tion of possible methods of protecting us and the rest of the world from the danger of sudden destruction.

I shall recommend that the Congress of the United States consider promptly the establishment of an appropriate commission to control the production and use of atomic power within the United States. I shall give further consideration and make further recommendations to the Congress as to how atomic power can become a powerful and forceful influence towards the maintenance of world peace.

MICROSCOPIC AND CHEMICAL PROPERTIES OF PRECANCEROUS LESIONS[1, 2]

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WHEN cells become cancerous they undergo a transformation, said to be malignant, because thereafter they and their descendants behave like criminals unrestrained by the controls which shape the behavior of their normal neighbors. We know that a great many agents, called carcinogens, can produce this change and further that there is a long interval, usually amounting to several years, between their initial action and the final transformation. A carcinogen may act once, or repeatedly, or be succeeded by another carcinogen, and modifying conditions often operate tending to facilitate or to inhibit the production of cancer. Long before the actual expression of malignant behavior by the cells it is often possible to demonstrate that these have been changed and are, therefore, far from normal.

The designation "precancerous lesion" is applied to a type of structural change in a tissue in which clinical experience shows that the cells are more likely to become malignant than in other kinds of lesions. Several types have been recognized: in the skin, pigmented moles of the junction type and senile keratotic areas; in the breast and uterus, chronic inflammatory lesions; in the colon, polypoid adenomas; and so on. But, when the fate of many individual lesions belonging to a single type is followed, it usually happens that the malignant transformation only takes place in but a few of them. The majority of the individual lesions are not in fact precancerous. The adjective "precancerous" relates to the type, not to the particular lesion. Perhaps two sorts of lesions are grouped under a single type, or they are all of one kind and some happen to be exposed to a carcinogen not acting on the majority.

Even with such outspoken lesions, some of which become malignant, it is not possible to localize the actual transformation to cells which are multiplying more rapidly or more slowly than normal; because, in a given lesion whether hypertrophic or atrophic, a few cells may not be acting like the majority which give character to it.

The problem is further complicated by our inability to discover any type of cell in the body capable of multiplication, or which can become so, which never undergoes a malignant transformation. We have to face the possibility that for each and every one of them a precancerous condition may occasionally develop which is individual and distinctive and depends on structural modifications which may or may not be demonstrable microscopically. When clinicians are confronted with lesions of a precancerous type they seldom know what caused them and they can not evaluate all the possibly modifying factors which have participated through the years in their development and persistence. It is high time that the problem be brought into the laboratory, where the precancerous type of lesion can be produced at will by a standardized technique in experimental animals and its evolution can be followed in a few weeks time. Indeed the main research project in the Barnard Hospital is analysis of the biological equation:

Chemically pure carcinogen (methylcholanthrene) + epidermis (an avascular tissue composed of cells of a single type) of closely inbred strain of mice = squamous cell carcinoma in a very high percentage of animals.

This analysis is limited to the properties of epidermis that can be quantitatively determined. Our purpose is integrative, to discover whether the properties increase, decrease or remain constant; and, when there is a change in a property, whether it is paralleled by alterations in other properties. It is, of course, not feasible to investigate many properties in one and the same group of mice. Nevertheless, by standardizing the equation through elimination of the principal variables, the observations made on properties in different lots of mice can in a sense be superimposed.

[1] From the Department of Anatomy, Washington University School of Medicine, St. Louis, Missouri, and The Barnard Free Skin and Cancer Hospital.

[2] Adam M. Muller Memorial Lecture, Long Island College of Medicine, April 23, 1945.

Because each property studied is to some extent a problem in itself, though an integral part of the whole, the papers by various members of the team are units. This is helpful, for it promotes individual initiative, gives credit where it is due and makes it unnecessary to head the contributions by a long series of names of authors.

