The Warburg Hypothesis Fifty Years Later

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It is just about 50 years ago that Otto Warburg announced his famous theory of respiratory impairment in cancer (Warburg, 1926). Proposed and defended with evangelical fervor, it so captured the imagination of scientists that even today it serves for many as a guiding principle for the understanding if not the cure of cancer. It is natural for people, even scientists, to seize upon the words of prophets who promise salvation, and here was a truly heroic figure in science, providing an answer to one of humanity's scourges.

At the request of the editors of this journal, I am presenting my view on the present status of the Warburg hypothesis. This brief essay is not meant to be a comprehensive review, but rather a personal reflection from the vantage point of a half-century of research. I have, however, included representative references for the reader who wishes to examine the historical and technical background of this long-standing controversy. I accepted this assignment reluctantly, for the following reasons.

Twenty five years ago, when we first obtained and published experimental evidence that failed to support the Warburg hypothesis, I was unhappy at the necessity of disputing with one of the world's illustrious figures in biology. I have never relished confrontation, and I relish even less the continuation of a debate when the protagonist is not here to defend himself. Most importantly, I feel that as our perspectives have broadened over the years, the burning issues of glycolysis and respiration in cancer now flicker only dimly; they have receded in importance, and are no longer in the mainstream of cancer research.

Experimental Basis for the Warburg Hypothesis. Despite the overwhelming impact of the Warburg hypothesis, I suspect that few are familiar with the experimental background, and there are many misconceptions of what Warburg has said or done. It will be worthwhile, therefore, to review his experiments and his interpretation of the results. Warburg made two observations and proposed an hypote-
sis. It is important to differentiate the hypothesis and the observations. The first observation was that in the absence of oxygen both tumor slices and normal tissue slices utilized glucose and produced lactic acid, a process which he termed anaerobic glycolysis. He also found that generally but not always, cancer slices produced more lactic acid than normal tissue slices. The second observation was that both normal and neoplastic tissue slices produced less lactic acid in oxygen (aerobic glycolysis) than in nitrogen (anaerobic glycolysis). This phenomenon he called the Pasteur Effect, based on Pasteur's observation that yeast cease fermentation when exposed to oxygen. These are fundamental observations of primary importance; and although we still do not understand all of the mechanisms that regulate glucose utilization in cells, anaerobic and aerobic glycolysis and the Pasteur Effect have served as focal points for many years of fruitful research on metabolic regulation. As far as I am aware, these observations have not been and are not now in dispute, and no one questions their validity, albeit recognizing that they represent data on a highly restricted experimental system.

The hypothesis, which is central to the dispute, states in Warburg's words, taken from the preface of his book on tumor metabolism (Warburg, 1926).

"Whilst, however, normal cells die if they glycolyse aerobically, the glycolysing tumour cell not only continues to exist, but is even able to grow to an unlimited extent, turning to account the chemical energy of the glycolysis.

The aerobic glycolysis of the tumour cell is derived in any case from a disturbance of the respiration. As a rule, the respiration of the tumour cell is small, but in recent years tumour cells with a large respiration have also been found...

Whether the respiration of the tumour cell is large or small, aerobic glycolysis is present in every case. The respiration is always disturbed, inasmuch as it is incapable of causing the disappearance of the fermentation (i.e. glycolysis). Thus the two kinds of disturbances of respiration which can be artificially produced in normal cells—limiting the extent of respiration, or hindering the effect of respiration—occur in nature, in tumours."

To delineate the quantitative data on which these statements are based I collected in Table 1 the data on glycolysis and respiration of representative normal and tumor tissue slices which I tabulated earlier (Weinhouse, 1956) from data collected by Burk (1939) from the early experiments of Warburg and his contemporaries. These data cover 14 normal, adult tissues of various animals, and 15 solid tumors, and truly exemplify the glycolysis and respiration data upon which Warburg formulated his hypothesis. In view of Warburg's insistence on respiratory impairment of tumors, one should note that the average respiration of the 15 tumors was actually slightly higher than that of the 14 normal tissues, each set exhibiting similar ranges of variation.

The degree to which glycolysis is reduced by aerobiosis, that is, the Pasteur Effect, is also depicted in Table 1. The 14 normal tissues had on the average an anaerobic glycolysis, \( Q_{\text{CO}_2} \), of 7.2, and an aerobic glycolysis, \( Q_{\text{CO}_2} \), of 2.1. Thus the Pasteur Effect, measured most directly by the difference between anaerobic and aerobic glycolysis, was on the average, 5.1. The 15 representative malignant tissues had an aerobic glycolysis of 25.6 and an aerobic glycolysis of 14.0; giving a Pasteur Effect of 11.6. Thus, not only was the Pasteur Effect operative in these tumors, but aerobiosis reduced glycolysis more than twice as much in the tumor slices as in the normal tissue slices.