THE METABOLISM OF CARCINOMA CELLS[1]

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When the problem of carcinoma is approached from the metabolic aspect, the first question which arises is: how does the metabolism of growing tissue differ from that of resting? The prospects of finding an answer to this question are good. Whether the mass of a given tissue is to remain constant, or, within a short period to increase many-fold, must be determined by the velocity of those processes which supply the driving forces for growth. Our task is to search for such processes and to compare their velocities in resting tissues and growing tissues.

If this question is solved, then the further inquiry must be made as to whether the manner of arrangement of growing cells is manifested in their metabolism. Does the metabolism of tumors, growing in a disorganized manner, differ from the metabolism of orderly cells growing at the same rate. The hope of solving this question must be considered slight in general, and rightly so, if it is only the form-building forces which tumors lack. For of all problems of physiology, that of form is the least approachable.

Yet it seems doubtful that only minute and unimportant differences should exist between the growth of young cells and those of tumors, instead of considerable physico-chemical differences. Progress in the carcinoma problem implies the adoption of the point of view involved by the latter alternative.

[1] This paper was delivered as an address before the Rockefeller Institute in the autumn of 1924. While most of the facts which it contains have been already published in the following papers, Warburg and Minami, Klin. Woch., 1923, ii, 776; Warburg, Negelein and Posener, Klin. Woch., 1924, iii, 1062; Warburg, Biochem. Zeit., 1923, cxlii, 317; Warburg and Minami, Biochem. Zeit., 1923, cxlii, 334, the address affords so admirable a résumé of the work of Professor Warburg that it may be of interest to those who do not have access to the German literature.

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This has been done and I shall try to show that it is the correct point of view.

The experiments which I shall here report would not have been possible without assistance. I should like to mention my coworkers, Seigo Minami, Carl Posener, and Erwin Negelein, as well as the assistance of the Rockefeller Foundation.

I. The starting point has been the fact that the respiration of sea urchin eggs increases six-fold at the moment of fertilization. Here we have a transition from a state of rest to that of development, which is bound up with an extraordinary acceleration of energy-supplying reactions. A similar acceleration of respiration in the transition from resting epithelium to carcinoma might well be expected.

The Flexner-Jobling carcinoma, a tumor of the seminal vesicle of a rat, discovered at the Rockefeller Institute in 1906 and transplanted for many generations since, was chosen for the experimental material. Thin sections of the tumor tissue were made and their respiration measured in Ringer's solution at body temperature. The rate found was compared with that of kidney and liver tissue of adult rats. The respiration of the carcinoma tissue was not, as expected, greater than the respiration of kidney and liver, but considerably less.

This result seemed so startling that the assumption seemed justified that the tumor lacked suitable material for combustion. In order to test this, various nutritive substances—amino acids, fatty acids and glucose—were added to the Ringer's solution in the expectation that the respiration of the tumor would increase. The result was not what we had anticipated. Amino acids and fatty acids had no effect, while glucose brought the respiration to a standstill. In trying to discover why this happened, it was found that lactic acid appeared in the Ringer's solution, produced by glycolysis, and that this inhibited the respiration.

Since liver and kidney under similar conditions produced only very small quantities of lactic acid, it seemed that in this glycolysis was the metabolic process sought, the velocity of which is greater in growing tissues than in resting tissues.

II. These observations led to a thorough and quantitative investigation of the glycolytic activity of carcinoma tissue.

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The glycolytic activity of animal cells was discovered by Lépine, but was first recognized as a splitting of dextrose to lactic acid by P. A. Levene and G. Embden. According to Levene and Embden the equation for glycolysis is as follows:

$$C_6H_{12}O_6 = 2C_3H_6O_3$$

that is, under the influence of the cell substance one molecule of dextrose breaks down into two molecules of lactic acid, a process which is not an oxidation but rather a splitting-up process and which consequently may occur in the absence of oxygen. Despite this, however, oxygen does affect glycolysis, so that we must draw a sharp distinction between glycolysis under anaerobic and aerobic conditions. The simpler conditions are obviously those of anaerobiosis—those in which respiration is shut out. Therefore the anaerobic glycolytic activity of the Flexner-rat carcinoma will be first considered.