In the past seven years the following investigators have published papers advancing this project: V. M. Albers, J. P. Baumberger, J. J. and M. McA. Biesele, Z. K. Cooper, E. V. Cowdry, Wm. Cramer, H. I. Firminger, H. C. Franklin, C. E. Lischer, P. F. Max, B. Milder, F. X. Paletta, H. C. Reller, A. Schiff, W. L. Simpson, R. E. Stowell, V. Suntzeff, H. C. Thompson, F. Urban, L. F. Wicks and D. Ziegler. Their contributions are specified in a recent report.[3] They have worked in the laboratories of Barnard Hospital or of Washington University, or to a less extent in those of the C. F. Kettering Foundation for the Study of Chlorophyll and Photosynthesis at Antioch College. Without financial aid, gratefully acknowledged in the same report, but little progress could have been made.

By fluorescence microscopy and spectrography the carcinogen has been followed into the skin, where it soon disappears as such. Other fluorescent compounds make their apparance. To unravel them is quite a task. But a glimpse has been obtained of the conditions, somehow established in the epidermis by the carcinogen, which antedate the expression of malignant behavior by the altered cells. These include a new chemical equilibrium the discovery of which was made possible by devising a method for the removal of epidermis from dermis in a state suitable for chemical analysis and by adapting polarographic and other techniques to epidermis. As has been reported in various papers this equilibrium is characterized by marked decreases from the normal in calcium, iron and lipid; while sodium, potassium, magnesium and ascorbic acid show no noteworthy changes. In addition, unpublished observations by Wicks and Suntzeff reveal a decrease in cholesterol; of Carruthers and Suntzeff, a decrease in copper and zinc; and of Tatum, Ritchey and Cowdry, a decrease in biotin. The new equilibrium is established promptly, within less than 10 days, and is maintained, with but slight variations equally balanced, for several weeks (a long time in the life of mice) until the malignant transformation makes its appearance in a few cells.

Obviously we must learn more about this new equilibrium. Other properties may be found to remain constant during this period and still others, in this relatively steady chemical environment, to change slowly or suddenly. The equilibrium, whatever its limitations, is created by the reacting cells and they in turn are subject to it. The new lives which they and their descendants live during this long period, on amounts of iron, calcium, cholesterol, copper and biotin reduced approximately 50 per cent., are likely to be very different from the normal. We find that the cells are larger, and that the increase in volume is greater in the cytoplasm than in the nucleus so that the nucleocytoplasmic ratio is decreased and remains at about the same level (when graphically expressed) during the whole period. As early as 12 hours after a single application of carcinogen there is a striking increase in the cytoplasmic content of ribonucleic acid, which attains a maximum from the 3rd to the 10th day, and then decreases. The rate of mitosis increases progressively, attains a high level, which is sustained for days, only to fall and rise again just before the time when cancers show themselves. An enlargement, usually a doubling of chromosomes (measured in the metaphase), noticeable on the second day, is manifested by 13 per cent. of metaphases on the third day, after which it is apparently maintained at a somewhat lower frequency to the fifty-seventh day. Thymonucleic acid is increased and the displaceability of basophilic chromatin and nucleoli, when subjected to ultracentrifugal force, is increased. This suggests a fundamental decrease in intranuclear viscosity. Thus, what little evidence we have is consistent with the prevalent idea that the malignant transformation is conditioned by some change in the nucleus. A technique, recently devised for separating out the nuclei from epidermis, and their collection *en masse,* opens up several attractive lines of investigation.

But *where* and *when* the transformation occurs elude us. Concerning the first, several observations point to the spinous layer. We do not know why the change is restricted to one or more small foci, nor why most of the epidermis treated with the carcinogen does not react to it by cancer production. But, if the malignant transformation is conditioned by a mutation, it would hardly be expected to appear in a very large proportion of the cellular population. Generally speaking, a mutation occurs in but a few of a great many cells or organisms, all of which have been subjected to the influence bringing it about.

Our analyses are of treated epidermises from several mice taken together to give sufficient amounts. Therefore we have no means of knowing how uniformly the new conditions prevail in our specimens. Yet we think that the malignant change originates in an area or areas in which the new equilibrium, or a condition closely resembling it, has previously been established.

[3] *Jour. Invest. Dermat.*, 6: 15–42, 1945.

