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Read by Clayton Rous,  
1946, who had  
nothing to say.

## The Nature and Causes of Cancer

By Linus Pauling

During the life of <sup>an organism</sup> there occurs continuously the process of synthesis of molecules, simple and complex. The nature of the molecules <sup>that</sup> which are synthesized is determined by the nature of the environment in which the synthesis takes place - by the genes, enzymes, cytoplasmic substances, cellular constituents in general. A striking illustration of the effect of change in environment (presence of molecules of antigen) is the production of specific antibodies, which are presumably formed with the power of combining with the antigen as the result of the tendency of a system to assume the configuration of minimum energy, which in this case is a configuration of the globulin molecule

<sup>that</sup>  
~~which~~ has the greatest degree of complementarity  
 to the surface <sup>structure</sup> of the antigen molecule.

Let us consider the normal life history of an organism. The fertilized egg carries out the process of early development and the first cell division in the way determined by the molecular structure - the genes, cytoplasmic constituents, molecular framework - of the fertilized egg. These cells continue to divide, to differentiate; and the organism develops, reaches maturity, and ultimately dies - all in the way determined by the molecular structure of the fertilized egg, with whatever variations ~~are~~ are produced by interaction with a varying environment.

One way to change the nature of an organism is to change the configuration of one of the important molecules in the fertilized egg; in particular, of one of

Glycocalyx  
 proteins,  
 Antigenic  
 reactivity

What  
 stage?..

the genes; that is, to produce a mutant.

~~A~~ <sup>of this sort, a</sup> change,  $\lambda$  mutation, can be made to occur by irradiation with x-rays or ultraviolet light, <sup>or neutrons,</sup> by treatment with antibodies, <sup>?</sup> by ~~change in temperature, or~~  $\lambda$  by treatment with chemical substances.

~~heat?~~ ~~such as aromatic hydrocarbons~~ Mutations also occur spontaneously, perhaps usually in response to cosmic radiation.

A striking aspect of normal growth is the control of the growth of differentiated cells of different sorts. The different parts of an organism normally develop to a certain extent, <sup>which is</sup> essentially the same in different individuals of the same strain. Biologists have not found it easy to propose a simple mechanism by which this control of growth could be achieved; and it is ~~is~~ ~~hard~~ hard to imagine ~~a~~ satisfactory ~~how~~ how this is done.

?

In general, indeed, we might expect that ~~with~~  
~~changing conditions~~  
 during the sequence of changes representing  
 the development of an organism conditions  
 would at some stage be such as greatly  
 to favor the growth of cells of one sort at  
 the expense of those of other sorts, and that  
 in consequence these cells would proliferate  
 wildly — and presumably lead to the death  
 of the individual. I believe that a very great  
 part of the process of the origin and  
 evolution of living plants and animals  
 has been the selection of just those  
 molecular ~~structures~~ complexes (for the  
 fertilized egg) <sup>that</sup> which lead to <sup>what we may call</sup> ~~the~~ normal  
 differentiation and growth, and which that

?

manage to avoid the uncontrolled preferential  
catachismic growth of one class of differentiated  
cells.

We are now ready to discuss the nature  
and causes of cancer.

Our postulates are:

1. Cancer is the uncontrolled proliferation  
of differentiated cells of one type at the expense of <sup>those of</sup> other  
types.

2. The molecular constitution of an organism  
which leads to controlled ("normal") development  
and function is not a likely one, but an unlikely  
one; and random changes are expected to  
destroy the control.

Cancer cells  
have not gained  
more power -  
rather lost  
control.

3. In the development of species of organisms natural selection has operated to eliminate molecular constitutions with lethal factors, and in particular those which lead to cancerous growths before reproduction occurs.

From these postulates we make the following deductions:

1. Cancer might occur as a part of the normal course of life of an individual with a certain genetic constitution. A native pure strain produced under natural conditions of competition would not, however, be expected to have a normal history of cancer which would place it at a <sup>competitive</sup> disadvantage. On the other hand, if conditions are changed artificially in such a way as to increase the normal span of life, the regular development of cancer during the added life period might occur as the normal consequence of the genetic constitution of the pure strain.

A hybrid of two native pure strains would have a considerable chance of having such a genetic

constitution which would permit the regular development of cancer at some stage in the development of the organism.

2. The introduction of a virus molecule (a vagrant gene) in a cell might so change the molecular constitution of the organism as to lead to the development of a cancer (Rous sarcoma, Shope rabbit papilloma).

✓

2 Fish  
Pardon  
Puppy + squirrel  
Macromolecules  
get out of control

3. A determinative molecule in a cell (a gene or plasmagene) might be so changed in configuration by thermal agitation, by irradiation with x-rays, ultraviolet light, neutrons, or other waves or particles, or by some chemical substance as to cause a changed course of development, leading to cancer, which can be described as due to spontaneous or induced somatic mutation.

Native strains would presumably be selected so that the probability of cancer from somatic mutation under normal conditions would be small. Our postulates lead to the deduction that this probability would be greater for hybrids.

4. A foreign substance present <sup>in sufficient amount</sup> in the cells during a period of time which would permit a cancer to develop, or a normal cell constituent present in an abnormal quantity, might so influence the process of growth as to lead to cancer. This effect might occur, for example, by the inhibition by the substance of the normal mechanism of control.

Substances with this effect might be due to parasitic infection, or to ~~the~~ long-continued inflammation.