BIO-ELECTRIC PROPERTIES OF CANCER-RESISTANT AND CANCER-SUSCEPTIBLE MICE

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It seems reasonably clear that the eventual solution of the cancer problem will come only with a better understanding of fundamental biological principles. Cancer is unquestionably closely related to the phenomenon of growth. It differs from normal growth in that it is unrestricted overgrowth atypical in organization. It follows, therefore, that to understand the natural history of neoplasms, knowledge of growth and organization must be widened and deepened. While much is known about growth because of the marked increase of studies of this phenomenon in recent years, the more fundamental problem of biological organization still lacks any definite answer.

As a first approximation to the solution of this age-old problem Burr, in 1932, formulated an electrodynamic theory of organization and, in 1935, Burr and Northrop further developed and elaborated the idea. As formulated, this theory held that all living organisms possess a relatively steady state electrodynamic field, generated as a part of the fundamental attributes of protoplasm, and organized to form an electrical field which imposes a characteristic pattern on the development of the living organism. Should this theory eventually prove to be sound—and numerous studies suggest that it is—the presence of cancer should show signs of a determinable deviation in the electrical pattern of the normal organism.

The development of an adequate technique by Burr, Lane and Nims (1936) made it possible to initiate a series of studies designed to investigate the bio-electric properties of an organism before, during, and after the onset of cancer. The animals chosen for this study were from the mouse colonies of Dr. Leonell C. Strong (1936). Each strain has been inbred for many generations so that the genetic constitution of each animal is as nearly like that of others of the same strain as is possible. One strain, the CBA, was bred for relative immunity to adenocarcinoma of the mammary gland. The second strain, A, has been inbred so that approximately 90 per cent of the population of breeding females acquire mammary cancer during their normal lives. The electrical measurements were begun as early as practicable in the life history of the animals, about the 130th day. These measurements were carried on until the individual died or was killed.

THE TECHNIC

The technic employed in determining the potential differences in the intact living organism is relatively simple. The basic element in the procedure is the vacuum tube microvoltmeter. This is a balanced bridge circuit capable

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of detecting voltage differences of 5 microvolts or better with a suitable galvanometer. As designed, the current drawn from the living organism is not more than 10^{-12} amperes. As a result, there is probably little or no disturbance in what Voedlin (1929) has called "electron equilibria." Contact with the animal was made through a pair of silver-silver chloride electrodes as modified by Nims from the procedure of Harned. Each electrode was immersed in physiological salt solution which was conveyed to the animal through glass and rubber tubing. In this manner probably most of the artifacts of contact potential were reduced to a minimum.

The animals were prepared for study by a minimal dose of sodium amytal sufficient to quiet them for as brief a period of time as possible. While the effects of the anesthesia have not been extensively studied, the evidence suggests that, as Davis found, there is a slight increase in potential difference during the anesthetic period. When a mouse became quiet it was placed on its back on a corkboard as shown in Fig. 1. The hair over the symphysis, the sternum, each of the groins, and each lateral aspect of the chest, was shaved. The skin was then moistened by salt solution and the glass tips of the electrode tubes gently lowered into the salt pools. Determinations were made between the xiphoid and the symphysis for an axial potential and across the groins and across the chest for transverse potentials. In addition, with the xiphoid as a reference point, potential differences were determined between it and each groin and between it and each side of the chest. Thus the body was roughly triangulated.

It was found early in the studies that the most reliable determinations were made when the potential differences between the apices of equilateral triangles algebraically summated. Determinations were made approximately every two weeks with a period of eight hours of fasting before each set of readings.

**Fig. 1. Photograph of Mouse Showing Approximate Points between Which Potential Determinations Were Made**
The relatively long interval between determinations was allowed in order to avoid the cumulative effects of anesthesia. Eight hours of fasting were found to be necessary since determinations made immediately after feeding were apt to be erratic. From the data thus collected graphs were drawn to show the correlation between the voltage difference and the age of the animals, as well as between the voltage difference and both the incidence and the course of adenocarcinoma of the mammary gland. Approximately 10,000 determinations on 78 animals are included in this study.

