BLOOD FLOW IN TRANSPLANTED TUMORS: QUANTITATIVE APPROACHES TO RADIOISOTOPIC STUDIES**

Descriptions of the weight of a tumor and the magnitude of its blood flow have been of interest for a number of years. Despite this, there have been no reported attempts to provide quantitative relationships between the tumor's weight and its rate of perfusion. An initial approach to such a relationship, which adequately describes all known data in the literature thus far, is given in the present communication. In this inquiry, we are hampered by a lack of knowledge as to possible "cause and effect." However, we will arbitrarily describe blood flow as a function of tumor weight, and seek interrelations. Such an approach has only become possible in the last few years with the availability of radioisotopic techniques for estimating "functional" blood flow distribution.

TECHNIQUES FOR OBTAINING DATA

Prior to analyzing results on blood flow to tumors, it is prudent to examine briefly the techniques reported in the literature that have been employed in gathering the data. The abnormal vasculature of tumors has been recognized for over 100 years, and Rogers and co-workers have provided a useful compilation of pertinent references. Since an aberrant vascular supply is present, we must inquire if radioisotopic techniques are valid in estimating tumor blood flow. The answer to this will have to be analyzed separately for each method. Gullino and Grantham found that the distribution of radiopotassium or radiorubidium (Sapirstein's technique) closely agreed with a direct procedure (cannulation) in estimating blood distribution to tumors in rats. Flow estimation, by use of a rapidly diffusing radio-labeled indicator (131I-antipyrine), had been found by several workers to give a reasonable estimate of tissue blood flow; the technique has been modified by Rogers and associates and extended to the measurement of tumor blood flow. These workers also studied blood flow to the hamster amelanotic melanoma by means of 131I-antipyrine in some cases and 51Cr-microspheres in other instances. Results of the two procedures were approximately comparable (although not carried out simultaneously on the
same piece of tissue). Lewis, Edlich, and Borner carried out a dual-labeled study, utilizing radiolabeled ceramic microspheres as well as radiorubidium. These investigators concluded that the two radioactive tags had the same distribution to a hind limb tumor in dogs.

A tentative conclusion, at least as far as studies have progressed, is that radioisotopic procedures can be employed to estimate tumor blood flow. Careful scrutiny must be maintained, however, for possible deviations. For example, Gump and White measured blood flow in the rabbit V-2 carcinoma by counting the beta emissions from $^{85}$Kr. It is uncertain in such an instance as to how much of the tumor was within the field of view of their Geiger-Mueller detector.

**BACKGROUND**

We can conceptualize a broad scheme, by equating the specific rate of change of blood flow and the specific tumor growth rate. Let $m$ be a con-

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**FIG. 1.** Blood flow (ml/min.) in the hamster amelanotic melanoma (data from Rogers and co-workers), given on a log-log plot as a function of the weight of the tumor. The least squares equation was $\log F = -0.118 + 0.522 \log W$. The correlation coefficient was 0.94.
stant, $F$ the flow, $t$ the time, and $W$ the weight. Proportionality between these rates can be written as:

\[
\frac{dF}{F} \cdot \frac{1}{dt} = m \frac{dW}{W} \cdot \frac{1}{dt}
\]

The time-independent relationship between weight and flow is thus:

\[
\frac{dF}{F} = m \frac{dW}{W}
\]

This integrates to:

\[
\ln F = m \ln W + \ln c
\]

or:

\[
F = cW^m
\]

The prediction of equation (3) is that the logarithm of flow should be a linear function of the logarithm of tumor weight. While equation (4) can be matched to experimental points by a matrix inversion technique, we will follow a simple least squares solution of equation (3) in the following discussion. Tests of equation (3) are provided by means of data of Rogers and co-workers\(^1\) on the hamster amelanotic melanoma (plotted here in Fig. 1). We can also utilize the results of Cataland and associates\(^2\) on a mouse mammary carcinoma (Fig. 2) and a mouse sarcoma (Fig. 3). The fit of the

![Graph](image-url)

