electrolyte content of the malignant tissue in a group of patients with lymphoma or leukemia. It should be noted that in this group of specimens there has been no correction for collagen. With two exceptions, H.P. and R.S., this was probably not necessary, since all these tumors were highly cellular and contained little stroma. The fat content of the specimens has not been recorded but was, for the most part, insignificant, being less than 2 per cent of the gross weight.

In comparison with the majority of normal body tissues, the water content of this group of tumors is uniformly high. While the nitrogen content expressed on a wet weight basis is low, when this is expressed on a dry weight basis it approaches the value seen in normal tissues which do not contain much glycogen.

The sodium values are not excessive, so that even if one assumes that all this is extracellular the calculations still ascribe the excessive water content to the intracellular space. The potassium and

TABLE 1

<table>
<thead>
<tr>
<th>ELECTROLYTE CONTENT OF NORMAL HUMAN TISSUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE OF TISSUE</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Muscle</td>
</tr>
<tr>
<td>Lymph node</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Bowel mucosa</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Testicular tissue</td>
</tr>
</tbody>
</table>

TABLE 2

<table>
<thead>
<tr>
<th>ELECTROLYTE CONTENT OF NEOPLASTIC TISSUE FROM PATIENTS WITH LYMPHOMA AND LEUKEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>J.F.</td>
</tr>
<tr>
<td>J.A.</td>
</tr>
<tr>
<td>J.S.</td>
</tr>
<tr>
<td>H.K.</td>
</tr>
<tr>
<td>J.P.</td>
</tr>
<tr>
<td>H.P.</td>
</tr>
<tr>
<td>H.P.</td>
</tr>
<tr>
<td>B.M.</td>
</tr>
<tr>
<td>B.M.</td>
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<tr>
<td>B.M.</td>
</tr>
<tr>
<td>B.M.</td>
</tr>
<tr>
<td>B.M.</td>
</tr>
<tr>
<td>J.E.</td>
</tr>
<tr>
<td>J.S.</td>
</tr>
<tr>
<td>A.M.</td>
</tr>
<tr>
<td>J.G.</td>
</tr>
<tr>
<td>R.S.</td>
</tr>
<tr>
<td>F.R.</td>
</tr>
</tbody>
</table>
the phosphorus content were both very high—
higher than in any normal tissue other than brain.
Even with the calculated high intracellular fluid
content, normal concentrations of these two elec-

trolytes in the intracellular fluid were not found.

The ratio of nitrogen to phosphorus in all spec-

cimens except H.P.'s second biopsy (which was
obtained after a partial remission was induced by
x-ray therapy) was lower than the value generally
ascribed to normal protoplasm, i.e., 14.7:1(1).

It should be noted that the five samples ob-
tained on B.M., obtained over a 2-year period, did
not vary significantly in their composition, with
the exception of the autopsy specimen. It appears
that an exchange of sodium for potassium had oc-
curred in this specimen before it was taken for
analysis. As explained above, the two samples on
H.P., obtained about 8 months apart, were taken
before and after x-ray therapy. The increase in
connective tissue in the second specimen was obvi-
ous by microscopic examination, and the changes
in the analysis of the whole tissue are of interest.

Malignant tissue from patients with carcinoma
and sarcoma.—The analytical values for all the
other malignant tissues studied are shown in
Table 3. The results are much more variable,
which is to be expected, since we are dealing with
a more heterogeneous group of tissues than in the
lymphoma group. Certain trends are apparent,
however.

The water content of these tumors, again, was
uniformly high and in those of epithelial or con-
nective tissue origin even higher than in the lym-
phomatous group. The nitrogen content showed a
trend similar to the first group discussed, i.e., a
relatively low value when no correction for the in-
creased water content of these tissues is made but
a value in the range of normal when this is done.

The higher total sodium and chloride content of
the samples in this group as compared with those
of the first group discussed is immediately appar-
ent from examination of the table. This is true
even after a correction is made for the amount of
these electrolytes in collagen and is in agreement
with the work of Kiskis and others who have found
a high total sodium content in experimental hepa-
tomas (8). This suggests that much of the in-
creased H2O content in these tumors was due to
extracellular fluid or that there was an abnormal
concentration of intracellular sodium in these
specimens.

None of the potassium and phosphorus values
are as high as in the lymphoma group. It can also
be seen from examination of Table 3 that, of all
these tumors, those that were metastatic generally
had a higher concentration of these electrolytes.

As might be expected, necrosis of any significant
portion of the biopsy specimen invariably caused
a reduction in the amount of both the phosphorus
and potassium. Again, if one calculates the ap-
proximate concentration of these in the intracel-
larular fluid the values are considerably higher than
those for normal tissues and similar to those seen
in the lymphoma group.

The N/P ratios shown in Table 3 are variable.
Although the correlation is not entirely consistent,
it does appear that the presence of a larger amount
of stroma or any amount of necrosis (with its as-
associated decrease in total phosphorus content) will
elevate the N/P ratio.