III. The carcinoma splits not only glucose to lactic acid, but also mannose, fructose and galactose, the velocity of the glycolysis being:

For galactose	1
For fructose	2.5
For mannose	17
For glucose	18

Glucose is obviously attacked most rapidly and we might add the alpha-form of glucose as rapidly as the beta-form.

IV. The influence of a series of external factors on glycolysis is shown in figures 1–4, in which the ordinates signify the velocities of glycolysis. One can see how great the influence of hydrogen ions, bicarbonate and glucose concentration is, and that all these factors must be kept constant if the glycolytic activities of various tissues are to be compared. The following conditions have been chosen for our measurements.

Temperature	37.5°	
Glucose concentration	1×10^{-2}	moles per liter
Hydrogen-ion concentration	$10^{-7.6}$	" " "
Bicarbonate concentration	2.5×10^{-2}	" " "

Special attention should be drawn to the remarkable influence of the bicarbonate, which, with increasing concentration at

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constant pH, accelerates the glycolysis. One finds only a very slight glycolytic activity in Ringer's solution which is free from bicarbonate. This explains why Russell, working on the carbohydrate metabolism of tumors, overlooked the glycolysis. He states that, for reasons of technic, he employed Ringer's solution free from bicarbonate.

V. The magnitude of the glycolytic activity may be expressed in parts by weight of lactic acid produced per hour per 100 parts of dried tissue. Several hundred measurements upon the rat carcinoma have been made and a high glycolytic activity is always observed. For anaerobic glycolysis we found values ranging from 8 to 165, average 12 per cent; in other words, the tumor produces 12 per cent of its weight in lactic acid per hour.

How tremendous this splitting metabolism is becomes clear on a comparison with the well-known data available on glycolysis in blood or frog muscle. In a unit time, tumor tissue produces 100 times as much lactic acid as does blood, two hundred times as much as frogs' muscle at rest, and eight times as much as frogs' muscle working to the limit of its normal efficiency.

VI. It is remarkable how long after the removal of the tumor from the body this conversion of material continues. Tumor sections, kept at body temperature in sterile Ringer's solution, continue to break down glucose for days with undiminished velocity. When we transplant sections three days old into rats they grow as well as those obtained from fresh tumors and immediately transplanted. On the other hand, when the glycolytic activity of the tumor is destroyed, for instance, by freezing in liquid air, it is no longer transplantable, in our experience. In general it has been found that only tissue with unimpaired glycolytic power can be transplanted. The conclusion drawn from this is that the glycolytic activity is an integral property of the tumor cell.

VII. Proceeding now to the more complicated aerobic conditions, it will be found that in addition to the splitting of glucose, oxidation occurs.

Since the famous researches of Pasteur on life without oxygen,

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we know that cleavage and oxidation are not independent of each other. If a cell, which breaks down glucose under anaerobic conditions, is brought into an atmosphere containing oxygen, the effect of the ensuing respiration is to decrease the splitting metabolism or cause it to disappear.

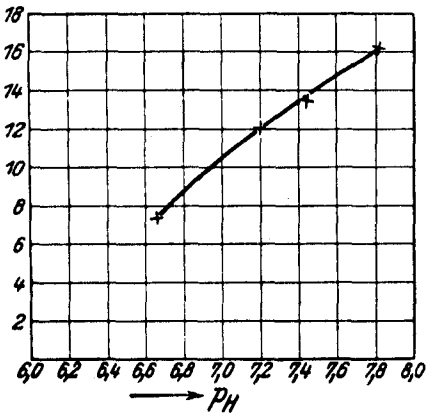

FIG. 1.

