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CANCER RESEARCH AND THE SCIENTIFIC METHOD[1]

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CANCER is the most important problem of our time, for two reasons: first, because it kills people more than any other single disease (heart disease, which is higher in the mortality records, is a combination of heart and kidney and other diseases); second, because it has increased so greatly in incidence in recent times —62 per cent. more deaths in Pennsylvania in twenty-five years, 40.5 per cent. in Australia in ten years, 58.2 per cent. increase in 50 American cities with more than thirty million total population in twenty-five years, and in somewhat lesser degree in all civilized communities. In Great Britain in 1928, more than 12 per cent. of all deaths were from cancer, and a great insurance company has estimated the yearly loss from cancer in the United States to be about eight hundred million dollars.

Obviously the disease is a subject to warrant careful consideration and organized effort, for it touches the life of a great number of people. What has been done about it? A devoted group of medical men in a number of countries have studied the disease in man and in animals for many years, with the result that the treatment of cancer has improved in two directions—improved surgical treatment and treatment by radiation, x-rays and radium.

In medicine, as in all other forms of human endeavor, real ideas are rare; methodical development of ideas, after these are suggested or discovered, is common. The development of the automobile, for example, was only an elaboration of detail after the

[1] Address before the American Pharmaceutical Association, Philadelphia, April 14, 1931.

idea of the internal combustion engine was discovered. All else that followed, to our smooth-running motor cars, was elaboration and development of a central idea. In surgery, for these fifty years, the Pasteur idea of defense against the invading parasite has been the central purpose, and all surgery has been the elaboration of the idea of infection by micro-organisms of that French chemist, and this elaboration has been carried to a degree of detailed sophistication. Cancer has had its share in gaining better surgical methods, improved technique and earlier diagnosis, to gain better results than the old results which were nil. But surgery is only applicable to such cancerous growths which are easy of access, which do not involve a vital organ or have not produced additional subgrowths called metastases. In other words, if the cancer can be completely cut out, surgery is of use; if it can not, surgery had better not be attempted. Yet in the best clinics and under the best auspices, 75 per cent. of cancers are not suitable for surgical treatment because extension of the disease has already occurred.

Another accident led to the knowledge of the value of radium, when Becquerel carried a small amount of that strange substance in his coat pocket and found that after some time a destruction of the tissue of his skin, amounting to an ulcerating sore, occurred. This led to the idea that radiation from radium and, by analogy, radiation from x-rays, might be of use in the treatment of cancer. Since 1910, we have been concerned with elaboration of detail in the use of radiation, with improving methods of application and perfecting apparatus. So that now with surgery, aided by radiation under the very best auspices, about one third of all cancer cases, as they come, can be cured. In this country, under the disorganized methods, it is very difficult to estimate the total number of cures of cancer; but, after several years of collection of opinions and statistics, the total percentage of cures in cancer is estimated at less than 10 per cent. and more than five per cent. of all cases treated.

In fifty years of antiseptic surgery following the beginning of the Pasteur idea, and in the twenty years following the idea of Becquerel and Curie, we have been able to develop only two methods of treatment for cancer, neither of which gives anything like satisfactory results, but we use them because they are the only ones available. Both of these methods resulted more from happy accident than from any really intelligent investigation of the problem. They were not even the result of trial-and-error method of research, but they happened because one was interested in the care of vineyards and because another received a burn from a rare and new substance. Yet these two methods, surgery and radiation, are at the present time the only available and responsive measures for the treatment of cancer, and, with them, the very best we can hope is to cure one third of all cancer cases, obviously a confession of failure.

In these fifty years, research in cancer has not been without earnest activity, yet the pertinent facts collected have been few. Many men have devoted their lives to this or that phase of cancer research and yet the total sum of knowledge has not been noticeably advanced. It reminds me of my daughter, who has recently become engaged to be married and brought home four great books. Being always interested in books, I asked, "What have you there?" She said: "Before beginning any problem, you told me to collect all the available data, and these are cook books." Maybe cooking is the most important phase of the marital state and yet possibly other uncorrelated human activities, in a lifetime of mutual association, may also enter. In research into cancer (and it has been almost entirely by medical men), there has been a similar lack of correlation and lack of coordination. No definite consideration of the problem has been taken any more than in any other medical problem, except that "here was a disease and how can we cure it." Such research as has been done in cancer has followed the trial-and-error type of research, as is familiar to the medical investigator under the term the empirical method.