The analytical values for the fibroma of the
breast are included simply as confirmatory evi-
dence that collagen and stromal tissue do not con-
tain a significant amount of potassium or phos-
phorus.

DISCUSSION

Comparative studies of the composition of hu-
man malignant tissue should ideally be done on
samples which contain only viable tumor cells and
a minimal amount of supporting structure. Even
under these circumstances, accurate correction for
the supporting structures would be desirable, for
the most informative values would be those ex-
pressed as moles or mEq of each component per
liter of intracellular tumor water.

Unfortunately, the vagaries of the growth pat-
tern of the various human malignant neoplasms do
not permit such a strict analysis of tumor com-
position. It is not surprising that the presence of
considerable stroma and necrosis in the analyzed
specimen considerably distorts the total elec-
trolyte composition, and this is readily apparent in
Table 3. However, considering only the specimens
without necrosis and those where the correction for
collagen could be quantitated, it appears that cer-
tain consistent differences do exist in the group of
tissues studied. For example, in certain malignant
tissues derived from bowel mucosa, the values for
intracellular electrolytes were lower than in most of
the other tissues. When metastatic tissue was ob-
tained from lymph nodes of patients with carcinoma
or melanoma (A.D., J.D., S.R.) and little but tumor
cells could be seen in the section, none of the total
values for potassium and phosphorus were as high
as in the lymphoma group, but considerably higher
than in the primary tumors. Thus, the electrolyte
composition of tumors seemed to vary with the
site of origin as well as the ability of the cells to
metastasize. As will be seen later in the discussion,
it seems more likely to us that these analytical dif-
fences reflect variations in the mode of growth of
<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Histology*</th>
<th>Stroma</th>
<th>Necrosis</th>
<th>Per cent H2O</th>
<th>Per cent CN†</th>
<th>Per Kg. Fat-free Tissue</th>
<th>Per 100 Gm. Fat-free Solids</th>
<th>N/P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.W. #1</td>
<td>Rhabdomyosarcoma</td>
<td>+++++</td>
<td>0</td>
<td>87.1</td>
<td>18.1</td>
<td>19.0</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>R.W. #2</td>
<td>Rhabdomyosarcoma</td>
<td>+++++</td>
<td>0</td>
<td>83.7</td>
<td>22.5</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>J.F.</td>
<td>Fibrosarcoma, ovary</td>
<td>+</td>
<td>0</td>
<td>84.9</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>A.D. #1</td>
<td>Malignant melanoma</td>
<td>+</td>
<td>0</td>
<td>85.2</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>A.D. #2</td>
<td>Malignant melanoma</td>
<td>+</td>
<td>0</td>
<td>87.0</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>A.B.</td>
<td>Carcinoma, breast</td>
<td>+ + + + +</td>
<td>0</td>
<td>84.8</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
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<td>0</td>
<td>85.7</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>J.S.</td>
<td>Carcinoma, breast</td>
<td>+ + + + +</td>
<td>0</td>
<td>85.8</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>J.D.</td>
<td>Carcinoma, colon</td>
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<td>0</td>
<td>87.3</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>M.K.</td>
<td>Carcinoma, colon</td>
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<td>0</td>
<td>84.7</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>A.T.</td>
<td>Carcinoma, colon</td>
<td>+ + + +</td>
<td>0</td>
<td>83.5</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>J.M.</td>
<td>Carcinoma, colon</td>
<td>+ + + +</td>
<td>0</td>
<td>85.4</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>G.P.</td>
<td>Carcinoma, kidney</td>
<td>+</td>
<td>0</td>
<td>81.5</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>G.F.</td>
<td>Carcinoma, kidney</td>
<td>+</td>
<td>0</td>
<td>80.9</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>T.W.</td>
<td>Carcinoma, lung</td>
<td>+</td>
<td>0</td>
<td>86.1</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>T.M.</td>
<td>Carcinoma, pancreas</td>
<td>+ + + +</td>
<td>0</td>
<td>85.9</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>I.E.</td>
<td>Carcinoma, bladder</td>
<td>+ + + +</td>
<td>0</td>
<td>85.5</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>E.C.</td>
<td>Carcinoma, prostate</td>
<td>+ + + +</td>
<td>0</td>
<td>85.1</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>H.W.</td>
<td>Teratocarcinoma</td>
<td>+ + + +</td>
<td>0</td>
<td>84.1</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>S.R.</td>
<td>Squamous-cell cancer</td>
<td>+ + + +</td>
<td>0</td>
<td>86.4</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>D.B.</td>
<td>Anaplastic carcinoma</td>
<td>+ + + +</td>
<td>0</td>
<td>86.1</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>M.W.</td>
<td>Anaplastic carcinoma</td>
<td>+ + + +</td>
<td>0</td>
<td>85.6</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
<tr>
<td>F.D.</td>
<td>Fibroma, breast</td>
<td>+ + + + +</td>
<td>0</td>
<td>80.8</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
<td>16.0</td>
<td>8.1</td>
</tr>
</tbody>
</table>

