17. R. Llopis and G. R. A. Starck, *J. Virol.* **38**, 91 (1981).
18. N. Bouck, N. Beales, T. Shenk, P. Berg, G. diMayorca, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 2473 (1978).
19. D. Nathans, *Harvey Lect.* **70**, 111 (1976).
20. ———, *Le Prix Nobel-1978* (Almqvist & Wiksell International, Stockholm, 1979), p. 198.
21. T. J. Kelly, Jr., and D. Nathans, *Adv. Virus Res.* **21**, 85 (1977).
22. M. Fried and B. E. Griffin, *Adv. Cancer Res.* **24**, 67 (1977).
23. J. Tooze, Ed., *DNA Tumor Viruses* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1980), chaps. 2 to 5.
24. A. D. Hershey, E. Burgi, L. Ingraham, *Proc. Natl. Acad. Sci. U.S.A.* **49**, 748 (1963).
25. R. Wu and A. D. Kaiser, *J. Mol. Biol.* **35**, 523 (1968).
26. D. A. Jackson, R. H. Symons, P. Berg, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 2904 (1972).
27. P. E. Lobban and A. D. Kaiser, *J. Mol. Biol.* **78**, 453 (1973).
28. D. E. Berg, D. A. Jackson, J. E. Mertz, *J. Virol.* **14**, 1063 (1974).
29. *Science* **196**, 159–221 (1977).
30. *Science* **209**, 1319–1438 (1980), entire issue.
31. J. E. Mertz and P. Berg, *Virology* **62**, 112 (1974).
32. S. P. Goff and P. Berg, *Cell* **9**, 695 (1976).
33. ———, *J. Mol. Biol.* **133**, 359 (1979).
34. R. C. Mulligan, B. H. Howard, P. Berg, *Nature (London)* **277**, 108 (1979).
35. R. C. Mulligan and P. Berg, *Science* **209**, 1422 (1980).
36. S. Subramani, R. C. Mulligan, P. Berg, *Mol. Cell. Biol.*, in press.
37. P. J. Southern and P. Berg, in preparation.
38. D. H. Hamer and P. Leder, *Nature (London)* **281**, 35 (1979).
39. D. H. Hamer, M. Kaehler, P. Leder, *Cell* **21**, 697 (1980).
40. A. Buchman and P. Berg, unpublished results.
41. P. J. Southern, B. H. Howard, P. Berg, in preparation.
42. R. T. White, L. P. Villarreal, P. Berg, in preparation.
43. B. H. Howard, P. J. Southern, R. C. Mulligan, P. Berg, in preparation.
44. R. C. Mulligan, P. J. Southern, B. H. Howard, M. Yaniv, A. I. Geller, P. Berg, in preparation.
45. R. L. Miller, G. A. Ramsey, T. A. Krenitsky, G. B. Elion, *Biochemistry* **11**, 4723 (1979).
46. T. A. Krenitsky, R. Papaioannou, G. B. Elion, *J. Biol. Chem.* **244**, 1263 (1969).
47. E. H. Szybalski and W. Szybalski, *Proc. Natl. Acad. Sci. U.S.A.* **48**, 2026 (1962).
48. R. C. Mulligan and P. Berg, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 2072 (1981).
49. T. J. Franklin and J. M. Cook, *Biochem. J.* **113**, 515 (1969).
50. P. Medawar, *The Hope of Progress* (Methuen, London, 1972).

Warburg Effect Revisited: Merger of Biochemistry and Molecular Biology

Efraim Racker and Mark Spector

There are no rules of architecture for a castle in the clouds.

—G. K. CHESTERTON

In his last lecture on the "Prime cause and prevention of cancer" on 30 June 1966 at Lindau, Germany (*1*), Otto Warburg stated: "Oxygen gas, the donor of energy in plants and animals, is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose." He ended his lecture emotionally: "But nobody today can say that one does not know what cancer and its prime cause is. On the contrary, there is no disease whose prime cause is better known, so that today ignorance is no longer an excuse that one cannot do more about prevention. That the prevention of cancer will come there is no doubt, for man wishes to survive. But how long prevention will be avoided depends on how long the prophets of agnosticism will succeed in inhibiting the application of scientific knowledge in the cancer field. In the meantime, millions of men must die of cancer unnecessarily."