Yet why should it be so? Life is a very definite reaction which occurs and recurs according to definite constancy, and cancer is only a problem in the reproduction of a life history of cells, for cancer is a problem in cell division. A disease, such as cancer, is not a thing but a state, a deviation from normality. The cells, after our youthful growing period, have ceased to grow with arrival at adult age, or certain inhibitions to growth have occurred. In cancer, which is generally a disease of the latter half of life, certain cells have lost their inhibitions to growth and renew their power of division into a multiplicity of cells, almost always beginning in a local area. These cells are carried to distant parts of the body and maintain there the characteristics of the original cells, including their power of division and multiplication. Death occurs from extension of these cells as a growth to some vital organ impairing its functions, to a general extension of the growth producing such poisons as to alter the functions of the blood and other parts of the human organism, or by creating such obstruction, or lowered resistance, so that a terminal and fatal bacterial infection results.

The disease is a cellular disease so that the cell, the smallest particle capable of sustaining life, is our unit, as the atom is the unit of the physicist and the molecule of the chemist. All life forms are colloid in character and we have to do with a heterogenous system, elaborated into a polyphasic organization and with definite structural arrangement. The chemical complexity of the cell would be baffling were it not that there are phenomena which are common to all cells. Nature at some stage in her complexity rejuvenates her simplicity. The atom, the unit of the physicist, by structural associations, forms the molecule which is equally satisfying to the chemist. The molecules form the cell where there is again renewal of the simplicity.

The cell, in the study of cancer, is the unit and has a definite arrangement or organization. It is possible to create a model for thought exactly as the physicists create a model of the atom. In fact, cancer research is going through the same stages of development as has physics. Twenty years ago, physics seemed at the end of its great discoveries and all else seemed to be elaboration of detail. There was an atom, the smallest unit; which was described in terms of (1) words. Along came Nels Bohr and Lewis with the construct or (2) a fixed model of the atom. This was developed into Bohr's atom with its moving orbits and relation to Planck's constants, (3) a model in terms of operation. This was again extended to the Schroedinger wave dynamics which only can be described in the language of (4) mathematics.

In cancer, and indeed in all biological and medical research, we are just emerging from the (1) word stage. But it is possible to begin the advance to the second stage of construct or (2) the fixed model. Lord Kelvin said: "I never satisfy myself until I can make a mechanical model of a thing. If I can make a mechanical model of a thing, I can understand it. As long as I can not make a mechanical model all the way through, I can not understand it."

In cancer research, it is possible to take as a construct, or a fixed model for thought, the cell with the component parts of its system. The cell consists of (1) the nucleus, (normally with a pH of about 7.5), (2) the protoplasm (normally with a pH of about 6.6), (3) the cell membrane, and (4) the environment, which is the blood (with a normal pH of 7.38 and more alkaline in cancer) and tissue juices. The environment must be considered, for the cell and its environment are one. All energy forms, and the cell is an energy adapter, are brought to the cell and so enter the cell through the environmental phase. In consideration of alteration in cellular reactions, the environmental phase is of the greatest importance because alterations in this phase determine the reactions of the cell, and through this phase must go any influence, excepting radiation, which will prevent the cell division or cure cancer. Part of the mistakes in the study of cancer in the past have been the consideration of the cell alone as studied through the microscope in dead and stained preparations. In this, the most important phase in determining cell activity, the environment, was not considered.

Our unit system may therefore be thought to consist of four distinct portions: (1) nucleus, (2) protoplasm, (3) semi-permeable cell membrane, and (4) the environment from which the cell receives its energy-producing materials and through which the products of reaction are removed. The protoplasm is an intimate association of salts, carbohydrates, fats and proteins, many of which are specific to a high degree and which are partly contained in true solution and partly in a poly-dispersoid state.

In the continual exchange of materials and energy, the processes of oxidation-reduction are of outstanding importance. If we deny a cell oxygen, it either gradually ceases to function and dies or, like yeast, it adapts some form of anaerobic break-down in place of oxidation; if anaerobic break-down fails, the cell then perishes.

Life is an oxidation-reduction rhythm dependent upon oxidation-reduction potential which decides which one of two systems will oxidize the other. Since the process involves a transfer of electrons from oxidant to reductant, we may, by an adaptation of the Nernst formula, arrive at the following equation:

$$E_h = E_o - \frac{RT}{nF} \ln \frac{(\mathrm{Red})}{(\mathrm{Ox})}$$

where E_o is the voltage with respect to the hydrogen electrode as 0; E_o is the normal electrode potential; *Red* and *Ox* the concentrations of the reductant and oxidant, respectively, T the absolute temperature, and R the gas constant. It is important to recognize that this treatment applies to only perfectly reversible processes and herein lies the difficulty of applying it to vital systems whose processes are not generally reversible. However, many biological oxidations which are apparently irreversible proceed by a number of stages, some of which are truly reversible.