![Graphs showing average potentials of "A" mice at successive age intervals](image)

**Fig. 2. Graphs showing average potentials of "A" mice at successive age intervals**

**Results**

For convenience of description these correlations and potential differences may be presented with reference to: (1) strain differences of mice used in the study; (2) ages of animals; (3) appearance of cancer in the cancer-susceptible strain.

It will be possible to present here only a brief summary of the extensive data. The statistical analysis of the material was prepared with the assistance of Professor F. K. Shuttleworth.

**Strain Differences:** In general it may be said that the axial potentials tend to show the xiphoid negative and the symphysis positive (Figs. 2 and 3). In the chest and in the groin, the right side tends to be negative with respect to the left side. In the axial potentials there is a large and highly significant strain difference. The cancer-susceptible mice show an average potential difference of 1777 microvolts and the cancer-resistant mice 3398 microvolts. The difference is 1621 or 10.7 times as large as its probable error of 151. There is a suggestion that the potentials become more negative after the appearance of cancer, but the difference is only a little more than twice the probable error. The only significant difference in the chest potentials between the two strains of mice seems to lie in the fact that the standard deviations indi-
cate a slightly greater variable of potential in the cancer-susceptible mice as compared with the cancer-resistant mice. In the readings across the groins large and significant strain differences appear in both the averages and in the standard deviations. In general, the data indicate somewhat higher potential differences in the cancer-susceptible mice than in the cancer-resistant mice. Moreover, the potentials in the cancer-resistant group are less variable than those to be found in the cancer-susceptible group. The difference between the standard deviations of this group is 7.9 times the probable error. Consideration of the above data shows that each group under consideration has its own electrical pattern and there is a suggestion that each individual in the group possesses its own characteristic electrical pattern. In general, it will be seen that the cancer-resistant group has higher axial readings, more variable chest readings, and more stable groin readings than the cancer-susceptible group.

Age of Animals Used: The correlations between age and potential difference have been studied in three ways: (a) correlations with chronological age; (b) correlations of the mean potentials with chronological age intervals; (c) correlations of the standard deviations with age.

(a) As shown in Figs. 2 and 3, the most significant changes with age occur in the cancer-susceptible group. The axial potentials and those of the right chest become more negative with age. The correlations of $-0.174$, $-0.132$ for the axial and chest potentials respectively are clearly significant and suggestive of a definite trend. In the cancer-resistant group the correlations are less significant. The variability is probably due to inherent factors not controlled in this experiment.
(b) If the mean potentials are plotted for chronological age at intervals of approximately two weeks, a number of valid findings emerge. The axial potentials of the cancer-susceptible group show a clearly defined tendency to increase. The average potential in the age group from 266 to 279 days is 607 microvolts. Two months later this value is 3092, nearly six times as large as the probable error. A similar rise is to be found in the chest potentials. Mice from 126 to 279 days old show an average chest potential of 80 microvolts. From 280 days to 349 days the average chest potential has increased to 1280 microvolts. From 350 days to 531 days it drops again to 400 microvolts. The average groin potentials of the cancer-susceptible mice are too irregular to define a trend.

![Graphs showing correlations of chest potentials with incidence of cancer in young and middle-aged mice](image)

**Fig. 4. Graphs showing correlations of chest potentials with incidence of cancer in young and middle-aged mice.**

In the cancer-resistant group a somewhat similar situation is found. Before the 200th day the average axial potential is 2040 microvolts. During the next 50 days it rises to 4605 microvolts and after 250 days it drops to 3353. Neither the average chest nor groin potentials in the cancer-resistant group show significant trends with age.

(c) If the data be analyzed by means of standard deviations, the axial potentials of the cancer-susceptible group seem too irregular to define a trend. The chest potentials, however, seem to show a greater variability during the period from the 200th to the 300th day, decreasing again in the last 100 days. The standard deviations of the groin potentials are high up to the 350th day, following which they drop abruptly to less than half their former values. The standard deviations of the axial potentials of the cancer-resistant group are too irregular to define a trend, although the two greatest standard deviations are significantly different from the smaller one. In the same way the standard deviations of the chest potentials yield high differences, exceeding their
probable errors by 4 or more times, but again the data are too irregular to define a trend. In the groin the data suggest a tendency toward less and less variability with increasing age.