Meyerhof has show how respiration affects the splitting in muscle. This cycle occurs: Process 1, the splitting of carbohydrate to lactic acid occurs spontaneously. Process 2, the reconversion of lactic acid into carbohydrate, requires the addition of energy and occurs only in the presence of oxygen, when the oxidation supplies the necessary energy. Obviously the velocity of process 2 is dependent on the magnitude of respiration, since respiration supplies the driving forces. Slight respiration cannot cause the disappearance of any large amount of lactic acid; there is a relationship between the two, determined by the energy requirement of the reconversion process and the energy supplied by the respiration. This relationship has been determined for muscle by Meyerhof, who found that for each molecule of oxygen which is consumed, one or two molecules of lactic acid disappear. We have found the same values for lactic acid bacteria, carcinoma tissue, embryonal tissue, and many others. As a rule, therefore, one molecule of oxygen consumed causes the disappearance of one to two molecules of lactic acid.

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This fact is important for two reasons: First, because it shows that even in carcinoma the effect of oxidation on the splitting process is normal; second, because it makes it appear probable that Meyerhof's explanation of the influence of respiration in the case of muscle holds true generally. Whatever one's personal judgment, the relationship between the magnitude of respiration and the effect of respiration, does exist.

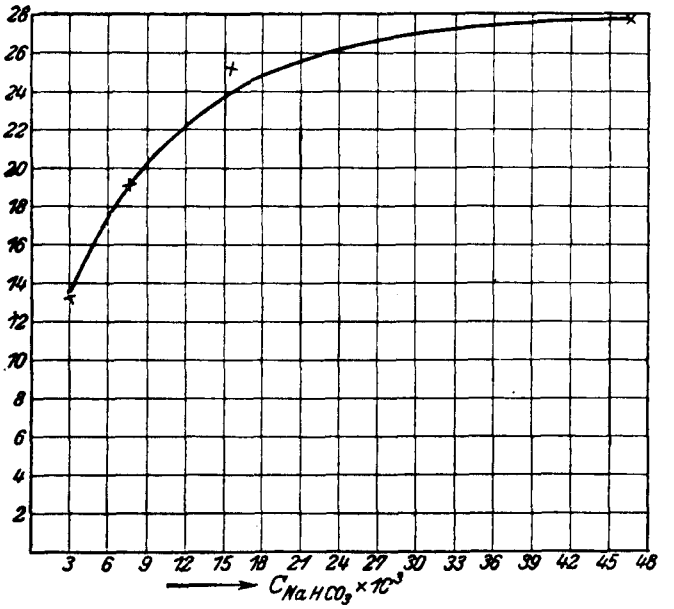

FIG. 2.

Let us take this as our starting point, and ask what occurs when we bring cells which break down glucose anaerobically into an aerobic environment.

When the velocity of splitting is great and the respiration slight, then, on transfer to aerobic conditions, the greater part of the splitting metabolism will still go on. If, on the other hand, the oxidation suffices, or is large in comparison with the velocity of splitting, then the splitting metabolism will cease in the presence of oxygen. An example of the first sort is found in yeast, the respiration of which is slight in comparison with the

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velocity of the splitting process; wherefore it breaks down equal quantities of glucose aerobically and anaerobically. An example of the second is muscle, the oxygen-consumption of which, under aerobic conditions, suffices to bring about the disappearance of lactic acid. The same is true for Pasteur's *Mucor mucedo*, which, on change from anaerobic to aerobic conditions, stops fermenting.

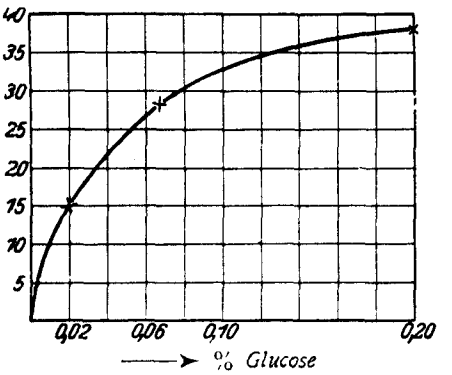

FIG. 3.

When a splitting metabolism is spoken of, we have in mind only the end products which actually appear and disregard cleavage phases, which may appear and disappear within an inner cycle.

