must be excessively rare. Under conditions like those which now prevail in the neighborhood of the sun, a star will only experience an approach close enough to generate planets about once in every million, million, million years. If we suppose the star to have lived under these conditions for about 2,000 million years, only one star in 500 million will have experienced the necessary close encounter, so that at most one star in 500 million will be surrounded by planets. This looks an absurdly minute fraction of the whole, yet when the whole consists of a thousand million million million stars, this minute fraction represents two million million stars. On this calculation, then, two million million stars must already be surrounded by planets and a new solar system is born every few hours. The calculation probably needs many adjustments; for instance, conditions near our sun are not at all typical of conditions throughout space and the conditions of to-day are probably not typical of conditions in past ages. But even so the calculation suggests, with a large margin to spare, that although planetary systems may be rare in space, their total number is far from insignificant. Out of the thousands or millions of millions of planets that there must surely be in space, a very great number must have physical conditions very similar to those prevailing on earth.

We can not even guess whether these are inhabited by life like our own or by life of any kind whatever. The same chemical atoms exist there as exist here and must have the same properties, so that it is likely that the same inorganic compounds have formed there as have formed here. If so, we would like to know how far the chain of life has progressed but present-day science can give no help. We can only wonder whether any life there may be elsewhere in the universe has succeeded in managing its affairs better than we have done in recent years.

THE MECHANISM OF SPECIES ADAPTATION TO CARCINOGENS

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INTRODUCTION

THAT the cancer cell is the result of a slow process of adjustment of normal cells to an unusual environment over a period of time embracing several or many cell-division cycles is the simple hypothetical basis upon which the experiments described herein were undertaken. The concept is not new, but as far as known, little if any experimental evidence has been produced in support of it. Therefore it was thought that some light might be thrown on the process of cancer induction by observing the behavior of small free-living organisms in the presence of carcinogenic agents over a considerable period of the racial history involving numerous successive generations.

We do not believe that the past experience of cancer investigators, either in the clinical or in the experimental fields, warrants the assumption that the genesis of a cancer cell involves a sudden change of a normal cell. All pathological entities barring those due to wounds and hereditary defects are the result of a process—a process of adjustment to an unusual or unfavorable environment. Cancer, we suspect, is no exception unless it be that the process here is slower than in most other diseases, and this slowness may be due in part to the fact that the genetic mechanism of the cell is primarily affected.

The clinically observed association of cancer with chronic irritation, the prolonged incubation period in experimentally induced cancer and the various precancerous lesions and stages that have been described, all seem to fit in with the concept of *gradualism* as a reasonable hypothesis in the genesis of cancer. The clinical examples of a step-like derivation of malignant growth does not exclude completely, of course, the alternative concept of a sudden mutational change as an occasional mechanism, for it is true that mutations can be induced experimentally with some of the same agents that are known to induce cancer and as the result of a single stimulus of great magnitude (x-rays, gamma rays of radium, heat). Such agents may either destroy one or more genes or disarrange the genic pattern and sequence. But in nature these highly artificial procedures are certainly the exceptions rather than the rule. It seems reasonable then to assume that a genetic change may be very frequently the culmination of a series of subliminal stimuli which have extended through many cell-divisions or generations.

The successful immunization of individual animals to multiple lethal doses of various toxins is well known, and can be achieved best by means of interval injections of increasing doses over a considerable period. Naturally one suspects that the permanent and successful adaptation of a race or species in contrast to the adjustment of the individual cell or organism would require a much longer time. However, it is believed that the underlying biochemical mechanism of species adaptation must of necessity be basically similar to the mechanism of adjustment of an individual organism.

For the past three years our experiments have been concerned with species adaptation of small organisms to carcinogenic agents. The results have led us to the suggestion that a cancer cell is a normal cell that has been able to make a more or less successful adjustment to an unusual environment—successful only from the standpoint of the cell itself. The adjustment is, of course, a fatal one from the standpoint of the organism as a whole. The continuous exposure of several widely separated species (bacteria, paramecia and worms) to such agents has yielded very different results. Nevertheless, there has been a certain consistency to which we now wish to invite attention and which we believe gives us a little better insight into the process by which species gradually become adapted to specific environments.