The oxidation-reduction potential decides in which direction the reversible reaction will proceed, but the rate is determined mainly by the oxidative catalysts whose influence must therefore be a most essential factor in the problem. In these cell oxidation-reduction processes, there are living catalysts which are known as "the dehydrogenases or dehydrases." Their function is to activate molecules so that they act either as hydrogen donators or hydrogen acceptors, depending upon the nature of the molecule and the conditions of reaction. The so-called inorganic ferments, or heavy metal catalysts, also play a great rôle in vital oxidation-reduction processes. In the living cell, other chemical substances form reversible oxidation reduction systems, the most important of these being the sulfur compounds of the type RSH–R-S-S-R, the former being the reduced form. In this class are the cystine-cysteine and the glutathione-reduced glutathione systems and, in addition as oxidation-reducing systems the fatty acids and carbo-hydrates.

There is no doubt, in life processes, that a steady dynamic state exists which is not chemical equilibrium, but which may be conveniently spoken of as biological equilibrium, and through which energy may be liberated.

The normal processes of the living cell are brought about by a continuous energy interchange which is dependent upon the physical, chemical and colloidal state of the cell constituents and which, in its explanation, must be correlated to the fixed model of the cell with its four component systems of (1) nucleus, surrounded by (2) protoplasm, enclosed by (3) cell membrane, and existing in (4) environment.

These processes are dependent upon two great factors: (1) conditions of biological equilibrium or balance, and (2) catalysts of the oxidation-reduction type. Their alteration in activity is influenced by conditions of biological equilibrium. For example, F. G. Hopkins has shown that glutathione (GSH) promotes the oxidation of certain unsaturated fatty acids, the O being transferred to the unsaturated linkage of the fatty acid, while the original SH groups are reconstituted. At pH 7.4–7.6 the system, GSH + unsaturated fatty acid, behaves differently; here the O uptake is equal to the amount required to oxidize the SH. The SH group is no longer an oxygen carrier but becomes represented by $AO_2 + B \rightarrow AO + BO$ where A is an auto-oxidator and B an acceptor. On the acid side of pH 7.4 the protein SH is oxidized and the total O amounts to ten times the O equivalent of the SH; at pH 7.4–7.6 the O uptake amounts to only sufficient to oxidize the SH. This is significant of the influence of conditions of biological equilibrium on the effect of catalysts (or as the biologists call them: enzymes). It is also significant that, in cancer, the blood, or (4) environment of our fixed model, has been found, by us, to be considerably more alkaline or averaging pH 7.44, where normal blood plasma is pH 7.38.

The oxidation-reduction equilibrium (rH) which is the analogy to the intensity of acidity or pH, is of enormous importance to these vital oxidation-reduction systems. The rH is a negative logarithm of the hydrogen pressure in equilibrium with the oxidation-reduction system in question. In simple systems, rH is a function of pH and Needham and Needham have shown that it holds similarly for living cells, that rH is a function of pH. Our only and main interest in pH is that it gives some measure of rH and is an easy and exact measurement capable of statistical estimation. The ideal is rH measurement; the means are pH measurement.

There is, therefore, to be considered (always remembering our fixed model with its four component system) a scheme as follows:

VITAL CELL SYSTEM INFLUENCES

Catalysts (enzymes, etc.)	Condition of biological equilibrium
Glycolytic enzyme	pH
Co-enzyme	rH
Fe in the hemin form	Ionic concentration of inorganic substances
Glutathione-reduced glutathione	Glucose concentration
Cystine-cysteine	Aggregation and dispersion of the colloid
Dehydrogenases including (1) heat labile catalysts acting on the substrate (2) intermediate reversible H and O acceptors and (3) heat labile oxidants sensitive to CN	*Buffer systems* Phosphates Carbonates Proteins oxy Fe–red Fe RSH–R-S-S-R

In such a scheme as this, it must be decided where these reactions take place, in what part of our four component system? This is the mechanism of energy adaptation in the cell and, in cell division, there is an enormous increase in energy turnover, over one thousand per cent. increase in certain cells, as has been shown by Joseph Needham, after fertilization of the *Ameba Proteus*.