We regard it as the most important of our findings, that in its metabolism carcinoma tissue does not behave like muscle or *Mucor mucedo*, but like yeast. If we bring carcinoma tissue from nitrogen, in which it is breaking down glucose, into oxygen, the glycolysis, though decreased, does not disappear, but continues for the most part. In nitrogen the carcinoma produces an average of 12 per cent of its weight in lactic acid per hour, in oxygen an average of 10 per cent. Even though in the case of the tumor each molecule of respired oxygen is just as effective as in the case of muscle, yet the respiration does not cause the disappearance of the glycolysis. The respiration of carcinoma tissue is too slight in comparison to its glycolytic activity.

VIII. The metabolism of carcinoma tissue in oxygen is, then,

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not a pure oxidation-metabolism, but a mixture of oxidation and splitting metabolism. In order to express the degree of this mixture quantitatively, the aerobic glycolysis is divided by the respiration and there is thus obtained the quantity of lactic acid which appears per molecule of oxygen respired.

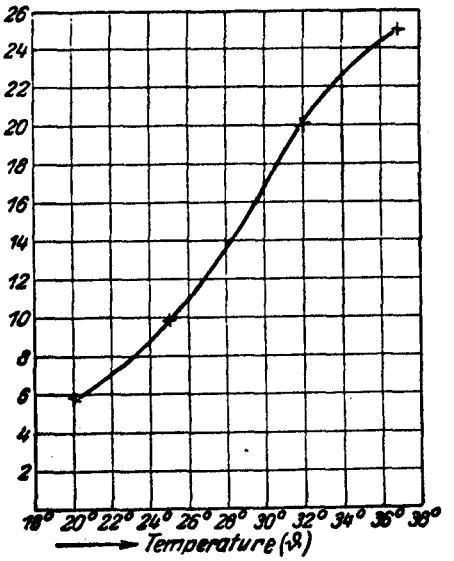

FIG. 4.

For the rat carcinoma this ratio, which, from this point on, will be the central point of our interest, is on the average 3.9. This means that the tumor produces 3.9 molecules of lactic acid for every molecule of oxygen respired.

The significance of this figure becomes more evident if the glycolysis and respiration are expressed in terms of glucose used up in both reactions. One molecule of lactic acid means the splitting up of one molecule of glucose, one molecule of respired oxygen the oxidation of one sixth of a molecule of glucose; from which it is evident that of thirteen molecules of glucose which the tumor attacks, it oxidizes one molecule and splits up the remaining 12. The metabolism of carcinoma tissue in oxygen is, then, preponderantly a splitting metabolism.

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IX. Striking as are the facts concerning the metabolism of rat carcinoma, their significance seems at first far from clear. The pioneer work on glycolysis, that of P. A. Levene and G. Embden, shows that liver cells and white blood cells possess glycolytic activity, but leaves its magnitude essentially undetermined and does not distinguish between anaerobic and aerobic conditions.

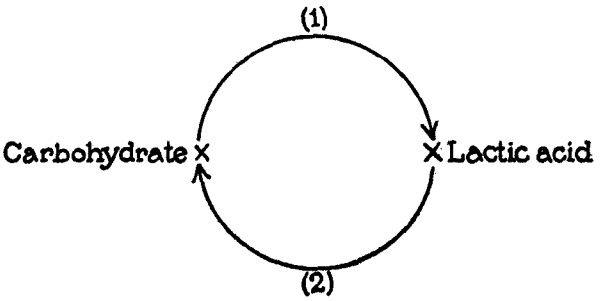

FIG. 5.

In order to obtain a survey of the field of glycolytic activity, various normal and tumor tissues were examined in the same manner as rat carcinoma, measuring the respiration and the aerobic and anaerobic glycolysis. For every type of tissue examined two values were thus determined: first, that representing the anaerobic glycolysis and, second, the ratio aerobic glycolysis-respiration.

If the metabolism of human carcinoma is to be compared with that of rat carcinoma, it must first be remembered that rat carcinoma consists of epithelium preponderantly, while human carcinoma contains, in addition, variable amounts—often very large—of connective tissue. A human carcinoma—say a scirrhous carcinoma—cannot, therefore, be compared directly with the Flexner rat carcinoma. The connective-tissue content must be allowed for or such carcinomas chosen as consist of epithelium preponderantly.