Evidence for this assumption is found in a less complete study of the conditions of cell life in a resulting transplantable carcinoma. To analyze any and all tumors developing from transplants of this carcinoma in mice is as futile as to analyze skin consisting of epidermis plus dermis. Experience has shown that to obtain worthwhile data the analyses must be limited to very small young tumors in which necrotic material is not a complicating factor. The chemical composition of such tumors—almost devoid of dead material, and therefore largely made up of active cancer cells—is, as far as we know it, in an equilibrium which definitely seems to be a carry-over from the pre-existing new equilibrium of the hyperplastic epidermis. Thus, the decrease in iron, noted in the hyperplastic epidermis, is found also in the cancer; while the decreases in calcium and copper and the increase in displaceability of nuclear contents, characteristic of the hyperplastic epidermis, are all carried to a greater degree in cancer.

Accurately to state *when,* after the first treatment with carcinogen, the malignant transformation takes place is beyond us. The new equilibrium is established long before any epidermal cells break loose and behave in a malignant fashion. However, the possibility must be borne in mind that a few cells may undergo this fundamental change early in the reaction and are unable to behave malignantly because they are, at least for a time, so closely bound together in a tissue remarkable for the tightness of cellular connections. Perhaps some hitherto unrecognized spreading factor later operates to break down the cellular connections and also to liquefy the ground substance of the dermis in this fashion facilitating detachment and invasion. This idea stems from the curious behavior of the mast cells in the dermis.

In our experimental material we set the stage by arranging for the same carcinogen to act to the same degree on the same tissue of mice of the same closely inbred strain for selected lengths of time. In so-called precancerous lesions in man we can only take what we can get unarmed by such accurate information, yet definite progress is feasible in several directions. Precancerous lesions of the skin and of the mucous membrane of the mouth and vulva are the most susceptible of attack because they are easily seen and samples can readily be collected as biopsy specimens. Not all carcinogens are fluorescent, but it would be a simple matter quickly to search for fluorescent ones by the techniques used. Since the epithelial components can be separated from the underlying tissue by the heat method, they can be collected in suitable condition for chemical analysis. Because these lesions persist for long years without grossly noticeable change—in fact for periods occupying roughly the same fraction of the human life span as the new equilibrium does that of mice—it is probable that these human cells are also, at least in some respects, in a new equilibrium, or balanced state, differing from that of corresponding normal tissue. It would be interesting to determine whether this equilibrium is the same in individual lesions of the same clinical type and, by so doing, to check the possibility already mentioned that the lesions, though looking alike, may be of different sorts, and that this difference may explain the fact that the malignant transformation only appears in some of them. It would also be worthwhile to compare the new equilibria, if such are present, in atrophic and hypertrophic lesions with each other and with the one which we have noted in our series. These and many other opportunities present themselves, including efforts to heal the lesions by reconstituting the old normal equilibrium.

In conclusion, I wish to explain that these measurements of the properties of epidermis subjected to methylcholanthrene before malignancy sets in, are but part of the principal Barnard Hospital cancer project. They may be considered as work on the first and lowest level in this project, for we are building constructively. Obviously such studies are limited merely by the number of properties that can be investigated quantitatively, and the more included the more valuable their integration becomes.

Work on the second level is restricted to the same premalignant stages in the response. It is intended, however, not to discover more facts; but, on the basis of the facts observed on the first level, to organize and carry out experiments designed to prevent the malignant change from taking place in tissue sufficiently exposed to the carcinogen otherwise to produce cancer. First, one would try every possible device of holding the reacting epidermis in the previous normal equilibrium and of counteracting the decreases in calcium, iron and other substances which give character to the new precancerous equilibrium. The swelling of cytoplasm and of nuclei and the evidence for decreased intranuclear viscosity suggest the advisability of exposing the epidermis to strongly hypertonic solutions despite the lack of chemical data pointing to increase in water content. But one should try all influences likely to affect epidermis in any way consistent with continued life of the animals, for unexpected factors may achieve the desired results. Those which accelerate the malignant transformation, such as injections of estradiol benzoate, are not to be neglected because they may serve as clues to inhibitors. While the first level obviously is fact-finding, the second is therefore one of purposeful control.

On the third level comes more fact-finding investi-

gation now of the chemical equilibrium of the resulting cancer and of all other possibly significant properties. Here we have made considerable progress; but much remains to be done, and the chances of expansion by adding other unit projects, as parts of the whole, are almost unlimited.

And on the fourth, or highest level, are purposeful efforts based on knowledge of the equilibrium in the cancer to disturb it and cure the cancer, and also to determine the specific vulnerability of the cancer cells by bringing to bear on them influences of wide variety, for again an unexpected agent may prove to be most effective. To concentrate on the first and third levels requires restraint bolstered by the belief that so doing will pay in the long run.

At all four levels, whether of fact-finding or of control, so many opportunities unfold that it requires no stretch of the imagination to see how at least 100 workers could profitably be employed, all integrated through investigation of the same biological equation by quantitative methods so that the results will all stack up. Our project is not unique in this regard. It is not difficult to think of others which can likewise be organized in such a way as fully to justify an almost wholesale approach.

What is needed is for the public to shed its colossal complacency concerning cancer and to insist on research being carried on as an "essential" activity, dominated by the spirit of *must,* not being shocked by the *cost,* which has achieved wonders in the war. The least we can do is to support the National Campaign of the American Cancer Society and to let our Senators and Representatives in Washington know that we confidently look to them to support the plans of the U. S. Public Health Service for Cancer Research.

OBITUARY

MAX BERGMANN
1886–1944

MAX BERGMANN, member of the Rockefeller Institute for Medical Research, died in New York on November 7, 1944, in his fifty-ninth year and at the height of his powers as an investigator in the field of organic biochemistry.

Born in Fuerth, Bavaria, on February 12, 1886, Bergmann received his college training in Munich. Like several other distinguished biochemists, he approached chemistry through the biological sciences. His original inclination had been towards botany, but in his early studies he was so much impressed by the need for chemical answers to botanical questions that he decided to acquire a fundamental training in organic chemistry. To this end he enrolled in the chemical department of the University of Berlin, then under the leadership of Emil Fischer; there he graduated in 1911, the work for his dissertation, on acyl polysulfides, having been directed by Ignaz Bloch. He then joined Fischer's group of collaborators in the investigation of amino acids and carbohydrates.

With the outbreak of war in 1914 Bergmann was selected by his chief as confidential scientific assistant, an appointment which brought with it exemption from military service. During the subsequent five years he was thus closely associated with all of Emil Fischer's research activities, which included not only the topics mentioned above, but the investigations of tannins and polyhydroxylic phenols. Among the important publications that bear Bergmann's name during that period are reports on the acylation of polyhydroxylic compounds partially protected by combination with acetone, on the synthesis of glucosides of gallic acid and mandelonitrile, on new methods for the preparation of α-monoglycerides and on the chemistry of glucal. After Fischer's death Bergmann almost automatically became his scientific executor, assuming the responsibility for the completion and publication of unfinished researches.

In 1921 he was appointed to the Kaiser Wilhelm Institut für Lederforschung in Dresden, where he continued his investigations in the field of carbohydrates and initiated his studies of the synthesis of unsymmetrical glycerides. A logical extension of this work to amino alcohols led on the one hand to the recognition of the migration of acyl groups and on the other to his abiding interest in amino acids and peptides.

Bergmann's duties in Dresden comprised, besides academic research, chemical studies of leather and tanning processes, and he was obliged to spend a large part of his time in consultation with industrialists. In view of the extensive traveling involved in this phase of his activities, his scientific productivity through the following decade was truly remarkable. Among the major problems which he attacked during this period was the general theory of the structure of polysaccharides and proteins. In 1925 he published his first papers on the chemistry of diketopiperazines derived from serine and cystine, with the aid of which he established a general method for the preparation of derivatives of dehydro amino acids. In the following year he first exploited the useful properties of azlactones for the synthesis of dipeptides, particularly those of phenylalanine, which he produced by the condensation of benzaldehyde and oxazolone with subsequent hydrogenation and con-