Mechanism, in cancer research, is much more important than cause or end results, which have heretofore been the main efforts. Cancer may be produced by tar and other means which points to the fact that the cause of cancer is a state of the cells, favorable for division and produced by more than one stimulator. The end result is the tumor or the fixed dead stained preparation under the microscope. To attempt to reconstruct the mechanism of cancer from the microscope preparation is as hopeless as to reconstruct a bolt of lightning from the devastation it produces.

Glycogen is the sole source (or almost) of cell energy. Warburg and his coworkers have shown that in cancer the glycolytic activity of tumor tissue is greatly increased. For every thirteen sugar molecules attacked, twelve are split up into lactic acid and one oxidized, while in normal tissue this ratio is approximately 1:1. Mellanby and Harrison have shown that cancer tissue does not form lactic acid from the Robison ester, while normal tissue does. These findings make it necessary to postulate a different *mechanism* for the formation of lactic acid by cancer tissue or, in other words, there is deviation of the reaction in cancer cells from normal cells. As an energy adapter, the cancer cell follows a different mechanism from normal. This is one of the most significant facts of present-day cancer research. If it were possible by alteration in the cell influences, as shown in the table, toward restoration of normal metabolism (or reactions) cancer would be cured, because the only perceptible difference between a cancer cell and a normal cell is a difference in metabolism. The nature of the injury to the oxidative processes in the cell is the fundamental metabolic problem in cancer and the cure of cancer will come through the production of a more oxidizing potential than the limiting oxidation-reduction potential necessary to cell proliferation.

In our laboratories, we have shown that, in general cancer blood plasma (or (4) environment) there is a relative alkalinity amounting, in untreated internal cancers, to a change from normal pH 7.38 to pH 7.47, or approximately 18.7 per cent., more alkaline. These changes of pH may seem small to the chemist but they are enormous to the biologist. In cancer, therefore, there are alterations in conditions of biological equilibrium (see table) of pH which involves alteration also in rH and alteration in the action of the catalysts as each, no doubt, has an optimum pH at which it is effective and with alterations in pH, the catalyst either is not effective, or new catalysts come into play. In other words, alteration in conditions of biologic equilibrium may produce alterations in mechanism of reaction.

Our observation that, in untreated cancer, the duration of life is a function of pH and the more alkaline the blood plasma pH of the untreated patient, the quicker the disease kills, is significant of the influence of conditions of biological equilibrium upon the growth of the tumor and course of the disease.

Another interesting finding, which apparently has considerable evidence, is that cancer patients have relatively more sugar in their blood than normal and that, generally speaking, the more sugar in their blood, the worse is their expectation of life. This is borne out by our preliminary investigations, although the problem is still being studied.

In addition to these facts, it has been pointed out by Clowes, Rohdenberg and others, that cancer cells have relatively less calcium than normal and relatively more potassium and that, with increase of potassium content, there is an increase of the virulence of the tumor, or the virulence of the tumor is (in part, at least) a function of the potassium content. In our own laboratories, we have often found that, in spontaneous mouse tumors, calcium salts have an inhibiting influence on the growth of the tumor.

With these few facts, we can begin to state the direction in which research must tend. In order to have a cure of cancer, conditions must be produced which will: (1) alter glycogenolysis toward normal from the cancer type, (2) produce conditions of biological equilibrium towards normal from the alkaline state (pH 7.47 in internal untreated cancer blood plasma), (3) reduce the high blood glucose, (4) produce a calcium-like effect, (5) reduce or prevent the potassium-like effect.

These criteria are few, but at present these are the sole criteria for a cancer cure and the future will lay down more and more specifications until these become so obvious to some genius, who will say that with those specifications the answer can only be one thing to satisfy all the requirements.

In any consideration of these criteria, due consideration must be given to the conditions of mechanism as shown in the table, because mechanism is more important than results of reaction. If we know the mechanism, it may be possible to throw a monkey wrench into the wheels, and alter that deviation from normal reaction which is characteristic of cancer cells.

Trial-and-error methods of experimenting with one thing after another, characteristic of past cancer research, is a hopeless job. Human experimentation is limited because it takes at least six years for one experiment and, during that time, one can not deny to the patients the beneficial effects of radiation treatment, which masks the result of the experimental treatment. Animals with their shorter lives are available for treatment with chemical substances, but it takes at least six months to put one substance to trial, and, in the three years, we have been continuing some animal experimentation in our laboratories and testing a comparatively few substances, at least 100,000 new substances have been produced by the organic chemists. So the trial-and-error type of experimentation offers little hope, only a gambler's chance—a 20,000 to one shot. The past experiment offers no indication as to what the next should be.