While the correlations of the electrical potential with age seem to yield relatively little of value, in general it may be said that in all probability potential differences in the organism are to some extent related to the age of the organism. In other words, the age factor is only one of the many variables influencing potential differences.

**Correlations With the Appearance of Cancer in Cancer-Susceptible Mice:**

The most interesting data collected in this study were those dealing with the appearance of adenocarcinoma of the mammary gland in the cancer-susceptible strain. Of the 39 mice in the cancer-susceptible group, 19 developed cancer during the experimental period. Five of the cancers appeared around the 250th day, 7 appeared between the 320th and 390th day, and 7 between the 417th and 459th day. This grouping was determined by the fact that the bio-electric picture incident to cancer differed in young, middle-aged, and old mice (Figs. 4 and 5). All the cancer-susceptible mice were studied antecedent to the appearance of cancer, triangulations being carried out in the usual manner. As soon as a tumor was detected, determinations were made of the voltage difference between it and each side of the chest, each groin, and the xyphoid process. While in general the electrical patterns seem to be individually characteristic, group characteristics appeared. In those mice in which cancer appeared before the 260th day, marked rises amounting to several thousands of microvolts were encountered in the readings across the chest. A curve typical of such a case is shown in Fig. 4. Corresponding changes in the other measurements were almost entirely lacking. One rather astonishing fact is to be noted, however. The voltage rise across the chest appeared in some instances from ten days to two weeks before the

**FIG. 5. SIMILAR GRAPHS IN OLD MICE AND "A" MICE WHICH DID NOT DEVELOP TUMORS**

\[ \text{Graph showing chest potentials.} \]
tumor was detected by palpation. For example, animal A2-114898 gave a chest reading of left $+6300$ — right on May 11, 1936; left — 100 + right on May 23, and on June 2, two days after the appearance of a tumor in left 4, right $+6300$ — left. Briefly, in twenty days the left chest had shifted from 6300 microvolts positive to 6300 microvolts negative or a total voltage shift of 12,600 microvolts. In this particular instance the voltage shift seemed to be lateralized. It will be noted that the side of the animal on which the tumor appeared seems to have been consistently negative. This, however, is not always true. For example, A2-115289 on Jan. 24, 1936, gave a chest reading of right $+6500$ — left. Three days later a tumor appeared in the right third position and on Jan. 28 the right chest was still positive 15,000, left negative. In the middle-aged group the same observations were made, but the value of the voltage increase was not so large. The 7 animals in the old group failed to show the anticipatory rise in the chest measurements and instead usually showed a rising potential lasting until the animal was sacrificed.

It seems clear from the above data that the onset of adenocarcinoma of the mammary gland does something to the electrical pattern of the organism which can be measured with some degree of certainty. In the absence of exact information, it would seem probable that this effect upon the bio-electric properties is initiated at about the time the new growth appears. The data suggest, moreover, that as the new growth proceeds the chest potentials go up until they reach a peak not long after the tumor becomes palpable. This increase in voltage across the chest is not unlike the increase in head-tail gradients recorded in the salamander and chick (Burr and Hovland, 1937). Unlike the growing embryo, however, the chest potentials return to within normal limits in from two to four weeks. This suggests that the animal has established a new equilibrium with respect to the new growth.

Measurements of the voltage difference between the cancer itself and any of the normal areas of the organism yielded rather interesting findings. So long as the tumors were in the phase of rapid growth they were usually negative, the voltage difference being in the order of one or more millivolts varying from 1350 to a maximum of 12,000 microvolts.

Eventually, however, the tumor frequently became positive with respect to other points on the body. In the absence of microscopic examination of the tumors at the time of readings, a procedure made impossible under conditions of the experiment, it could not be determined if this polarity shift was related to the break down of the tumor. Gross observation indicated, however, that when the tumors did break down, with necrotic areas, they were nearly always positive to other points on the body. This finding is parallel to other observations, as yet unpublished, which seem to indicate that the so-called "negative current of injury" is by no means always negative. Cuts and abrasions of the skin in humans also produce marked voltage rises, but the cut area itself is quite as apt to be positive to the normal area as negative. While voltage differences between the tumor and uninvolved areas of the body could be measured, the magnitude of the voltage difference was rarely outside normal limits. Thus it may be seen that cancer modifies in a significant way the bio-electric potential of a living organism.