*Explanation of histological appearance:
+ + + + + = 100% to 90% of the tissue showed fibrotic or necrotic changes.
+ + + + = 90% to 80% of the tissue showed fibrotic or necrotic changes.
+ + + = 80% to 70% of the tissue showed fibrotic or necrotic changes.
+ + = 70% to 60% of the tissue showed fibrotic or necrotic changes.
+ = 60% to 50% of the tissue showed fibrotic or necrotic changes.
+ = 50% to 40% of the tissue showed fibrotic or necrotic changes.
+ = 40% to 30% of the tissue showed fibrotic or necrotic changes.
+ + = 30% to 20% of the tissue showed fibrotic or necrotic changes.
+ + = 20% to 10% of the tissue showed fibrotic or necrotic changes.
+ = 10% to 0% of the tissue showed fibrotic or necrotic changes.

† CN = Collagenous nitrogen/kg of fat-free tissue.
‡ Dry coll. = dry collagen.
§ Denotes that the biopsy was of a metastatic lesion.
the whole tissues rather than actual differences within the tumor cells.

On the reasonable assumption that most of the chloride and sodium ions in tumor tissue, as well as in normal tissue, occupy an extracellular position, one can calculate the quantity of extracellular (ECF) and intracellular (ICF) fluid present in a sample of tissue. Calculations assuming these ions to be entirely extracellular can be made, with resultant derivation of the minimum amount of intracellular fluid that could be present. Such calculations applied to data from the leukemia-lymphoma group revealed that the quantity of ICF in these specimens was considerably higher than that in normal tissue. Because of the higher sodium content in the carcinoma-sarcoma group, relatively less ICF and more ECF appeared to be present. This difference in the fluid compartments of the various tumors is of considerable significance in interpreting the electrolyte composition within the tumor cell. Using the calculated quantity of ICF and the total amount of potassium and phosphorus, one can then roughly estimate the concentration of these two electrolytes in the intracellular fluid. When this is done, the relative discrepancies in the total potassium and phosphorus content in the two groups of tumors reported tend to disappear, and the concentrations in nearly all the tumors studied tend to be in the neighborhood of 200 mm/liter. This value is considerably higher than that usually ascribed to normal tissues. This again suggests that the variations observed in the total electrolyte composition of different tumors may depend more upon the differences in their mode of growth rather than on any difference in the electrolyte composition within tumor water itself.

One might anticipate the accumulation of large amounts of water, potassium, and phosphorus in actively growing, highly cellular tissues. It is conceivable that the ordinary restraint of supporting structures, which may be a limiting factor in the accumulation of these substances in normal growing tissues, is absent in malignant tissues, and that the high total quantity of electrolytes is simply a reflection of the greater amount of tumor protoplasm present. However, as noted above, the calculations showed concentrations of potassium and phosphorus well above that for any body tissues. It would be of considerable interest to know whether (a) the high concentrations mean a lack of osmotic equilibrium with the rest of the body or whether (b) some of the electrolytes occur in osmotically inactive form within the tumor cell. In support of the former there is some evidence that actively metabolizing tissue may have as much as 200–300 mm of base/liter of water and that this is all osmotically active, as long as energy-giving mechanisms are intact (14). In addition, certain malignant tissues are known to shrink less rapidly in high concentrations of saline than are certain non-neoplastic tissues (11). On the other hand, it has been suggested that potassium in a form not readily exchangeable exists in certain malignant tumors (19), so that this could mean that a fraction of the potassium as well as the phosphorus might be osmotically inactive. The experimental evidence supporting the former concept appears somewhat stronger.

It might be postulated that the large amount of phosphorus found in malignant tumors is present in the nucleoproteins which one would expect to be increased in highly cellular tissues. That this does not entirely account for the high values found is supported by recent data from this laboratory on the fractionation of the phosphorus within these tumors. Much of the increase in phosphorus appeared in the acid-soluble fraction.

Of most interest would be information relative to the functional activity of the phosphorus and potassium in these cells. Phosphorus metabolism within soft tissue is ordinarily closely associated with energy-yielding systems. Further biochemical studies on the actual phosphorus compounds which are responsible for the increased total concentration might well yield valuable information.

SUMMARY
1. A series of 42 biopsies of human malignant neoplasms have been analyzed for their water, nitrogen, and electrolyte content. These have been arbitrarily divided into a leukemia-lymphoma group and a carcinoma-sarcoma group for the purposes of presentation and discussion.
2. A high total water content was consistently observed. Total nitrogen, expressed on a dry weight basis, was for the most part within the range found in normal tissue.
3. Variations observed in the gross electrolyte values are discussed in the light of variations in the mode of structural growth of malignant tumors.
4. The significance of the apparently high intracellular concentration of potassium and phosphorus in tumor cells is discussed.

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