The attempt, however, to estimate the available data and to lay down specifications for the alterations required in producing a deviation from the cancer metabolism towards a normal mechanism, offers hope of the application of the scientific method to cancer research, so that each set of experiments will produce data to extend knowledge and lay the basis for future experimentation.

Cancer research in our laboratories is the study of oxidation-reduction rhythm in vital systems as influenced by conditions of biological equilibrium and affected by catalysts, always considering the four component system of the cell and its environment. The foregoing may seem a simple sentence but it has taken me thirty years of my life to get there.

Continuation of experimentation along lines of the scientific method, in distinction to the trial-and-error method, can not but end in that consummation, devoutly to be wished for, a chemical cure for cancer, which, in my opinion, is only a matter of time and trouble. How much time and how much trouble remains to be seen. Cancer study is a problem in applied science which needs the united efforts of chemist, physicist, cytologist and biologist, and this cooperative and coordinated union in scientific effort is as much the product of American adaptability as is quantity production in manufactures. This united effort implies no deterioration in quality from so-called pure science, and is the united determination to solve a problem, even such a difficult one as cancer, by the assemblage of knowledge and mutual cooperation of scientific men and women.

DR. HILLEBRAND AS I KNEW HIM[1]

By Dr. E. T. ALLEN

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THE purpose of this occasion is to honor achievement, past and present. A more fitting memorial to Dr. Hillebrand could not have been conceived. We think of him as a man of achievement; other aspects of his comparatively uneventful life would have little interest for us.

In recalling briefly the outstanding formative influences of his career, those early years in Honolulu come to mind. Dr. Hillebrand was born in the Hawaiian Islands, less than a century after the white man first set foot on those shores. But if the circumstance of that early environment left any permanent impress on his temperament or his imagination, I have been unable to find it. Dr. Hillebrand rarely alluded to this period of his life. It seems to have been but an episode.

Dr. Hillebrand's father was a German physician who came to Honolulu for his health. He became deeply interested in the luxuriant tropical plant life about him; studied it; became an authority on the subject, and is to-day I believe the classic authority on the botany of the Hawaiian Islands. Dr. Hillebrand once told me that he had accompanied his father on many of his botanical expeditions, but that he never became interested in botany. However, the fact that his father was an intellectual man, of broad training, with the ability and the initiative to make himself an authority in any branch of science, must, I think, be counted an important influence in the after life of his son.

Dr. Hillebrand's formal education was unusually complete. After two preliminary years at Cornell University, he was sent to Germany in the early seventies, where he remained for six years. He studied at Strassburg and at Heidelberg. At Heidelberg, where he took his degree, he became a pupil of Bunsen and of Kirchhof, colossal figures in the world of science then, as they are to-day. Twenty-five years ago, as chairman of the program committee of this society, I prevailed upon Dr. Hillebrand to give us his recollections of Bunsen. He regretted that much of a personal character had faded from his memory, but he left no doubt in the minds of his listeners of the profound respect he bore to Bunsen and the powerful influence Bunsen had exerted on his own career.

To the German university Dr. Hillebrand doubtless owed much besides his purely technical training; ideals of thoroughness, accuracy and breadth. While perhaps not a man of the widest interests, he had a very broad perspective, much broader, I should say, than that of the ordinary professional man. Much of this, I think, was derived from the grand precept of the German university, that any department of human knowledge, no matter what its popularity, was entitled to the same respect as every other.

At Freiberg Dr. Hillebrand attended one of the most famous mining schools in the world, where he was grounded in such subjects as geology, assaying and metallurgy (metall'urgy, as he always called it after the German pronunciation).

In 1879, we find Hillebrand in Leadville, Colorado, one of the important ore-producing centers of the day, where he worked as an assayer. Shortly afterwards he joined the Geological Survey and a little later came to Washington where he remained in the government service to the end of his life.

I first met Dr. Hillebrand thirty years ago at the old Hooe Building on F Street, then occupied by the Geological Survey, since razed to make room for the National Press Club. Had you called on Dr. Hille-

[1] Delivered before the Chemical Society of Washington on the occasion of the award of the Hillebrand Prize to C. S. Hudson, March 26, 1931.