We have done both. Carcinomas of the scirrhous type have been examined, as well as those rich in epithelium, and also those originating from skin, mucous membrane, or gland structures.

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The values for scirrhous carcinomas were corrected on the assumption that the connective tissue of these tumors possesses as negligible a metabolism as that of connective tissue in general.

It was found, first, that the epithelium of human carcinoma possesses strong glycolytic activity under anaerobic conditions, producing an average of sixteen per cent of its weight in lactic acid per hour.

It was found, second, that in passing from anaerobic to aerobic conditions, the glycolysis not only did not disappear, but remained at a high value. The ratio aerobic glycolysis-respiration for a human carcinoma is 3 to 3.5; in other words, the metabolism under aerobic conditions is preponderantly a splitting-up metabolism, just as for rat carcinoma. The high anaerobic glycolysis and the low respiration are therefore not characteristic of the Flexner rat carcinoma, but of human carcinomas as well.

Sarcoma seems to behave like carcinoma, but too few sarcomas have been examined up to date to permit definite statements on this point.

XI. Among benign tumors bladder papillomas and nasal polypi have been studied, the former as examples of epithelial tumors, the latter as examples of connective-tissue tumors. We found that the anaerobic glycolysis of the papillomas is as great as that of the epithelium of carcinomas; that the anaerobic glycolysis of polypi is smaller, being about half as great as in the case of epithelium. This indicates that, as regards the anaerobic glycolysis—at least in its order of magnitude—there is no difference between malignant and some types of benign tumor.

On the other hand, when we pass to aerobic conditions, a difference becomes apparent. The ratio aerobic glycolysis-respiration for benign tumors is not, as in the case of malignant tumors, 3 to 4, but much smaller, namely, 1. Indeed benign tumors glycolyze in the presence of oxygen, and the respiration of benign tumors does not suffice to cause the cessation of glycolysis. The ratio splitting metabolism-oxidation metabolism for benign tumors is, however, displaced a long way in

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the direction of the oxidation metabolism. Malignant tumors produce three to four times more lactic acid per molecule of oxygen consumed than do benign tumors.

Thus the investigation of the metabolism confirms the experience gained from pathology, namely, that the differences between malignant and benign tumors are differences in degree rather than kind.

XII. If the disorder of growth in malignant and benign tumors is manifested in the high value of the ratio of the splitting-metabolism to the oxidation-metabolism, then we should expect still lower values than those obtained in benign tumors when we pass to the rapidly but orderly growing embryonal tissues.

We chose for study, at the suggestion of Dr. Heinrich Poll, chick embryos in the first three to five days of incubation. At this time the velocity of growth is considerable and comparable to that of young rat carcinomas.

The first thing learned was that under anaerobic conditions the embryo produces lactic acid in large amounts—in fact almost as much as the epithelium of carcinoma. This shows that the glycolytic activity is not a property peculiar to tumors but that it is a characteristic of all growing tissues.

Second, we learned that under aerobic conditions the embryo produces almost no lactic acid; in other words, that the respiration suffices to cause the cessation of the glycolysis. The metabolism of the embryo under aerobic conditions is a pure oxidation metabolism. I believe glycolysis still occurs, but only as an intermediate phase.

Thus the quantitative difference between malignant and benign tumors becomes a qualitative one, when we pass from benign tumors to normal growth. *The respiration of normally growing tissues suffices to bring about the disappearance of the glycolysis-products, whereas in tumors the respiration is too small for this. This, then, is the difference between ordered and disordered growth.*

XIII. On considering how the tumor type of metabolism arises from the embryo type, it becomes obvious that this is

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through a disturbance in the relationship between respiration and glycolysis, either an acceleration of glycolysis without a corresponding acceleration of respiration, or an inhibition of respiration without a corresponding inhibition of glycolysis.