It is not improbable that similar explorations of the body may eventually
A2-114598 gave a left + 100 + right — of a tumor in left 4, est had shifted from a total voltage shift on which the 7 measurements were made. The animal was sacrificed in the absence of the nervous system lead to the conclusion that one of the factors imparts direction to a growing nerve fiber is a mass of rapidly growing cells. Moreover, it has been shown that in the case of the regenerating cerebral parasolm, Amblystoma punctatum, a reciprocal relationship exists between the growing olfactory nerve and the rapidly growing mass of ependymal cells formed at the site of the amputation of the cerebral hemisphere. By integrating this data with Kappers' theory of neurobiotaxis, Ingvar's galvanotropism, and the studies of A. B. Mathews and E. T. Lund, the electrodynamic field theory was evolved. Analysis of the development of the bioelectric potentials associated with the development and differentiation of the embryos of chick and salamander (Burr and Hovland, 1937) gave results entirely consistent with the theory. It seemed possible, therefore, that there were available a new technic for the study of growth and better grounds for a more adequate understanding of growth.

In view of this an analysis of the bioelectric properties of the atypical growth occurring in cancer in mice was undertaken. The results of more than 10,000 measurements presented above give added reasons for believing that the electrodynamic theory of life makes possible a clearer concept of some of the important factors underlying the age-old problem of biological organization. The Burr-Lane-Nims technic made it possible to examine the bioelectric properties of living things with very satisfactory validity. The results of the present study show that the field of the entire organism, as measured in terms of bioelectric potentials, reacts in a quite characteristic fashion to the tumor of the mammary gland. In young animals the potentials across the chest increase in amount antecedent to the detection of the tumor by palpation. Mice in middle group show greater variability in the potential determinations. Old animals show no anticipatory rise but rather a continuous and marked rise from the time when cancer appears, to death.

It is to be noted that these findings were found only in the chest potentials. A possible explanation for this lies in the fact that, in general, the groin potentials are the most variable of any of those studied. This is not surprising since other studies show (Burr and Musselman, 1937) that the activity of the genital tract has a profound influence upon bioelectric potentials. Variability in the groin potentials would, to some extent at least, modify the axial potentials, since one point from which these are taken is the symphysis pubis.
The chest potentials, on the other hand, show the least variability, probably because the local physiology of the chest, namely respiration and heart action, possesses a reasonably stable day-to-day constancy. Disturbances in the field, therefore, anywhere in the organism could perhaps be detected with greater certainty in the chest potentials. This suggests, of course, that the bioelectric concomitants of cancer produce some generally profound effect upon the whole organism. In fact, the totality of this effect seems to be much greater than what may be called an eddy in the electrical field produced by a pathological lesion.

If, as seems reasonable, the bioelectric properties of the organism lie at the heart of its organization, it ought to be possible to define the difference objectively between the bioelectric field of a portion of the body in which cancer develops and the field of that same region under normal conditions. A beginning is being made on such studies, but obviously a great deal of work must be done before even tentative answers can be given.

Another factor of some importance is the presence of potential gradients between cancerous and normal tissue of the same organism. The exact determinations of these gradients might form the basis for a rigorously controlled experimental attack in which these potential gradients could be reversed. In the light of modern physical chemical theory, moreover, it is by no manner of means impossible that the movements of ions and the transport of chemicals are conditioned and determined by electrical phenomena. The results presented in this paper are sufficiently striking to make it very worth while to push the studies on as wide a front as possible for, whatever may be the opinion of the validity of the theory, the facts themselves are as objectively determined as is at present possible.

The Summary

Evidence is presented in this study:

(1) Of the existence of bioelectric differences between cancer-susceptible and cancer-immune mice;
(2) Of the correlation of electrical pattern with the age of the mice;
(3) Of a characteristic change in the electrodynamic field of a mouse incident to the development of cancer;
(4) Of the presence of a potential gradient between the tumor and normal areas of the organism notably during the early development of the tumor.

Bibliography


* More complete references will be found in the papers listed above.