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Thus, for over 50 years Warburg maintained that the primary cause of cancer is a defect in respiration (*2*), and in the same lecture (*1*) he proposed treatment of cancer patients (particularly following surgery) with "active groups of respiratory enzymes": iron salts, riboflavin, nicotinamide, and pantothenic acid (no mention was made of ascorbic acid).

Warburg's formulation of the primary cause of cancer was not accepted by most biochemists and oncologists mainly because the experimental evidence for a defective respiratory chain was lacking. Many tumor cells respire actively (*3*) and their efficiency of adenosine triphosphate (ATP) generation does not seem to be impaired (*4*). Moreover, Warburg's rejection of the importance of viruses as causative agents of tumors (*1*) did not endear him to molecular biologists, who ignored him.

In the confusion of the polemic battles that followed Warburg's belligerent pronouncements, sight was lost of the fact that he had made an important biochemical discovery which I have called the Warburg effect (*5*): Malignant tumors exhibit a high rate of aerobic glycolysis (*6*). Only few investigators studied this phenomenon and for 50 years no answer was forthcoming to the basic question: Why do tumor cells glycolyze?

Adenosinetriphosphatase Is Required for Glycolysis

Although it is common knowledge that glycolysis requires inorganic phosphate (P_i) and adenosine diphosphate (ADP), textbooks of biochemistry do not acknowledge the fact that the hydrolysis of ATP is an essential step in the phosphate cycle of glycolysis and they do not address the question of what mechanisms of ATP hydrolysis contribute to steady-state glycolysis. Yet it is clear from analyses of the rate-limiting steps of glucose utilization in yeast, Ehrlich ascites tumors, HeLa cells, and many other cells [see (*7*) and (*8*) for historical reviews] that ATP hydrolysis is not only required for glycolysis but is rate-limiting. However, an epidemic of allosteria has swept through the biochemical community to the extent that the control of phosphofructokinase by ATP (*9*, *10*) receives prime billing [see, for example (*11*)] while the need to hydrolyze ATP to release the inhibition is ignored. With or without allosteric control stoichiometry sets the price: For each molecule of lactic acid formed one molecule of ATP has to be hydrolyzed.

In 1965 we (*7*, *12*) pointed out that the allosteric regulation of phosphofructokinase and hexokinase were part of a remarkable cascade of glycolytic control mechanisms that were governed by the bioenergetic budget of the cell, especially its ATP-consuming reactions.

How much do we know about the bioenergetic budget of mammalian cells? Although the concept of chemical thermogenesis was formulated around the turn of this century (*13*), our knowledge of the quantitative bioenergic expenditures involving heat production has remained rather scant. We find broad statements in textbooks that between 30 and 70 percent of our resting energy expenditures are devoted to maintaining

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cellular disequilibrium of sodium and potassium ions in various organs of the body. However, individual estimates vary (*14*) and some are considerably lower, for example, about 6 percent for adipose tissue (*15*) and about 25 percent for diaphragm (*16*). We mention these reports in spite of the fact that some of the experimental procedures have been criticized (*14*). It seems likely that there are variations in the energy expenditures of different organs because we find considerable variations in individual cell types grown in tissue cultures (*17, 18*). We shall return to the problem of chemical thermogenesis.

Summary. Over 50 years ago Warburg discovered that malignant cancers ferment glucose to lactic acid much more rapidly than most normal cells. In analyzing this phenomenon in a variety of tumors we found one common denominator: a high rate of adenosine triphosphate hydrolysis that delivers the adenosine diphosphate (ADP) and inorganic phosphate (P_i) required for glycolysis. However, the source of adenosinetriphosphatase (ATPase) activity varies; in some cells it is the sodium- and potassium-dependent ATPase, in others the mitochondrial ATPase, and in some perhaps a viral ATPase. In Ehrlich ascites tumor cells the sodium and potassium pump of the plasma membrane operates inefficiently. For each sodium ion pumped out of the cell, several ATP molecules are hydrolyzed. Thus, ADP and P_i, which are rate-limiting for glycolysis, are generated and permit the rapid formation of lactic acid. The Na^+, K^+ pump consists of two subunits. The α subunit contains the active center of the ATPase enzyme and the β subunit is a glycoprotein with unknown function. The pump is rendered inefficient by phosphorylation of the β subunit catalyzed by a protein kinase, PK_M, which is present in the plasma membrane of the tumor. This protein kinase is activated in turn by a cascade of the three other kinases PK_S, PK_L, and PK_F. The PK_F is immunologically related to the *src* gene product of Rous sarcoma virus. Each of the members of the protein kinase cascade phosphorylate other protein substrates, including components of the cytoskeleton. This may help to explain the remarkable pleiotropic manifestations of a transformation event controlled by a single gene.

Which Adenosinetriphosphatases Participate in Glycolysis?

In 1973 we (*19*) reported that in Ehrlich ascites tumor cells glycolysis is driven to a large extent by the Na^+,K^+-dependent adenosinetriphosphatase (Na^+,K^+-ATPase) of the plasma membrane. Table 1 shows that ouabain, a specific inhibitor of the Na^+,K^+-ATPase, diminished lactate production from glucose by about 65 percent. Rutamycin, an inhibitor of oxidative phosphorylation, stimulated lactate production slightly by eliminating mitochondrial competition for ADP. In the presence of dinitrophenol, which activates mitochondrial ATPase, there was a threefold increase in lactate production, demonstrating once again that ATP hydrolysis is rate-limiting for glycolysis. Rutamycin, by inhibiting mitochondrial ATPase, returned lactate production to the rate observed in the absence of dinitrophenol.

Cells from some other tumors responded in the same way as those from Ehrlich ascites tumors, but cells from many other tumors did not (*18*). What other ATP hydrolysis reactions contributed to glycolysis? As shown in Table 2, mitochondrial ATPase was a major source of energy in some cell lines but variability in sensitivity to energy transfer inhibitors was noted in our own as well as in other laboratories (*20*). In some cells rutamycin stimulated glycolysis very considerably, indicating a large contribution of oxidative phosphorylation to the consumption of ADP in competition with glycolysis. In neuroblastoma cells glycolysis was inhibited partly by ouabain and partly by rutamycin. But in several cell lines neither rutamycin nor ouabain inhibited glycolysis. A possible candidate for such an inhibitor-resistant ATPase is the enzyme associated with some tumor viruses (*21, 22*).

Table 1. Effect of ouabain, rutamycin, and 2,4-dinitrophenol on the aerobic glycolysis of Ehrlich ascites tumor cells.

Addition to tumor cells	Lactate formation (μmole/30 min-mg protein)	
	Without dinitrophenol	With dinitrophenol
Buffer	0.36	1.24
Rutamycin	0.43	0.41
Ouabain	0.12	1.03

Although the origin of this viral ATPase is probably an enzyme of the host cell (*23–25*), there is no other ATPase known that resembles the viral ATPase (*26*). Current experiments suggest that in a cell line transformed by Harvey virus ouabain-insensitive ion fluxes were responsible for a high rate of glycolysis (*27*).

A Defective Na^+,K^+ Pump in Tumor Cells

Do tumor cells with ouabain-sensitive glycolysis have an excess of Na^+,K^+ pumps or is the pump operating inefficiently, thereby generating excessive ADP and P_i?

A simple calculation convinced us that the pump operates inefficiently. The calculations shown in Table 3, which are no more than approximations, indicate that the ouabain-sensitive fraction of glycolysis is not accompanied by the expected movement of rubidium-86 (assuming that the efficiency ratio of ^{86}Rb transported to ATP hydrolyzed is 2). The ATP hydrolysis in the intact cell was calculated from the formation of lactate. Such indirect measurements did not convince the biochemical community.

We then observed that some bioflavonoids, such as quercetin, appeared to regulate the mitochondrial ATPase (*28*) in a manner somewhat similar to the action of the natural regulatory subunit, the mitochondrial ATPase inhibitor described by Pullman and Monroy (*29*). Quercetin blocked excessive hydrolysis of ATP without impairing oxidative phosphorylation. We found a similar effect on the Na^+,K^+-ATPase: at low concentrations quercetin raised the ratio of ^{86}Rb transported to lactate produced from values well below 1 to over 2, suggesting the repair of a defective pump (*18*). To these indirect experiments objections were again raised (*30*), objections that were somewhat justified in view of the multiple effects of bioflavonoids.

The direct measurement of pump efficiency required isolation of the Na^+,K^+-ATPase from plasma membranes of Ehrlich ascites tumor cells (*31*). The enzyme was reconstituted into liposomes and observed to pump inefficiently (Table 4). A control ATPase isolated from the brains of the animals from which we obtained the tumor cells pumped efficiently. Quercetin at appropriate concentrations raised the efficiency of the tumor pump fourfold and had no effect on the brain pump. We think that we have established that the tumor pump is inefficient.

The Lesion in the Inefficient Na^+,K^+ Pump

The next task was to determine the lesion that is responsible for the inefficiency. We found that the β subunit (molecular weight 53,000) of the tumor Na^+,K^+-ATPase was phosphorylated. Removal of the phosphate group with alkaline phosphatase restored the ability of the enzyme to pump efficiently after reconstitution into liposomes (*32*). The plasma membrane of the tumor contained a protein kinase which, in the presence of ATP and magnesium ions, phosphorylated the β subunit of the Na^+,K^+-ATPase. Now we could approach the question of whether there are basic differences between the tumor enzyme and the brain enzyme or whether the key difference is phosphorylation of the β subunit. The answer was unambiguous. The brain enzyme was phosphorylated by the tumor protein kinase (PK_M), and was thereby rendered inefficient after it was reconstituted into liposomes (*32*). But why was the native brain enzyme not phosphorylated? By radioimmunoassay the PK_M was also found in the brain, yet it did not give rise to a phosphorylated β subunit. It seemed to be controlled. The problem was clearly not a simple one and I shall return to it later.

A Protein Kinase Cascade

The PK_M was purified from Ehrlich ascites tumor membranes (*33*) and, like some other protein kinases, the enzyme was active only when phosphorylated. This led to the isolation of the next protein kinase, PK_S, which was also active only when phosphorylated. With PK_S as substrate a third protein kinase, PK_L, was isolated from the plasma membrane. PK_L was activated on phosphorylation by a fourth enzyme, PK_F, which was isolated from cytoskeleton preparations of the Ehrlich ascites tumor cells.

The apparent molecular weights and subunit composition of these four protein kinases are listed in Table 5. Of particular interest was the observation that PK_F, which in polyacrylamide gel electrophoresis had a mobility corresponding to a mass of 60,000 daltons, resembled the so-called *src* gene product of cells transformed by Rous sarcoma virus. This transforming gene product was shown to be a protein kinase (*34, 35*). A rabbit antiserum against PK_F and a serum against rabbit-sarcoma virus precipitated the same 60,000-dalton protein (PK_F) from Ehrlich ascites tumor as well as from cell lysates of several Rous sarcoma transformed cell lines (*36*). PK_F was phosphorylated by PK_S, thus establishing a positive feedback mechanism:

$$PK_F \rightarrow PK_L \rightarrow PK_S \rightarrow PK_M \rightarrow \beta \text{ subunit of } Na^+,K^+\text{-ATPase}$$

The phosphorylations by the purified kinases all took place on tyrosine residues of the protein substrates, as is the case for the phosphorylation catalyzed by $pp60^{src}$ (*37*). However, Ehrlich ascites cells in vivo contained multiple forms of PK_S, PK_L, and PK_F, some unphosphorylated, some phosphorylated on tyrosine or on serine or on both. The only enzymatically active species in all instances were the monotyrosine phosphorylated enzymes, whereas the serine or serine plus tyrosine phosphorylated species were inactive as established by phosphorylations in vitro with the catalytic subunit of adenosine 3′,5′-monophosphate (cyclic AMP)-dependent protein kinase (*33, 38*).

The presence of PK_M in brain raised the question of how its activity is controlled. In fact, according to radioimmunoassays all four kinases of the cascade are present in brain, yet the Na^+,K^+-ATPase does not become phosphorylated. It appears that the cascade is kept under control by a 6000-dalton polypeptide (*33*) that inhibits PK_S activity. Why should nature invent a protein cascade that impairs the efficiency of a pump and then keep it under control? An obvious answer is that the cascade has another

Table 2. Effect of inhibitors of glycolysis in various cell lines. The experimental conditions were as described (*18*). The values are expressed as micromoles of lactate formed in 30 minutes per milligram of protein.

Addition to medium	L-1210	P-388	Neuroblastoma	Polyoma-transformed		RSV transformed CEF
				3T3	BHK	
None	0.40	0.40	0.98	0.86	0.7	1.0
Ouabain (1 m*M*)	0.24	0.11	0.57	0.76	0.7	0.74
Rutamycin (8 μg/ml)	0.48	0.57	0.60	0.27	1.7	1.57
Dinitrophenol (0.1 m*M*)	0.68	1.65	1.63	1.40	2.0	3.06

Table 3. Efficiency of the Na^+, K^+ pump in Ehrlich ascites tumor cells.

Addition to cells and calculated quantity	Lactate formation (μmole/30 min-mg protein)	$^{86}Rb^+$ uptake (μatom/30 min-mg protein)
Salt medium and glucose	0.36	0.27
Salt medium, glucose, and ouabain (1 m*M*)	0.12	0.08
Calculations		
Ouabain-sensitive fraction	0.24	0.19
Expected Rb^+ uptake (if Rb^+/ATP ratio = 2)		0.48
Efficiency of Rb^+ pumping		39 percent

Table 4. Effect of quercetin on Na^+/ATP ratio in vesicles reconstituted with Na^+,K^+-ATPase from tumor and normal cells. The experimental procedures were as described (*31*).

Source of Na^+,K^+-ATPase	Quercetin (μg/mg lipid plus protein)	Oxidation (nmole/min-mg protein)		^{22}Na/ATP ratio
		^{22}Na uptake*	ATPase	
Ascites tumor	0	510	1509	0.34
	16	497	495	1.0
	24	305	229	1.33
Mouse brain	0	492	295	1.67
	16	436	248	1.76
	24	296	179	1.65
Electric eel	0	380	210	1.81
	24	275	156	1.76

*ATP dependent.

purpose and the phosphorylation of the β subunit is a biological by-product. Although there are indeed multiple substrates for some of the other cascade enzymes, we have not seen as yet any substrate for PK_M besides the β subunit of Na^+,K^+-ATPase.

There is considerable evidence that the Na^+,K^+-ATPase is involved in thermogenesis (*15, 39*). In the case of thyroid thermogenesis there is evidence (*15*) for an actual increase in the number of Na^+ pump sites (as indicated, for example, by ouabain binding). However, such findings do not preclude the possibility of regulation by way of altering also the efficiency of the pump. Since there is ample evidence for hormonal control of thermogenesis (*39*) and since humoral factors in fever are well known, we propose that the polypeptide that inhibits PK_S activity could be the key target for such control mechanisms. If we could find a compound that temporarily displaces the PK_S inhibitor, we would have in our hands an ideal prescription for the lazy man's way of jogging. It would be much safer to increase ATP utilization in this manner than to tamper with ATP generation by administering uncouplers of oxidative phosphorylation, a deadly means of losing weight (*40*). Indeed, Ehrlich ascites tumor cell membranes contain a 6000-dalton polypeptide which activates the phosphorylation of PK_S.

Other Substrates for the Cascade Kinase

On transformation of cells by Rous sarcoma virus several phosphorylated proteins can be detected in autoradiograms of electrophoresed cell lysates. Among them is a 36,000-dalton protein (*41*) and vinculin, a 130,000-dalton component (*42*). In Ehrlich ascites tumor cells the major substrate for PK_F is PK_L, but several other proteins become phosphorylated as well. A phosphorylated band is visible at 35,000 daltons and a less pronounced band at 130,000 daltons. PK_S phosphorylates mainly PK_M and PK_F, but a phosphorylated 80,000-dalton component of the cytoskeleton can also be seen. PK_L phosphorylates PK_S as well as the epidermal growth factor receptor, and the only phosphorylated substrate for PK_M, seen thus far, is the β subunit of the Na^+,K^+-ATPase. Let us remember, however, that biochemical specificity is only a vague concept and subject to aging. It is not unlikely that with time and increased sensitivity of assay, additional substrates for all of these protein kinases will be found. In fact, we observed the appearance of new phosphorylated bands when antibodies against the kinases were used to block their phosphorylation. Whether such artificial observations have physiological relevance remains to be seen.

Table 5. Molecular weights, subunit compositions, and substrates of the cascade protein kinases.

Protein kinase	Molecular weight	Subunits	Substrates
PK_M	60,000	20,000 plus 40,000	β Subunit of Na^+,K^+-ATPase
PK_S	57,000	Single chain	PK_M, PK_F, 80,000
PK_L	44,000 to 48,000	Four chains (?)	PK_S
PK_F	60,000	Single chain	PK_L, 34,000, 130,000

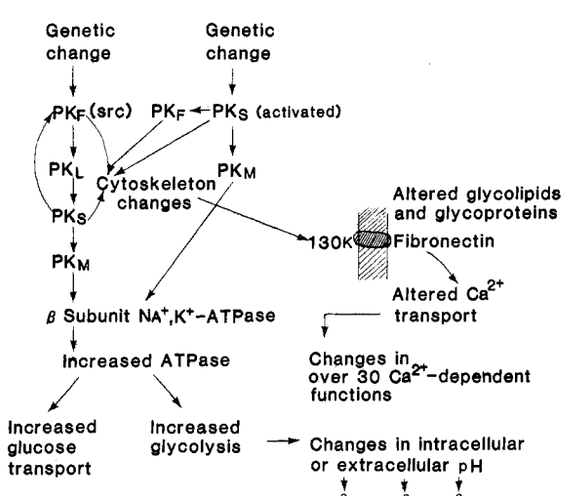

Fig. 1. Models of transformation.

The Multiple Faces of Cancer Cells

The extent of polymorphism and variability in biochemical and social behavior of cancer cells may make one wonder whether there could possibly be a single common denominator of causation. Yet we know that the transformation of a chick embryo fibroblast into a malignant sarcoma cell is achieved by a single gene product (*25, 43*).

Many years ago when I (Racker) worked on glycolysis I objected to the view (held mainly by graduate students) that glycolysis is glycolysis is glycolysis and no longer of interest to intelligent biochemists. Although I have quoted in the past with pleasure the statement of my mentor Colin MacLeod that glycolysis in the pneumococcus is the same process that took place in the brain of Plato, I have not done so without marking two footnotes. The first one concerns the environment. A bacterium growing in a test tube or even in a pocket of the lung has metabolic problems that are quite different from those of a brain cell bathing in the security of a homeostatic supply of glucose. The second and more important footnote is that, in spite of the similarity of individual glycolytic enzymes from different sources, the response pattern of glycolysis in cells may be so diverse (for example, to sodium fluoride) as to suggest different pathways. Differences in enzyme levels, regulating substances, and in the competition for intermediates often appear to transform quantity into quality.

About 10 years ago, Gordon Tomkins and his colleagues proposed the "pleiotypic response hypothesis" in which a single regulatory molecule coordinates multiple metabolic changes (*44*). A transformed tumor cell represents a case in which a protein kinase is just such a "pleiotypic mediator," modulated by its environment.

Let us look at some models of transformation shown in Fig. 1. Only three minor variants of a basic theme are listed and there may be dozens of others. We shall not discuss the variations since the same principle is operative. A gene product, either a kinase itself or an activator of a kinase, starts a cascade of phosphorylation which increases glycolysis and other metabolic pathways and alters components of the cytoskeleton which in turn affect structure and membrane processes such as ion transport.

In this connection there is one particular example that emerged from studies on Ca^{2+} transport in our laboratory. We observed (*45*) that HeLa cells, grown on a

substratum and then suspended, transport Ca^{2+} severalfold more rapidly than the same cells grown in fluid (Spinner) culture. When Spinner culture cells were incubated for 2 hours in complex medium containing fibronectin, Ca^{2+} uptake activity was markedly increased. We could also show that $^{45}Ca^{2+}$ became tightly bound to some components of the cytoskeleton within 30 seconds after exposure, whereas in the absence of fibronectin it took 30 minutes or longer to obtain similar $^{45}Ca^{2+}$ binding. It has been proposed (*46*) that fibronectin represents the surface counterpart for vinculin at the focal adhesion plaques [see, however (*47*)]. We can readily visualize how changes in phosphorylation of vinculin could affect the binding of fibronectin and consequently the rate of Ca^{2+} entry. There are over 30 physiological functions that are influenced by Ca^{2+} concentration in the cytoplasm (*48*) and it is not difficult to see how Ca^{2+} flux changes may influence the life of a cell.

We have related here the story of a classical biochemical approach to a biochemical problem. In the search for the cause of the high glycolytic rate of tumors we were helped by enzyme inhibitors (which were not always reliable), we had to go through the tediousness of purifying an unstable membranous enzyme from limited source material, we had to resort to reconstitution methods that could hardly be considered physiological, and we received support and ideas from virologists and geneticists who had tracked down the gene product of transformation. Above all, we have witnessed in this field a merger of biochemistry and molecular biology which was long overdue. We still do not know the significance of the high aerobic glycolysis of tumor cells. But Warburg's important discovery has led the way to a better understanding of the diversity of changes in physiological functions and morphological characteristics of cancer cells.

References and Notes

1. O. Warburg, *The Prime Cause and Prevention of Cancer* (Triltsch, Würzburg, Germany, 1967), pp. 6–16.
2. ———, *Biochem. Z.* **142**, 317 (1923).
3. S. Weinhouse, *Science* **124**, 267 (1956).
4. R. Wu and L. A. Sauer, *Methods Enzymol.* **10**, 105 (1967).
5. E. Racker, *Am. Sci.* **60**, 56 (1972).
6. D. Burk, M. Woods, J. Hunter, *J. Natl. Cancer Inst.* **38**, 839 (1967).
7. E. Racker, *Mechanisms in Bioenergetics* (Academic Press, New York, 1965).
8. ———, *A New Look at Mechanisms in Bioenergetics* (Academic Press, New York, 1976).
9. H. A. Lardy and R. E. Parks, Jr., in *Enzymes: Units of Biological Structure and Function*, O. H. Gaebler, Ed. (Academic Press, New York, 1956), p. 584.
10. J. V. Passonneau and O. H. Lowry, *Biochem. Biophys. Res. Commun.* **7**, 10 (1962).
11. A. Ramaiah, *Curr. Top. Cell. Reg.* **8**, 297 (1974).
12. K. Uyeda and E. Racker, *J. Biol. Chem.* **240**, 4689 (1965).
13. M. Rubner, *Die Gesetze des Energieverbrauchs bei der Ernährung* (Franz Deuticke, Leipzig, 1902).
14. T. J. Smith and I. S. Edelman, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **38**, 2150 (1979).
15. A. Chinet, T. Clausen L. Girardier, *J. Physiol. (London)* **265**, 43 (1977).
16. V. A. Gregg and L. P. Milligan, *Gen. Pharmacol.* **11**, 323 (1980).
17. E.-M. Suolinna, D. R. Lang, E. Racker, *J. Natl. Cancer Inst.* **53**, 1515 (1974).
18. E.-M. Suolinna, R. N. Buchsbaum, E. Racker, *Cancer Res.* **35**, 1865 (1975).
19. P. Scholnick, D. Lang, E. Racker, *J. Biol. Chem.* **248**, 5175 (1973).
20. R. C. Carroll, J. F. Ash, P. K. Vogt, S. J. Singer, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 5015 (1978).
21. J. Beard, in *Cellular Metabolism and Infections*, E. Racker, Ed. (Academic Press, New York, 1954), p. 164.
22. J. W. Beard, *Adv. Cancer Res.* **7**, 1 (1963).
23. G. de Thé, *Natl. Cancer Inst. Monogr.* **17**, 651 (1964).
24. H. Beug, A. von Kirchbach, G. Döderlein, J.-F. Conscience, T. Graf, *Cell* **18**, 375 (1979).
25. H. Hanafusa, in *Comprehensive Virology*, H. Fraenkel-Conrat and R. R. Wagner, Eds. (Plenum, New York, 1977), vol. 10, pp. 401–483.
26. R. K. Banerjee and E. Racker, *J. Biol. Chem.* **252**, 6700 (1977).
27. J. Johnson and E. Racker, unpublished observations.
28. D. R. Lang and E. Racker, *Biochim. Biophys. Acta* **33**, 180 (1974).
29. M. E. Pullman and G. C. Monroy, *J. Biol. Chem.* **238**, 3762 (1963).
30. T. Bakker-Grunwald, J. S. Andrew, M. C. Neville, *J. Membr. Biol.* **52**, 141 (1980).
31. M. Spector, S. O'Neal, E. Racker, *J. Biol. Chem.* **255**, 5504 (1980).
32. ———, *ibid.*, p. 8370.
33. ———, *ibid.* **256**, 4219 (1981).
34. M. S. Collett and R. L. Erikson, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 2021 (1978).
35. A. D. Levinson, H. Opperman, L. Levintow, H. E. Varmus, J. M. Bishop, *Cell* **15**, 561 (1978).
36. M. Spector, R. B. Pepinsky, V. M. Vogt, E. Racker, *Cell*, in press.
37. T. Hunter and B. M. Sefton, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 1311 (1980).
38. M. Spector and E. Racker, *J. Biol. Chem.*, in press.
39. B. A. Horwitz, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **38**, 2147 (1979).
40. E. Racker, *Am. J. Med.* **35**, 143 (1963).
41. K. Radke and G. S. Martin, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 5212 (1979).
42. B. Geiger, *Cell* **18**, 193 (1979); B. M. Sefton, T. Hunter, E. H. Ball, S. J. Singer, *ibid.*, in press.
43. P. K. Vogt, in *Comprehensive Virology*, H. Fraenkel-Conrat and R. R. Wagner, Eds. (Plenum, New York, 1977), vol. 9, pp. 341–455.
44. A. Hershko, P. Mamont, R. Shields, G. M. Tomkins, *Nature (London)* **232**, NB206 (1971).
45. A. Rephaeli, M. Spector, E. Racker, *J. Biol. Chem.*, in press.
46. K. Burridge and J. R. Feramisco, *Cell* **19**, 589 (1980).
47. T. David-Pfeuty and S. J. Singer, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 6687 (1980).
48. E. Carafoli and M. Crompton, *Curr. Top. Membr. Trans.* **10**, 151 (1978).

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Participation of Soviet Scientists in International Conferences

Edwin L. Goldwasser and Francis E. Low

For a number of years scientists from all over the world have been working toward a true internationalization of science. There have been efforts to open communications in all fields of basic research, to share data and results, to cooperate in both experimental and theoretical work. There are joint experiments involving scientists from several different countries, and a completely open exchange of ideas, as well as results, at international scientific conferences has become commonplace. However, along with the successes of international scientific cooperation there have also been some notable failures. Not all scientists have always been given free access to scientific conferences and exchanges. There was a time when one nation might limit access of scientists from another nation to meetings within its borders. The International Council of Scientific Unions (ICSU) has worked steadfastly to remove barriers of that kind and has had some notable successes.

It is relatively easy to identify restrictions imposed by one nation on access of scientists from another. It is much more complicated to identify restrictions imposed by a nation on the participation of some of its own scientists in scientific conferences abroad. This kind of restric-

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