We have attempted—keeping in mind the question of the origin of tumors—to produce such disturbances, and wish to discuss two types of procedure which produce the desired effect.

If we add to the Ringer's solution containing an embryo, cyanide in amounts sufficient to check the respiration, but not enough to stop it, we find that the anaerobic glycolysis is not influenced by the cyanide. If we transfer this embryo with the cyanide from anaerobic to aerobic environment, then the respiration has a normal effect upon the glycolysis, in that one molecule of respired oxygen causes the disappearance of two molecules of lactic acid. Nevertheless the respiration, since it is checked by the cyanide, no longer suffices to cause the disappearance of the glycolysis, and there remains under aerobic conditions an excessive splitting, which is the higher the greater the concentration of the cyanide. In this manner we obtain from the embryonic type of metabolism the tumor type—the benign tumor type, when the concentration of cyanide is low; the malignant type, when it is high.

More important is the second procedure, because it simulates more closely the natural relationships. The embryo is kept for several hours at body heat in an oxygen-deficient Ringer's solution, the latter being saturated with nitrogen. If the Ringer's solution contains glucose, the oxygen deficiency is injurious to the respiration, but not to the glycolysis; for, if the embryo is transferred from the nitrogen back to the oxygen, we have the absence of relationship sought for between respiration and glycolysis. The respiration has become too slight for the glycolysis and no longer causes its cessation. From the embryonal type of metabolism there has again arisen the tumor type—benign or malignant, depending upon the duration of the oxygen deficit.

XIV. If glycolytic activity is a property of growing tissues, then every tissue, whether embryonal or adult, must possess

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glycolytic activity. For the state of rest of mature tissue is only apparent; actually it is a stationary condition, in which there is an equilibrium between growth and death. As a matter of fact, by application of sufficiently refined methods, one finds as a rule that every living tissue possesses glycolytic activity.

We have especially investigated those types of tissue from which carcinomas and sarcomas arise, namely, connective-tissue and epithelium. As an example of resting connective tissue, we chose muscle fascia; as examples of resting epithelium, intestinal mucous membrane, liver, kidney, pancreas, submaxillary, and thyroid.

The metabolism of connective tissue is minimal; neither respiration nor glycolysis can be measured with certainty. In epithelium, we could always find an anaerobic glycolysis, showing that the characteristic of the embryonal tissue never disappears during life. However, the glycolysis of resting epithelium is ten times smaller than that of tumors or embryonal tissue. The rise in glycolytic activity in the transition from the state of rest to that of growth is tremendous, even greater than is the increase of respiration following the fertilization of the sea urchin egg.

The aerobic glycolysis of resting epithelium is practically nil; the respiration, in other words, causes the cessation of the glycolysis. The metabolism of resting epithelium under aerobic conditions is an oxidation—not a splitting-metabolism.

From what has been said, it follows that young differentiated epithelium lies between resting epithelium and embryonal tissue. We found that the anaerobic glycolysis for the liver of new born rats is five times as great as that of mature rats, and that the anaerobic glycolysis for the kidney of new born rats is three times as great as that of mature rats. Thus the glycolytic activity of epithelium gradually decreases with increasing age, until it reaches the level of resting tissue.

XV. If it be asked what is the significance of glycolysis for growth, we must assume from what we have learned that glycolysis is the energy supplying reaction for growth. The splitting of carbohydrates to lactic acid—in which Meyerhof

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and Hill see the source of energy for muscle work—furnishes, to our mind, the driving forces for growth.

It seems that these two cases, muscle work and growth, are not the only ones in which the splitting of carbohydrate is of significance for the organism. A third was found in the course of our studies.

If the retina in a rat is separated from the choroid and placed in an oxygen-free Ringer's solution kept at body temperature, it splits glucose into lactic acid at such an enormous rate that lactic acid to the extent of thirty-five per cent of its weight appears per hour. If we change from anaerobic to aerobic conditions, the glycolysis decreases, but still remains high. The ratio aerobic glycolysis-respiration is 1 to 5.