It is believed that the experiments here described yield convincing evidence that an individual can readily withstand an environment which will ultimately kill the species, provided the exposure is continued over a sufficient number of successive generations. In other words an environment which has no visible or measurable deleterious effect on individual organisms at first and in fact may display a stimulating effect for a number of generations will nevertheless finally weaken and in some cases destroy the species, provided the exposure is continuous.

A. RESULTS WITH BACTERIA

In our first experiment[1] a strain of bacteria (*Eberthella typhi*) was treated continuously with methylcholanthrene (1 mgm in 10 cc of medium) for 240 consecutive daily transfers.

Besides an initial stimulation of cell-division rate, the only definite change noted was that the amount of visible growth in the culture tubes of the latter end of the series (two-hundredth to the two-hundred and fortieth) was considerably less than in the tubes of the first part of the series or of any of the tubes of the control series, as determined by the degree of turbidity. This suggested a gradual weakening of the strain of organisms, since all tubes contained the same amount of plain broth from the same batch. In further support of this, it was also observed that a much larger amount of inoculum from the latter tubes of the methylcholanthrene-treated series (two-hundredth to two-hundred and fortieth tubes) was needed in order to obtain a good growth and distribution of colonies on agar slants, although at the time of transplantation these latter cultures were not as old and had been incubated (37° C) for a less number of days than those of the first part of the series. At that time, the experiment was thought to have yielded essentially negative results and so was discontinued. In the light of subsequent observations on paramecia, however, it is believed now that a further weakening of the strain would have been apparent had the experiment been continued.

B. RESULTS WITH PARAMECIA

A strain of *Paramecium multimicronucleatum* has been exposed continuously to methylcholanthrene (1 mg per litre of medium) since May 8, 1939, to the present writing—January, 1942. Cultures have been transferred every ten days. For the first 20 to 30 transfers neither structural nor functional differences could be noted between the organisms in the control and in the methylcholanthrene-adapted series.

From the thirty-fifth to the forty-fifth transfer, however, a striking increase in the viability of the methylcholanthrene-treated organisms was apparent. The details of these tests have also been reported.[2]

Still later in the process of adaptation to methylcholanthrene (fiftieth to seventy-fifth transfer) the organisms displayed a further change in their behavior. At this time they had acquired the ability to reach population levels far higher than control organisms which at all periods throughout the more than 2-year adjustment period have displayed a fairly constant functional pattern as measured by our viability tests.[3]

The exposure of paramecia to methylcholanthrene has now reached the eightieth transfer and the organisms are displaying a loss of their former toughness and a decrease in their ability to reach high population levels. Repeated tests now indicate that they are far weaker than the corresponding unexposed control organisms. Structural changes have not been observed. The process of adjustment is being continued.

Paramecia exposed to the noncarcinogen but closely related polycyclic hydrocarbon phenanthrene in the same concentrations (1 mg per litre) multiplied for 3 transfers and the organisms were not apparently affected but the fourth transfer died. As a rule, we have found noncarcinogens more toxic than carcinogens. In our experience, untreated controls have always survived upon transfer and are as vigorous now on the ninetieth transfer as they were at first.

Paramecia were also exposed continuously to eosin in 10 separate series of dilutions graded from 1–1,000

[1] R. R. Spencer and M. B. Melroy, *Jour. Nat. Cancer Inst.*, 1: 129–134, 1940.

[2] *Idem, Jour. Nat. Cancer Inst.*, 1: 343–348, 1940.

[3] *Idem, Jour. Nat. Cancer Inst.*, 2: 185–191, 1941.

to 1–10,000. The organisms exposed to 1–10,000 eosin have grown and multiplied continuously for 85 ten-day transfers over a period of 2 years and 9 months. They have gradually become smaller in size than the control series, and this eosin-treated strain is slowly losing its vigor as measured by our viability tests referred to above. In fact, the organisms in the 1–1,000, 1–2,000 and 1–3,000 series thrived for 18 transfers, but it was not possible to make successful transfers afterward. Thus the strain was destroyed by long and continuous exposure to an environment which did not at first affect individuals in any measurable way.