**Fig. 2.** Blood flow (fraction of cardiac output) in the mouse mammary carcinoma. Points were calculated from values given by Cataland and co-workers.\(^a\) The least squares equation was $\log F = -1.71 + 0.59 \log W$. The correlation coefficient was 0.88.
Blood flow in tumors  |  SPENCER

Fig. 3. Blood flow (fraction of cardiac output) in the mouse sarcoma 180. Points were calculated from values given by Cataland and co-workers. The least squares equation was $\log F = -1.87 + 0.64 \log W$. The correlation coefficient was 0.89.

data to the anticipated log-log formulation is excellent. The values of the exponents (m) are 0.52, 0.59 and 0.64 in the three equations. There are three other literature reports from which quantitative values of blood flow in transplanted tumors can be derived. The paper of Gump and White describes the measurement of blood flow (by $^{85}$Kr, in terms of ml/gm/min.) in the rabbit V-2 carcinoma. Dr. Gump kindly supplied us with the weights of the tumors, so that total flow could be calculated in each case. The results are shown in Figure 4. There is an excellent fit to a log-log plot (with a correlation coefficient of 0.97). However, since the beta emissions of $^{85}$Kr were utilized by Gump and White, the entire tumor mass may not have been "seen" and the true value of the exponent may differ from the value of 1.05 that was found.

The report of Gullino and Grantham describes studies on blood flow in the rat hepatoma 3683. While the blood flow is reported in terms of ml/hr/mg. N, the tumor is described in terms of total weight (and not mg N). To obtain an approximation of total flow in each tumor the ml/hr/mg. N
was multiplied by the total weight to obtain an "NW" (nitrogen-weight) unit. This should be approximately correct except for a scaling factor. Results are shown in Figure 5. Again, there is a good fit to a log-log plot. The exponent in this case is 1.24.

Finally, Edlich and Tookenay described blood flow in implanted Katsumi sarcomas in dogs. From their Figure 3, we can obtain values that are shown here in Figure 6. There was a good fit to a log-log plot, with a value for the exponent of 0.96. It may be of passing interest that the first three tumors we have discussed had a mean value for the exponent of 0.58 while the last three had a mean value of 1.08. The true significance of this difference is not yet apparent. The values of the exponent m, and the correlation coefficient, are shown in Table 1.

DISCUSSION
Equations 1-4 were derived without reference to a "physically real" model of the shape of the tumor. It has been recognized for many years, however, that a number of growth phenomena appear to be related to a surface area. Turning to only the more recent literature, Von Bertalanffy has noted that "... anabolism is proportional to resorption, i.e., a sur-
### Table 1. Value of the Term m in Equation 4, and the Correlation Coefficient of the Equation

| Tumor                         | Value of m | Correlation coefficient |
|-------------------------------|------------|-------------------------|
| Amelanotic melanoma (hamster) | 0.52       | 0.94                    |
| Mammary carcinoma 755 (mouse) | 0.59       | 0.88                    |
| Sarcoma 180 (mouse)           | 0.64       | 0.89                    |
| V-2 carcinoma (rabbit)        | 1.05       | 0.97                    |
| Hepatoma 3683 (rat)           | 1.24       | 0.98                    |
| Katsumi sarcoma (dogs)        | 0.96       | 0.86                    |

**Fig. 5.** Blood flow in rat hepatoma 3683; points were calculated from values in Table 8 of the report of Gullino and Grantham. The original Table did not contain values for flow in terms of ml/min., but employed the expression ml/hr/mg. N. To approximate flow in the whole tumor, this value was multiplied by the tumor weight to obtain a nitrogen-times-weight or “NW unit.” The equation was \( \log F = -1.19 + 1.24 \log W \), with a correlation coefficient of 0.98.
Fig. 6. Blood flow in Katsumi sarcoma in dogs. Values were taken from the report of Edlich and Tookenay. The least squares equation, excluding the two quite low points, was: \( \log F = 1.98 + 0.96 \log \text{(weight)} \). The correlation coefficient was 0.86.

Payne and Wheeler reported that growth of the fetus could be accurately described by assuming that the time rate of change of the volume was related to its surface area. In addition, Dethlefson and co-workers reported on the time rate of change of the weight of various transplanted tumors; in many cases the descriptive equations could be viewed as representing a dependence of the growth rate on the surface area.