So far as this aerobic glycolysis is concerned, we believe that the respiration of the sensitive retina suffers as soon as its circulation is interrupted, and that under normal conditions in the intact body its respiration is sufficient to do away with all lactic-acid production. In support of this contention we may mention the fact that the less sensitive retina of the frog manifests considerable glycolysis under anaerobic conditions, but not aerobically. The metabolism of the frogs' retina under aerobic conditions is a purely oxidative one. So far as the anaerobic glycolysis in the retina is concerned, the possibility has been considered that the behavior of the retina might in some way be ascribed to the growth-phenomena, assuming that the state of rest of the retina as regards growth is much more an apparent one than the state of rest of connective tissue or epithelium. However, this assumption can scarcely be considered as final. We prefer to consider the retina as a case by itself, and conclude that the splitting reactions which the organism has at its disposal—the splitting of carbohydrate to lactic acid—are employed by it to serve various purposes.

The case of the retina obviously makes it necessary to proceed with caution in dogmatizing from our results. We may say for the higher organisms: no growth without glycolysis; but not conversely, no glycolysis without growth.

XVI. Thus, in comparing growth with rest, one tissue cannot

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arbitrarily be compared with any other, but only such as are related to each other. Adhering to this, carcinomas may be compared with embryonal tissue, or with growing and resting epithelium; sarcomas with growing and resting connective tissue. Doing so, the following picture is obtained of the development of carcinomas: At first we have the embryonal condition with the large anaerobic glycolysis and a respiration which is in accord with it. In the course of development there follows a stationary condition of the epithelium, with an anaerobic glycolysis which has fallen to one-tenth, and with a high respiration. From this stationary condition develop carcinomas, in which the glycolysis again rises ten-fold, without a corresponding rise in respiration. The same holds true so far as we can say at present for the development of sarcomas from resting connective tissue.

XVII. This shows what occurs when a carcinoma or sarcoma arises, but it does not show why it occurs. Why does the glycolysis increase ten-fold when a carcinoma arises from resting epithelium, and why is the respiration of the carcinoma so slow?

It is clear that our experiments cannot answer this question with certainty. On the other hand, our knowledge in regard to the characteristics and the development of tumors is now so definite that it would be strange if it did not put us upon the right track in regard to the causes.

During our work we repeatedly asked ourselves what can the causative factors be, and just as often has the idea obtruded itself that the causative factor in the origin of tumors is nothing other than oxygen deficiency. Allow me finally to enlarge somewhat upon this idea, which is merely a personal opinion.

Let us start with the fact that every tissue possesses in its stationary condition weak glycolytic activity. There is no reason why we should not suppose that there is an uneven distribution of the glycolytic activity, and to imagine, for example, resting epithelium as a mosaic, in which a very few cells glycolyze strongly, while the greater number of the cells do not glycolyze at all. If such a mixture of cells suffers an oxygen deficiency, as by pressure, sclerosis, action of bacteria, or other

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influence, then those cells which are not able to glycolyze must die, while those which are able to glycolyze can continue to live. We shall assume that some of these actually do so, that is, they are able to utilize the energy set free by glycolysis and to grow at its expense. If the oxygen-deficiency continues, then there will arise tissue possessing the glycolytic activity of embryonal tissue; but, since grown under conditions of oxygen-want, tissue whose respiration is abnormally slight—in other words, tumor tissue. As a matter of fact we know from the experiments with the embryo that oxygen-deficiency injures primarily the respiration.

This hypothesis substitutes for the general and indefinite conception "irritation," the definite conception "oxygen-deficiency." According to it, tumors originate from the differentiated growing cells which are an integral part of every living tissue. In so far as oxygen deficiency results in the death of all cells which do not glycolyze, it does, indeed, increase the glycolytic activity of the tissue, considered as a whole; but it does not increase the glycolytic activity of the individual cells which remain.

The question of the origin of tumors is entirely independent of the problem of why the disorder of growing tissue, whatever be its origin, is more pronounced the greater the lack of relationship between the splitting and oxidation reactions. For the present it will be wise to leave this question unanswered.

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