C. Results with a Species of Worm

Confirmatory and perhaps more convincing results have been obtained with a small flat worm, *Stenostoma tenuicaudatum.* The methods and details of this experiment will be published later. This species was exposed continuously to methylcholanthrene, to phenanthrene and to the gamma rays of radium (33 mg). At the same time a continuous series of untreated control cultures were carried. Transfers were made every 14 days. Each transfer consisted of 12 worms. Population counts were made on the forty-fifth day after transplantation. The methylcholanthrene-treated worms maintained consistently higher population levels over a period of 30 transfers (March, 1940, to May, 1941). This series has now (January, 1942) been transferred 43 times. Since the thirtieth transfer the populations have sometimes been above and sometimes below the control. The adjustment process is being continued.

The phenanthrene-treated series of worms, however, thrived for eight transfers, reaching much higher levels than the controls on the sixth transfer. The worms in the ninth culture dish of this series died. To prove that there was no substance in this dish fatal to the worms, twelve untreated control worms were added to it. They multiplied readily.

The same phenomenon was manifested with a series of worm cultures irradiated continuously with 33 mg of radium. The worms thrived in the presence of radium for nine transfers. On the seventh transfer the population was higher than the corresponding control or that of any of the other treated series. In the eighth and ninth culture of the series, however, the number of worms was greatly reduced. For this reason, the amount of radium was reduced from 33 to 23 milligrams. From the tenth to the twenty-second culture the worms again grew well and the populations remained sometimes above and sometimes below those of the control series. After the twenty-second culture, the populations of each successive dish diminished. All died on the thirtieth transfer. Thus it seemed that radiations from radium which manifested no deleterious effects on the individual worms of the first eight transfers were able later to destroy the species at the thirtieth transfer, even though the intensity of the irradiation was decreased at the tenth transfer.

Discussion

It is believed that the above-outlined tests suggest the existence of a cumulative effect upon a species exposed *continuously* to an unusual environment covering many cell-division cycles or generations. These experiments have also suggested to us that an alternating or rhythmic rather than a continuous exposure of a species to a harsh environment may yield more interesting and perhaps more significant results—results that may shed further light on the basic principles of species adaptation. In fact, recently inaugurated experiments in which bacteria have been exposed to unfavorable agents already have shown that such organisms can resist and adapt to much harsher environments when the exposure is rhythmic than when it is continuous. It may be that a period of rest and recuperation is necessary to the successful adjustment of all living things regardless of whether we have in mind a species or an individual of the species. Rhythmicity is an almost universal phenomenon in nature, but not many biological experiments have been devised to study the effects of a rhythmic exposure to unfavorable conditions.

In this connection it is recalled that Magoon,[4] of the U. S. Bureau of Plant Industry, showed that, contrary to the commonly accepted idea that bacterial spores once formed have a fixed resistance, have in reality a resistance which varies with age and with the conditions under which the spores exist. He was able to demonstrate that bacterial spores of *B. mycoides* derived from heat-resistant survivors in thermal death time tests possessed higher resistance to heat than the original spores and by a process of selection, a strain of bacteria was obtained whose spores attained a resistance to heat at least 25 times that of the original spores. Magoon was interested in determining the heat necessary to destroy spore-bearing organisms in canned goods.

Armstrong,[5] of the U. S. Public Health Service, attempted to develop a vaccine virus that would keep at room or body temperatures. He exposed the virus to incubator temperature (37.5° C.) and by continued selection and propagation of the virus in the rabbit was able to develop a strain which showed an "increase of several hundred per cent. in the period of time during which it will withstand a temperature of 37.5° C. and still give typical skin takes on rabbits." A notable increase in the virulence of the virus for animals was also noted, and this feature deterred him from employing the strain in man.