Each of the above relationships was between the weight of the system and time. We can introduce blood flow into consideration as follows. In the most elementary case, two assumptions are necessary to arrive at a descriptive equation.

1. The apparent surface area of a transplanted tumor can be approximated as a function of the two-thirds power of the weight.
2. The blood flow to the tumor is linearly related to the surface area.

These assumptions allow us to write:

\[
F = A \cdot W^{2/3} + B
\]  

(5)

This equation is identical to equation (4) when \( m = 2/3 \) and the constant B equals zero. A possible further physical meaning is as follows.
Nutrients arrive at a rapidly growing mass by means of vessels meeting the surface of the tissue. Growth of the tissue can be thought of as being limited by the nutrient supply (which in turn is limited by the availability of vessels at the tissue surface). The number of vessels intersected by the growing mass is proportional to its surface area. Grossly it appears that there is a "surface limited nutrient supply"17 although other phenomena such as diffusion may be involved. Even if a distinct surface is envisioned, there are cases that may cause significant deviation from a value of 2/3 for the exponent in equation (4).

(a) Let us assume that the tumor is approximately spherical, but that the surface is "non-smooth." The surface area \( S \) is therefore greater than the predicted value of \( 4 \pi r^2 \) for a sphere, and we have the inequality:

\[
S > \frac{V^{2/3}}{(6)}
\]

We may approximately say in such instances that:

\[
S = q \cdot V^a
\]

(7)

Here, \( n \) is a number greater than 2/3. Obviously other "explanations" are also possible (independent of the surface area) for exponents greater than 2/3.

(b) In some instances, the equipment utilized might impose a restriction on the apparent value of the exponent. Assume that a small collimated (cylindrical bore) external detector is utilized to monitor a spherical tumor. The collimated assembly views only part of the tumor (a cylinder composed of a surface of \( c \) cm.\(^2\) and a depth of \( 2r \)). Hence the flow seen is approximately

\[
F = P \cdot c \cdot 2r
\]

(8)

where \( P \) is a scaling term. This can be rewritten (since \( V \propto r^3 \)):

\[
F = z \cdot V^{1/3}
\]

(9)

In this case, then, due to the apparatus not viewing the entire tumor, the flow appears to depend on the one-third power of the tumor volume or tumor weight.

Another interesting conclusion can be drawn from the cases in which the flow is proportional to the two-thirds power of tumor weight. In those tumors describable in such terms, the expression \( F/W \) (flow per weight) will be a function of \( W^{-2/3} \) and will therefore fall as the tumor grows (and this is also compatible with observations in the literature). It follows, too, that while blood flow to the tumor is describable in terms of the square of the radius \( (W^{2/3}) \) the tumor mass is described by the cube of the radius. For the simplest conceivable extraction processes, such as those decreasing linearly or exponentially from the peripheral vessels towards the center of the tumor, it is apparent that the innermost parts of the mass will be less well perfused than the periphery (regional inhomogeneities might, however,
occur). Hence the value of $F/W$ will not be uniform, but will generally be less as the distance inward from the tumor surface increases. The end result, after continued growth, is that portions most distal to the outermost vessels have a blood supply insufficient to maintain viability, and necrosis results. The conclusion appears consistent with many reports in the literature. The results could also be interpreted in terms of a rapidly growing (and perfused) thin shell around major vessels and a more slowly growing component further away from the vessels.

SUMMARY

The availability of radioisotopic estimates of blood flow has resulted in several literature studies on the perfusion of transplanted tumors. To permit quantitation of blood flow in terms of the weight of the tumor, a predicting equation was written. The equation was derived by relating the specific change in blood flow rate to the specific tumor growth rate. The resulting prediction was that a log-log plot would describe tumor blood flow in terms of the tumor weight. The description gave a good fit to literature data in six different types of transplanted tumors. A limited case of the more general expression was pointed out. In this instance, the blood flow is linearly related to the surface area, and the surface area can be approximated as a function of the two-thirds power of the tumor weight.

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