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The Dynamics of Life, V. Applying the Steady-State Theory of Mutations to Human Cancer

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ABSTRACT **In papers I, II, and III of this series the steady-state theory of mutations was developed and applied to the extensive data on the effect of radiation on beagles acquired here during the past twenty years. In this paper the theory is used to interpret H. B. Dorn's data on the incidence of 21 kinds of cancer in both male and female Americans. The theory shows the nature of the heterogeneity in the population of various disorders. The agreement found confirms the steady-state theory of mutations in an interesting way.**

In paper II of this series (1) we developed the steady-state theory of mutations. The theory is based on the idea that n chromosome sites are subject to alteration at a rate ν_i per site, which may then lead to a mutation, and that each damaged site, r, is repaired, or disappears, at a rate ν_j. Then, assuming a steady state, this leads to the probability

$$q = \frac{r}{n} = \frac{1}{1 + \nu_j/\nu_i} \tag{1}$$

that a site will be damaged and to the probability

$$p = \frac{1}{1 + \nu_i/\nu_j} \tag{2}$$

that a site is undamaged. Using absolute rate theory we have

$$\nu_i = \frac{\kappa kT}{h} \exp\left[-\Delta G\dagger_{oi}/RT + \sum \ln c_i\right] \tag{3}$$

with an analogous expression for ν_j. The concentration of a substance c_i used in a reaction may be supposed to be varying with time according to the relation

$$-dc_i/dt = k_i c_i \tag{4a}$$

or

$$\ln c_i = -k_i t + \ln c_{oi}. \tag{4b}$$

Eq. **4a** is treated as first order, but not necessarily unimolecular. Introducing the Eq. **3** and **4b** into Eq. **2** with the analogous expression for ν_j leads to

$$p = \frac{1}{1 + e^{-k'(\tau - t)}} \tag{5}$$

where

$$k' = \left(\sum_j k_j - \sum_i k_i\right) \tag{6}$$

and

$$k'\tau = \left[(\Delta G\dagger_{oi} - \Delta G\dagger_{oj})/RT - \sum_i \ln c_{oi} + \sum_j \ln c_{oj}\right]. \tag{7}$$

There is a change in notation from that of ref. 1, in which k' replaces b and $k'\tau$ replaces a. Differentiation of p leads to the expression

$$-(dp/dt) = k'pq. \tag{8}$$

Now we suppose the probability of survival, S, is such that

$$-(dS/dt) = \nu pq, \tag{9}$$

where ν is the frequency of cell division and p is the chance that a site is intact, while q is the chance that the neighboring site is modified. This leads us to the equality

$$S = p = \frac{1}{1 - e^{-k'(\tau - t)}}, \tag{10}$$

since S and p should have the same limits of one and zero.

APPLICATION OF THE THEORY TO COMPLEX POPULATIONS

If the concentration of a reactive molecule, c_i, is proportional to the concentration, g_i, of the gene that makes it, **4a** may only be true because the genes are being used up according to the equation

$$-\frac{dg_i}{dt} = k_i g_i. \tag{11}$$

A cause of the degenerative diseases of aging is then to be traced to the drop in concentration of these auxiliary genes in the aging cells.

Since survival S is in fact due to the product from all causes (2),

$$S = \prod_i p_i \equiv \prod_i S_i \tag{12}$$

and

$$-\frac{dS}{dt} = -\sum_j \left(\frac{dS}{dt}\right)_j = -\sum_j \frac{dS_j}{dt} \prod_{i \neq 1} S_i. \tag{13}$$

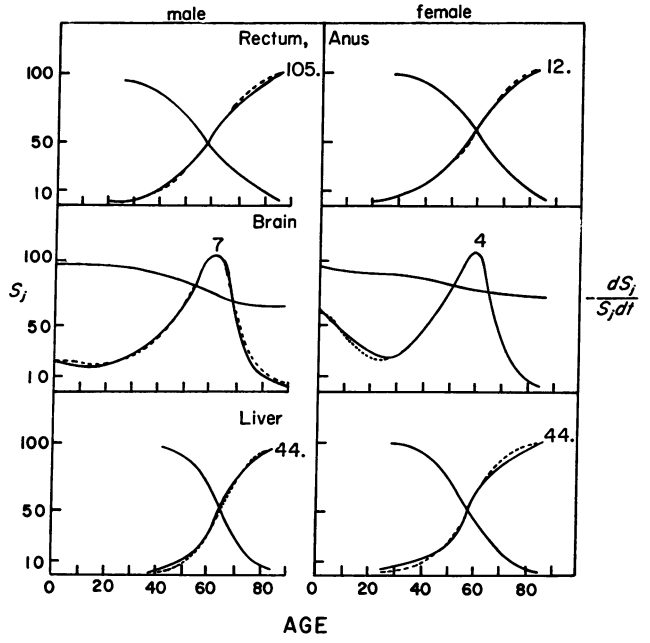

FIG. 1. The full-line curve starting at 100 is the postulated survival curve, S_j. The derivative of S_j divided by the corresponding ordinate gives the broken curve, which is superimposed on Dorn's curve for the number of cases of cancer occurring per 100,000 population at the age indicated by the abscissa. The agreement is good. The scale for each Dorn curve is determined by the number of cases of that cancer and is given on each curve.

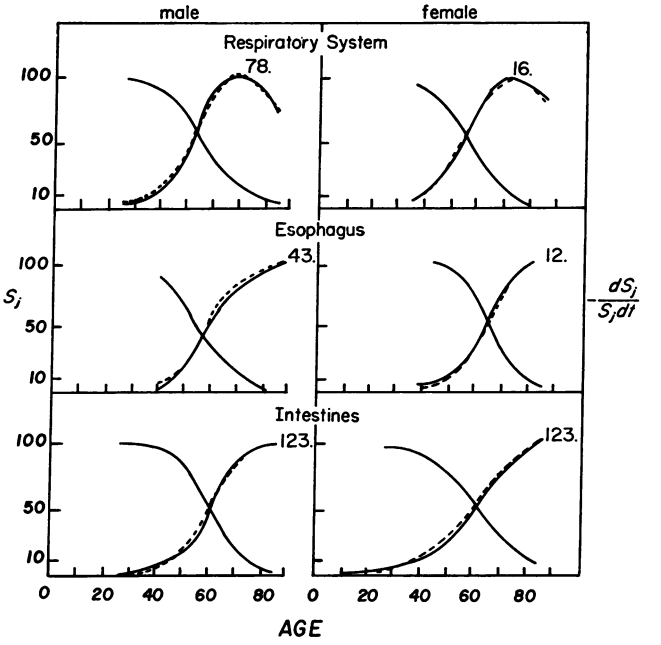

FIG. 2. Same as for Fig. 1.

The rate of succumbing to the jth cause is then

$$\left(\frac{dS}{dt}\right)_j = \frac{dS_j}{dt} \prod_{i \neq 1} S_i. \tag{14}$$

The term $-dS_j/dt$ is the ideal or limiting case for rate of decrease in survival resulting from the jth cause. It would be observed if only the jth cause were effective. In Eq. 14, $(dS/dt)_j$ is the observed effect of the jth cause when one or more other causes are operative.

In these considerations t should be identified with the age of the individual. Thus if one wants an expression for the rate of death from the jth kind of cancer per 100,000 population at some age, t, the appropriate expression is

$$-\frac{1}{S}\left(\frac{dS}{dt}\right)_j = \left[-(1/\prod_i S_i)\left(\frac{dS_j}{dt}\prod_{i \neq j} S_i\right)\right] = -\frac{dS_j}{S_j dt}. \tag{15}$$

Now if the population is complex with respect to the disorder j, we can write

$$S_j = \sum_i c_i S_i, \tag{16}$$

where

$$\sum_i c_i = 1 \tag{17}$$

and

$$S_j = \sum_i c_i [1 + \exp -k'_i(\tau_i - t)]^{-1}. \tag{18}$$

It is informative to apply our theory to Dorns' data (3) on death rates per 100,000 at age t from 21 different kinds of cancer for both men and women. The statistics are for the years 1937–1939 for the white population of the United States. Representative curves are given in Figs. 1 and 2. The rest of the 42 curves, not shown, fit the data equally well. The dotted curves are obtained from the S_j curves by dividing the time derivative of the latter by the corresponding ordinate, as theory requires. The parameters τ and k' are treated as constants, but in fact must be effective time-averages. τ is the age when half of a homogeneous population has succumbed and k' is four times the absolute slope of the survival curve for the homogeneous population at $t = \tau$. For many of the kinds of cancer, human populations break up into groups with quite different ages of half survival, τ, and rate of using up reserves k'. The half-survival time, τ, may conveniently be thought of as a reserve which protects against the onslaught of the particular disorder. How well the cell is engineered against the ravages of time and various aging agents is undoubtedly in part a matter of the gene composition of the individual cells. If in the chromosomes one has more than one gene which can supply a critical need, loss of one or more of these genes through damaging mutations may lessen the individual's vitality without immediate death and appear as a degenerative disease of aging.

Table 1 shows that individuals fall into at least four classes with respect to how well they are engineered to avoid cancer of the brain and there are at least three such categories with respect to cancer of the kidneys. These are presumably associated with differences in the gene makeup of individuals. τ values for very short lives or very long lives are not very accurately deter-

TABLE 1. *Parameters for cancer fits*

Type	τ_1 (yr)	k'_1 (yr)$^{-1}$	c_1	τ_2 (yr)	k'_2 (yr)$^{-1}$	c_2	τ_3 (yr)	k'_3 (yr)$^{-1}$	c_3	c_4
Pancreas (M)	60	0.1833	0.95	80	0.1250	0.05				
Pancreas (F)	58	0.185	1							
Kidney (M)	1	0.3	0.25	49	0.183	0.746	90	0.167	0.004	
Kidney (F)	0.5	0.6	0.0265	65	0.131	0.53	110	0.0091	0.4435	
Bladder (M)	66	0.121	1							
Bladder (F)	64	0.125	1							
Larynx (M)	55	0.146	0.994	100	0.150	0.006				
Larynx (F)	85	0.0706	1							
Mouth (M)	65	0.131	1							
Mouth (F)	100	0.06	1							
Stomach (M)	58	0.172	1							
Stomach (F)	70	0.107	1							
Urinary system (M)	0.5	0.20	0.05	64	0.109	0.95				
Urinary system (F)	70	0.129	0.70	115	0.0087	0.30				
Skin (M)	80	0.081	1							
Skin (F)	67	0.119	1							
Buccal cavity (M)	66	0.106	1							
Buccal cavity (F)	75	0.073	1							
Digestive system (M)	60.5	0.14	1							
Digestive system (F)	63	0.11	1							
Lip (M)	65	0.093	1							
Lip (F)	85	0.071	1							
Tongue (M)	68	0.096	1							
Tongue (F)	80	0.063	1							
Genital system (M)	69	0.174	1							
Genital system (F)	46	0.152	0.099	100	0.12	0.001				
Respiratory system (M)	55	0.146	0.95	85	0.0824	0.005				
Respiratory system (F)	55	0.146	0.985	92	0.109	0.015				
Esophagus (M)	58	0.172	1							
Esophagus (F)	64	0.172	1							
Intestines (M)	61	0.164	1							
Intestines (F)	62	0.113	1							
Rectum (M)	60	0.133	1							
Rectum (F)	61	0.115	1							
Brain (M)	0.5	0.15	0.07	38	0.11	0.15	58	0.19	0.20	0.58
Brain (F)	0.05	0.155	0.115	40.5	0.12	0.08	57	0.19	0.11	0.695
Liver (M)	62	0.177	1							
Liver (F)	57	0.158	1							
Bone (M)	5.0	0.06	0.4	60	0.16	0.6				
Bone (F)	5.0	0.06	0.5	59	0.136	0.5				
Lung, bronchus (M)	50	0.16	0.997	90	0.111	0.003				
Lung, bronchus (F)	52	0.154	0.995	95	0.105	0.005				

mined by the experimental data. τ values still have meaning up to 9 months, since the fetus can die.

The linear plot of logarithm of radiation dose against age at $S = 1/2$ for beagles injected with ^{226}Ra shown in paper I (ref. 4), Fig. 7 shows a clear break at intermediate doses. