Partition of Energy Expenditure between Host and Tumor

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SUMMARY

With a respirometer of suitable sensitivity and resolution, the total daily energy expenditure of an animal can be partitioned into a part attributable to all spontaneous motor activity and a part attributable to rest. The compartment attributable to all spontaneous motor activity is a constant fraction of the total in normal rats. This activity compartment declines in rats bearing a progressively growing Walker tumor and is immediately restored to the normal level on excision of the tumor. Since only the host can expend energy on motor activity, the observed activity compartment of energy expenditure can be used to partition total energy expenditure between host and tumor. In this partition, the metabolism of the host is defined as the energy that can sustain a normal, constant activity compartment. This partition between host and tumor and the partitions given by three other definitions of host metabolism are evaluated from the same experimental data. The estimate of tumor metabolism based on constant motor activity of the host is three to five times greater than the other estimates. Three compartments of energy expenditure of the tumor-bearing organism can be identified and evaluated: (a) the endogenous oxidative metabolism of the tumor; (b) the effective energy expenditure of the host, which is lower than would be expected from the body weight and food intake of the host and which is defined as that part of the host’s metabolism that is capable of generating normal spontaneous motor activity; and (c) a compartment that is imposed on or induced in the host by the tumor but that is unable to support or generate motor activity. The third compartment is quantitatively identical with the energy of the lactic acid produced by the tumor.

INTRODUCTION

It has sometimes been intuitively felt that knowledge of the partition of energy costs between host and tumor in a tumor-bearing organism would clarify the nature of the response of a host to a growing tumor and, particularly, would advance understanding of the anorexia and cachexia that frequently occur during growth of a tumor (19, 20).

Whether this intuition is justified or not, there is, unfortunately, considerable doubt that the primary partition problem can be solved.

For partition of energy expenditure between host and tumor to be possible, it is necessary to find a way of discrimination between the heat developed by the host and that developed by the host or between the respiratory exchange of the tumor and that of the host without physical dissection of the organism. As heat is heat and oxygen is oxygen whatever its source and as at least some of the heat generated by the tumor is eliminated via the host and all of the oxygen used by the tumor is acquired via the host, discrimination would seem to be unfeasible.

The sparsity of experimental studies on energy exchange during tumor growth reflects this difficulty (5, 17, 20, 28). In the only 2 attempts that have been made specifically to solve the partition problem (5, 17), the resting energy expenditure of the whole organism was measured, tumor metabolism was defined by an external value from in vitro respiration of tissue slices, and the host metabolism was defined as the difference between these. These experiments concluded that the resting metabolic rate of the host derived in this way was greater than that of a normal rat of equal body weight; that is the presence of a tumor increases the metabolic rate of the host. The converse procedure of definition of the metabolism of the host as equal to that of a normal animal of the same body weight and then comparison of the difference from the measured total with the external estimate of tumor metabolism could be equally justified and, with the same measured data, would lead to the converse conclusion.

In each case, there is a complementary forcing of the solution. Neither source of energy has been discriminated; an a priori partition has been built into the premises and, naturally enough, appears in the conclusion. Further, this approach is effectively restricted to accessible and measurable tumors and is dependent on an accurate estimate of the metabolizing mass of the tumor. (For the Walker tumor, with a large and variable necrotic core, this estimate is necessarily very imprecise.) However, although it is easy to see the shortcomings of this approach, there has not seemed to be any more satisfactory alternative.

Two recent developments have made it possible to circumvent some of the difficulties and have made it worthwhile to reassess the problem of partition. Gullino et al. (10–12) have developed a preparation in which the respiration of a tumor can be measured in vivo and in situ, thus meeting the objection of use of in vitro data. The other development is the demonstration that, for normal rats, the fraction of the total 24-hr energy expenditure that is attributable to all spontaneous motor activity is very constant and, particularly, is not affected by body size over a wide range or by food intake, food deprivation, or food availability (24). A tumor, on the other hand, does not devote any of its energy metabolism to motor activity. The necessarily zero activity compartment of the tumor and the constant activity compartment of the normal animal could make it possible to
identify and measure the metabolism of the host at the same
time that the energy expenditure of the total organism is being
measured (26). This discrimination does not require
accessibility of the tumor, any knowledge concerning its total
or metabolizing mass, or any external data about the
respiratory metabolism of the tumor. There are 2 distinct sets
of compartments involved here; the partition with respect to
rest and activity, which can be evaluated experimentally, is
used to deduce the partition with respect to host and tumor.

There are, then, various potential ways of getting an
estimate of partition of energy metabolism between host and
tumor, each one representing a different definition of the host
or, to put it another way, a different version of the
"appropriate control." In this paper, 3 different definitions of
the host have been used to derive 4 partitions of metabolism
from the same experimental data. The results do not yield an
unequivocal solution to the problem of partition, but they do
allow a more detailed analysis of it than has hitherto been
possible, and they reveal some novel features of tumor-host
relationships that are of theoretical and practical interest.

MATERIALS AND METHODS

Experimental. Adult male Sprague-Dawley rats of 206 to
256 g initial body weight were used. For each individual rat,
the oxygen consumption and carbon dioxide production were
recorded continuously for 24-hr periods in an open circuit
analytical respirometer (24, 27). This record was made for
successive 24-hr periods for 3 or 4 days prior to s.c. transplant
of 1-mg fragments of Walker 256 carcinoma and then for 4
days a week during tumor growth. Daily food intake, water
intake, evaporated water, urine weight, and fresh and dry fecal
mass were also measured. The response of the respirometer
was rapid enough (time constant, 7 min) to resolve the
continuous record of respiratory exchange into the resting
level and the elevations attributable to spontaneous motor
activity (24). The environmental temperature within the
animal chamber was 27 to 29°, a standard lighting sequence of
20 g (30). The metabolizing mass of the tumor is assumed to
be identical with the viable mass. The viable mass is measured
as the residual tumor after removal of all fluid and, by blunt
dissection, of all friable necrotic tissue. The metabolizing mass
of a tumor at any point during a calorimetric study was
estimated from the total mass of the tumor and a graphic
relationship between viable and total tumor mass, which was
obtained from dissection of tumors (1 to 100 g) from 40 other
rats.

In 5 rats in which the tumor grew progressively, attaining a
final weight of 47 to 118 g, the experimental calorimetric
procedures were followed during the week immediately prior
to transplant of the tumor and then during 4 or 5 weeks after
transplant. Five other rats in which the tumors grew
progressively were studied in the calorimeter during the week
prior to transplant and during the 4th week after transplant.
One rat in which the tumor grew slowly to a maximum size of
about 7 g and then regressed spontaneously to a final weight of
2.5 g was studied during the week prior to transplant and
for 5 weeks after transplant. In 5 of the rats with progressively
growing tumors, the tumor was excised under pentobarbital
sodium anesthesia at the end of the 4th week of tumor
growth. Two rats survived this very massive surgery, and
calorimetric studies on these were continued for a further 5
days.

In addition to the control data from the pretransplant
period of each experimental rat, 1 normal rat was studied in
the calorimeter for 4 days a week for 6 weeks. During the 5th
week of study, its food was restricted for 2 days and then
withheld for 2 days. During the 6th week, this rat was
subjected to a surgical procedure similar in duration and
extent to that necessary for excision of a tumor.

Computation of Tumor-Host Energy Compartment. The
total 24-hr energy expenditure of the whole organism was
computed from the measured O2 consumption and CO2
production, as described previously (24). Partition of this total
expenditure between host and tumor was made by 4 methods,
with the use of the following assumptions and procedures.

1. An estimate of tumor metabolism was derived from the
measured total size of the tumor, an estimate of metabolizing
mass of the tumor based on the observed relationship between
viable mass and total tumor size, an estimate of tumor water
content of 84% (11, 28), and an in vitro estimate of
respiratory rate of Walker tumor slices of 9 j.d of O2/mg of
dry viable tissue/hr (1). Taking a calorimetric equivalent of 5
cal/ml of O2, this represents 0.173 kcal/g of fresh viable
tissue/24 hr. This partition then becomes

\[
E = E_h + E_T = E_h + (0.173 \ W_{VT}) \tag{A}
\]

where \(E\) is total observed energy expenditure in kilocalories/24
hr, \(E_h\) is daily energy expenditure of the host, \(E_T\) is daily
energy expenditure of the tumor, and \(W_{VT}\) is the viable mass
of the tumor in grams. The value for \(E\) is measured, \(E_T\) is
estimated from external data, and \(E_h\) is found by difference.

2. An estimate of tumor metabolism for Walker tumor in
vivo and in situ was derived with the value of 0.8 ml of O2/g of
fresh viable mass/hr (10, 11), other assumptions being the
same as in Paragraph 1. This represents an energy expenditure
by the tumor of 0.095 kcal/g of fresh viable mass/24 hr.
[Gullino et al. (10) computed their results on the basis that
their tumors were substantially free of necrosis. Slaughter data
in the present work indicated that tumors of the size used (5
to 12 g) would have some necrosis, and so the original values
have been modified to assume a viable mass, in the basic in
vivo, in situ estimates, of 80%.] This partition then becomes

\[ E = E_h + E_T = \frac{E_h}{A_c} \] (B)

where the symbols and interpretation are as in Paragraph 1.

3. An estimate of the total metabolism of the host at each point of tumor growth for each animal could be derived from the observed weight, food intake, and energy expenditure of the rat before transplant and from the observed weight of the host (organism less measured tumor weight) and the observed food intake at each point during growth of the tumor in the same rat with the use of the equation

\[ E = [E_c + 0.077 (W_h - W_c) + 0.075 (F_h - F_c)] (1 - A_c) + E_{Ah} \] (C)

where \( E \) is 24-hr energy expenditure in kilocalories, \( W \) is body weight in grams, and \( F \) is apparent ingested absorbed energy in kilocalories (heat of combustion of ingested food less heat of combustion of feces) for pretransplant control (Subscript \( c \)) and for host (Subscript \( h \)).

However, the prediction of the host by Equation C is based on data from normal rats in which the activity compartment of total energy expenditure is constant. A primary result of the experiments to be described is that the activity compartment, which, by definition, arises only from the host, declines during tumor growth. The estimate of host metabolism has, therefore, been modified to be the sum of the predicted resting metabolism and the observed activity component (kilocalories):

\[ E_h = \frac{E_{Ah}}{A_c} \] (D)

The partition then becomes

\[ E = E_h + E_T = \left( E_c + 0.077 (W_h - W_c) + 0.075 (F_h - F_c) \right) (1 - A_c) + E_{Ah} + E_T \]

where \( A_c \) is the measured activity compartment of energy expenditure (fraction of total) during the pretransplant period and \( E_{Ah} \) is the measured activity component (kilocalories) during the appropriate 24-hr period of tumor growth. Other symbols in Equations D and E are the same as for Equations A, B, and C above. In this partition, \( E \) is measured, \( E_h \) is estimated and adjusted from internal metabolic data and measured tumor size, and \( E_T \) is found by difference.

The coefficients in Equations C, D, and E are taken from the general relationship among total daily energy expenditure, body weight, and food intake of normal rats (6, 23, 24) and are evaluated in this experiment from the control (pretransplant) data.

4. An estimate of the total metabolism of the host based on the constancy of the activity compartment of energy expenditure in normal rats was made for each animal during each 24-hr period of tumor growth with the use of the activity compartment \( A_c \) in the pretransplant control period and the observed energy expended on activity (\( E_{Ah} \)) by the same animal during 24-hr periods of tumor growth:

\[ E_h = E_{Ah} / A_c \] (F)

The partition then becomes

\[ E = E_h + E_T = \frac{E_{Ah}}{A_c} + E_T \] (G)

In this partition, \( E \) is measured, \( E_h \) is estimated from internal metabolic data only, and \( E_T \) is found by difference.

RESULTS

Total Energy Expenditure. On the average, the weight of the total organism increased during tumor growth, but that of the host increased initially and then declined (Chart la). In 3 animals, the weight of the total organism declined in the terminal stages of tumor growth.

Total 24-hr energy expenditure per rat increased along with...
the increase in weight of the total organism (Chart 1b). In the terminal stage of tumor growth, when the weight of the host was falling and the animal was becoming moribund, there was a precipitous decline in total energy expenditure (Chart 1b). This decline occurred when the tumor was large, but its occurrence was not closely associated with tumor weight.

**Rest and Activity Components of Total Energy Expenditure.** The rest component of total energy expenditure followed a course parallel to that of total expenditure (Chart 1c). The component attributable to all spontaneous activity declined with growth of the tumor (Chart 1d). This decline occurred in every rat with a progressively growing tumor (Table 1) and was qualitatively apparent from inspection of the records of $O_2$ consumption (Chart 2). The activity compartment (activity component as a percentage of total expenditure) declined even more rapidly, and significant depression of this compartment below the normal (pretransplant) level could be detected when the tumor weight was about 5% of the weight of the total organism (Charts le and 3a). The time after transplant at which the depression of activity became detectable was quite variable because of the different rates of growth of different tumors.

The activity compartment did not move outside its normal limits of variation with a normal rat studied for 5 weeks on ad libitum feeding, a restricted diet, or starvation (Chart 3c). With the rat in which the transplanted tumor grew slowly to a maximum size of 7 g and then regressed spontaneously, there was a slight depression of the activity compartment during the regression phase (Chart 3b).

**Partition of Energy Expenditure between Host and Tumor.** The partition of the average total 24-hr energy expenditure, derived by methods described in Paragraphs 1 through 4 ("Materials and Methods"), is shown in Chart 4 for the 5 rats with progressively growing tumors studied continuously.

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**Chart 2.** Total oxygen consumption and consumption attributable to spontaneous motor activity before tumor transplant and during the 4th week of growth of Walker tumor. All elevations above the resting base (- - -) are attributable to motor activity, and the diminution in these elevations is a measure of the diminution of motor activity. $BW$, body weight; $FI$, 24-hr food intake; $A\%$, activity compartment.

**Chart 3.** Activity compartment of total daily energy expenditure in individual rats (a) during progressive growth of Walker tumor (Rat 959), (b) during growth of Walker tumor to a weight of about 7 g followed by spontaneous regression to a weight of 2.5 g (Rat 947); and (c) in normal intact rat (Rat 029). Each point is mean of four 24-hr periods. The final point in a shows the activity compartment immediately following excision of the tumor. The 5th point in c is for a period when food was restricted for 2 days and withheld for 2 days; the final point in (c) is for activity compartment after surgery comparable to that necessary for excision of a tumor. Other than the 5th period in c, food was allowed ad libitum at all times. Hatched zones, 95% limits of 4-day means expected from the variation found in the initial 4-day period.
Responses of activity compartment of total energy expenditure to growth of Walker tumor in individual rats

Each value is mean and range of 3 days immediately before tumor transplant or of the final 3 days of tumor growth except where period of shorter duration is indicated by subscript. Rats 539 to 959, 947, and 029 were studied 4 days a week for 5 or 6 weeks in the calorimeter. Rats 967 to 986 were studied for 4 days immediately prior to tumor transplant and during the 4th week of tumor growth.

<table>
<thead>
<tr>
<th>Rat (g)</th>
<th>Mean carcass weight (g)</th>
<th>24-hr energy expenditure (kcal)</th>
<th>Mean activity compartment (%)</th>
<th>Final tumor weight (g)</th>
<th>Final viable tumor weight (g)</th>
<th>Final adrenal weight (mg)</th>
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<tr>
<td>539</td>
<td>2092</td>
<td>45.9</td>
<td>(44.8—47.1)</td>
<td>2493</td>
<td>45.1</td>
<td>17.7</td>
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<tr>
<td>584</td>
<td>239</td>
<td>45.0</td>
<td>25.8</td>
<td>329</td>
<td>46.4</td>
<td>17.9</td>
</tr>
<tr>
<td>594</td>
<td>227</td>
<td>43.0</td>
<td>27.5</td>
<td>229</td>
<td>37.0</td>
<td>15.2</td>
</tr>
<tr>
<td>624</td>
<td>208</td>
<td>45.4</td>
<td>24.8</td>
<td>289</td>
<td>50.8</td>
<td>19.6</td>
</tr>
<tr>
<td>959c</td>
<td>256</td>
<td>49.4</td>
<td>(48.5—50.5)</td>
<td>300</td>
<td>52.5</td>
<td>17.1</td>
</tr>
<tr>
<td>967f</td>
<td>206</td>
<td>42.1</td>
<td>24.1</td>
<td>277</td>
<td>48.0</td>
<td>16.7</td>
</tr>
<tr>
<td>970f</td>
<td>219</td>
<td>43.9</td>
<td>(41.7—42.4)</td>
<td>299</td>
<td>50.5</td>
<td>16.1</td>
</tr>
<tr>
<td>973f</td>
<td>235</td>
<td>41.3</td>
<td>(39.8—42.6)</td>
<td>2292</td>
<td>37.1</td>
<td>16.1</td>
</tr>
<tr>
<td>982c</td>
<td>209</td>
<td>42.7</td>
<td>(42.2—42.9)</td>
<td>286</td>
<td>57.4</td>
<td>19.0</td>
</tr>
<tr>
<td>986</td>
<td>217</td>
<td>43.1</td>
<td>(41.6—45.2)</td>
<td>2372</td>
<td>30.3</td>
<td>14.1</td>
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<tr>
<td>947</td>
<td>208</td>
<td>43.7</td>
<td>(42.5—44.8)</td>
<td>345</td>
<td>47.7</td>
<td>23.1</td>
</tr>
<tr>
<td>029</td>
<td>218</td>
<td>44.2</td>
<td>(43.2—45.1)</td>
<td>367</td>
<td>46.4</td>
<td>24.9</td>
</tr>
</tbody>
</table>

The estimate of tumor respiration from in vitro respiration of tissue slices (“Materials and Methods,” Paragraph 1) is about twice that from in vivo, in situ respiration of the whole tumor (“Materials and Methods,” Paragraph 2) (differences between total observed energy expenditure and estimates of host in Chart 4).

The partition derived by defining the metabolism of the host as the expected resting metabolism of a normal animal of equal body weight and food intake added to the observed energy expended on activity (“Materials and Methods,” Paragraph 3) does not differ significantly from the observed total metabolism of the whole organism up to a tumor weight of about 15 g (Charts 4 and 5a) and moves towards the partitions derived from tumor respiration with further increase in tumor weight (Chart 4). For the rat with a regressing tumor, total observed metabolism is lower than this estimate of host metabolism (Chart 5b), while for the nontumor-bearing rat this estimate and the observed metabolism are in close agreement (Chart 5c).

The partition derived by defining the metabolism of the host as that which would make the observed activity component equal to the normal fractional activity compartment (“Materials and Methods,” Paragraph 4) is clearly different from any of the other partitions (Charts 4 and 5a). This partition leads to an estimate of total host metabolism that is significantly lower than any of the other estimates (p < 0.01 for tumor weight of 5 to 40 g; p < 0.001 for tumor weight of >40 g) and falls progressively with tumor...
growth. For the rat with a regressing tumor, this estimate of host metabolism is also slightly depressed (Chart 5b).

The estimate of host metabolism derived from the activity compartment ("Materials and Methods," Paragraph 4) is dependent on the particular definition of the host adopted (as are the other partitions), but it is totally independent of any external measurements or assumptions, particularly those concerning the total or metabolizing size of the tumor. The estimates of total tumor metabolism derived from this partition vary linearly with the estimates of metabolizing tumor size used to calculate the partitions based on tumor respiration (Chart 6), so giving some corroboration to these estimates of metabolizing tumor size.

**Lactate Compartment of Tumor Metabolism.** Lactic acid production by the Walker tumor in vivo and in situ was also measured by Gullino et al. (11). By use of these results and the same assumptions and estimates of tumor size adopted for the calculation of O₂ consumption ("Materials and Methods," Paragraph 2), the lactic acid production of the tumors studied here was estimated and expressed as 0.37 kcal of lactic acid delivered to the host/g of fresh viable tumor/24 hr. These values closely approximated the difference between the partition for in vivo, in situ tumor respiration and the partition derived from the activity compartment. This means that the total tumor metabolism estimated for the in vivo, in situ preparation (oxidative metabolism plus lactic acid production) is equal to the total tumor compartment estimated from the activity partition when each is expressed as kilocalories (Chart 7). A numerical example of the calculation of this relationship is shown in Table 2.

**Tumor Excisions.** The activity compartment of the
The resting metabolism of the host is obtained by removal of the observed activity component from the estimate of total metabolism of the host. The estimate for resting metabolism derived from the activity compartment ("Materials and Methods," Paragraph 4) was significantly lower than any other estimate for tumors weighing more than about 10 g. The estimates derived from tumor respiration data did not differ significantly from the resting metabolism of the host predicted from the normal relationship with body weight and food intake.

However, during tumor growth, sudden large increases in resting metabolism of the whole organism were occasionally seen (Chart 9) of a form never seen in metabolic records from normal rats. These increases were transient, sustained for, at most, 2 days. They gave rise to isolated, very high 24-hr values for resting metabolic rate but were so infrequent that they did not affect the average values significantly.

**DISCUSSION**

The diminution of the activity compartment of energy expenditure during tumor growth was stated as a qualitative impression by Pratt and Putney (28) and would be expected to occur from the constancy of the activity compartment normally (24) and the necessarily zero activity compartment of the growing tumor. The activity compartment is, indeed, depressed, but the depression is not due simply to dilution of the metabolism of a motorially active mass (the host) by the metabolism of a growing inactive mass (the tumor). This dilution effect makes up only about one-sixth of the observed depression of the activity compartment (Chart 10). The remainder represents an active effect of the tumor on the host.

Both of the earlier studies on partition of tumor-host metabolism (5, 17) concluded that the resting metabolism of the host rose during tumor growth, and this has also been a frequent inference from clinical studies (7). Bramante et al. (5) used the Walker tumor and found an increase in resting metabolic rate of the host of 2%/day. From the partitions based on comparable assumptions, this study shows no evidence of a consistent change of this sort, although large but transient increases in total resting metabolic rate were seen.
Energy Costs of Host and Tumor

Chart 8. Change in observed energy expenditure (●) and in active host (○; “Materials and Methods,” Paragraph 4) on excision of tumor from Rat 959 and (b) on equivalent control surgery on normal Rat 029.

Chart 9. Changes in resting oxygen consumption occurring in a 12-hr period during tumor growth; Rat 539, 22 days posttransplant.

Chart 10. Change in activity compartment during tumor growth expected from dilution of a motorially active host with an inactive tumor, compared with the actual change in activity compartment. Based on data used in Chart 1.

irregularly. Possible sources of the discrepancy are use of different strains of rat, use of different type (17) or line of tumor, errors in estimate of metabolizing mass (the usual variability of necrotic mass in the Walker tumor could lead to differences by a factor of 2 in estimate of tumor metabolism by this method; compare measured total and viable tumor weights in Table 1), and errors in partitioning the activity and rest components. The application of an activity scale quantitatively determined for normal rats (4) to the markedly altered pattern of activity during tumor growth (5) could lead to an overestimate of resting rate. In this work, the activity compartment during the night might be systematically overestimated. An increased resting compartment of normal rats during the night has been reported (14) but has not been found here and probably could not be detected with the response times used here. (Such a systematic error in this work would not affect the derived tumor-host partition, as the pretransplant activity would be correspondingly overestimated.

The difference between the host-tumor partitions derived from the in vitro and from the in vivo, in situ data on tumor respiration arises entirely from the different values used for respiration per g of viable tissue, since all other assumptions and estimates in these computations were identical. It is doubtful if any biological significance can be read into this difference (10). Because the in vivo, in situ preparation (“Materials and Methods,” Paragraph 2) is physiologically more satisfactory, it will be taken to represent the partition based on tumor respiration.

The difference between the partition derived from the activity compartment (“Materials and Methods,” Paragraph 4) and all the others is highly significant statistically for any tumor weighing in excess of 10 g and is so large, from 10 to 30% of the energy metabolism of the whole organism, that it almost certainly has some biological significance. This view is reinforced by the close correlation between the value for tumor metabolism yielded by this partition, which is determined quite independently of any estimate of total or functional tumor size, and the estimate of metabolizing tumor size derived from direct measurement.

Since there is no evidence of enhancement of tumor metabolism when the tumor is in situ (11), the various partitions present a picture of 3 compartments of energy expenditure of the tumor-bearing organism rather than 2. First, there is the oxidative metabolism of the tumor, for which similar estimates are yielded from data on tumor respiration and from metabolism of the host based on body size and food intake. Second, there is the effective energy expenditure of the host, which is that host metabolism that is capable of sustaining a normal activity compartment. Third, there is a metabolic load imposed on the host by the tumor, which must be metabolized and dissipated by the host but cannot be utilized by it, at least not for generation of motor activity. The close quantitative identity between this 3rd compartment and the estimate of lactic acid produced by the tumor suggests that the load imposed on the host by the tumor is lactic acid.

The lactic acid produced by tumors does not lead to a systemic acidosis and is not excreted (19). The present results suggest that it is not utilized, either. The distinction must be drawn here between metabolism with release of energy, which obviously occurs, and utilization of the energy for performance of work, which does not seem to occur. In this respect, the effect is reminiscent of specific dynamic action.

For lactic acid to be unutilized, its metabolism need not fail to generate the appropriate amount of ATP (15 ATP/mole). Lactic acid would be effectively unutilized if it quantitatively suppressed free energy yield from other sources or if the free energy cost of metabolizing it were as great as the free energy yield from its metabolism. There are gross abnormalities of
l lipid mobilization and clearance during tumor growth (13), and lactate does inhibit the “utilization” of fatty acids (16) and possibly of other substances in normal animals; but this is in the sense of inhibition of turnover and oxidation. Lactate does have an added cost of utilization, the cost of gluconeogenesis in liver and kidney. The rate of gluconeogenesis can be shown by other methods to increase in men and in animals with cancer (15, 29), presumably from the metabolism of the lactic acid imposed on the host by the tumor.

It has recently been emphasized that the net energetic cost to the host of gluconeogenesis from lactic acid produced by a tumor is higher than the net energetic cost of gluconeogenesis from lactic acid produced in a normal animal or in the host itself (8). This is because of the unique situation in the tumor bearer, in which the energy of glycolysis is released exclusively in 1 compartment, the tumor, while the total cost of gluconeogenesis and the dissipation of metabolic end products, including heat, are borne by a separate compartment, the host. Even so, the cost of this process to the host, 6 ATP/mole of glucose reformed (as opposed to a net cost of 4 ATP for formation of glucose from lactic acid formed by the host itself) by the pathway generally regarded as predominant in normal animals, is only 20% of the total available free energy of the lactic acid produced by the tumor (18). Thus, only 20% of the apparent energy wastage can be accounted for by the conventional cost of gluconeogenesis.

Some attempts to calculate the energy costs of metabolic processes in normal animals from known and feasible biochemical pathways have yielded close agreement between theoretical and experimentally determined values, while others (on lactate utilization and fat synthesis) have yielded theoretically values of only one-third to one-fifth of experimentally determined values (2, 3). The pathway of gluconeogenesis commonly proposed in the normal mammal is one that minimizes the cost of gluconeogenesis. Other routes are possible at greater cost, as much as 1 mole of glucose/mole of glucose reformed (18), which, of course, would represent effective total nonutilization.

The depression of the activity compartment is experimentally demonstrable, while the concept of compartments of energy expenditure of the host, which is a central feature of the foregoing interpretation, is derived from the proposition that the constancy of the activity compartment in normal animals continues to hold, in some real way, for the host. There are many possible explanations of the data that do not invoke this concept and that effectively propose that some feature of the tumor specifically depresses the motor activity of the host. For example, the great increase in mass and activity of the adrenal cortex during growth of the Walker tumor (21, 25, 33) suggests that depression of the activity compartment might be an indirect response of the host to endocrine changes induced by the tumor. Hypercorticoidism by itself is unlikely to depress muscular activity, but the nitrogen that is translocated from the host to the tumor is largely derived from skeletal muscle under the influence of adrenal corticoids (9, 32), and this depletion might reduce the effective muscle mass sufficiently to depress muscle function. However, the immediate return to normal of the activity compartment on excision of the tumor requires that any explanation be based on a highly labile and rapidly reversible process. It is unlikely that an induced hormonal imbalance or a depletion of muscle mass could be restored quickly enough to meet this criterion.

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