[4] C. A. Magoon, *Jour. Inf. Dis.*, 38: 429–439, 1926.
[5] C. Armstrong, *Pub. Health Rep.*, 44: 1183–1191, 1929.

Neither Magoon nor Armstrong mentioned the principle of rhythmic exposure to an unfavorable environment as a possible factor of broad application in the study of the mechanism of species adaptation, although their technique involved this principle.

Huntington[6] is the only investigator of whom we are aware who has presented data and observations emphasizing the importance of an alternating environment. Huntington's thesis is that the highest human civilizations have arisen only in areas where there was an alternating climate. Continuously hot or continuously cold climates are enervating. A changeable climate is stimulating. A thorough search of the biological literature may reveal other examples that, in the light of our experiments, may now suggest the general biological importance of rhythmic exposure to unfavorable environments.

Summary

(1) Three widely separated species have been exposed *continuously* to carcinogenic and other agents over a considerable period of time and throughout many cell-division cycles.

(2) Evidence is presented to show that each of these species may be weakened and in some cases destroyed when exposed to amounts of these unfavorable agents which have no measurable deleterious effect on individual organisms, but which may in some cases at first be stimulating. The biological generalization that certain environments may be ontogenetically harmless but phylogenetically lethal is suggested.

(3) Preliminary tests suggest also that a *rhythmic* rather than a *continuous* exposure of a species to harsh environments may be a very useful technic to employ in the study of the mechanism of species adaptation.

OBITUARY

SIR WILLIAM BRAGG

On Thursday, March 12, in the passing of Sir William Bragg, death robbed physics of one of its most illustrious ornaments and all science of one of its best loved friends.

In an age when so much of discovery falls to the lot of youth, it is a comfort to ponder the cases in history which stand as proof that middle age does not always spell the death of originality and that maturity provides its own special seasoning in the realms of discovery, a seasoning which science would miss greatly were it deprived of it. Sir William Bragg stands as an example of rich development in years in which the prime of youth has passed; for though, naturally, he was a successful student and an eminently successful teacher, it was not until eighteen years after his departure from Cambridge to accept the professorship of mathematics and physics at the University of Adelaide that he published his first paper when he was more than 40 years old. It is very evident, however, that in the years which had preceded, there had been a great strengthening of mental forces to the point of readiness for service when once released in the search for new truth, for within three years of his first publication he had become a fellow of the Royal Society, and from that time onwards he was a continual contributor to the journals of science.

Bragg's first paper on the range and ionization of alpha particles is one of the fundamental stepping-stones in the science of radioactivity, and he continued to contribute richly to that field, partly in collaboration with Kleeman. In 1908 he returned to England as professor of physics at the University of Leeds, and it was not long before he became interested in x-ray research, coming into that field at a time when, with the principles of the quantum theory knocking at the doors of science, conventional electromagnetic views as to the behavior of nature held powerful sway in the halls of learning. Bragg was a strong advocate of the particle nature of x-rays and, while none can doubt the broadness of his concepts of the nature of what was then termed a particle, his natural desire for simplicity of expression caused his writings to take a form which invited considerable controversy with the extreme opposed school, represented prominently at the time by C. G. Barkla, who desired to retain classical electrodynamics in as pure a form as possible. It is characteristic of Bragg's broadness of view and his adaptability to changing pictures that, following von Laue's fundamental discovery in x-ray diffraction, he entered that field with enthusiasm and, in collaboration with his son, William Lawrence Bragg, became the most prominent worker in the field which established the science of x-ray spectroscopy. He was at Leeds when the war of 1914–18 broke out, but he became professor of physics at University College, London, in 1915. Most of his time during the war was devoted to government work and he became director of the Royal Institution and the Davy-Faraday Research Laboratory in 1923. In this position his powers reached their maximum field of usefulness. Endowed with all the personal charm so essential to the office, he was a worthy successor to Faraday, not only as a fruitful investigator, but also as an inspiring speaker possessed of a gift for lucidity which made his lectures a joy, both to the man of science and to the layman.

[6] Ellsworth Huntington, "Civilization and Climate." Yale University Press, 1922.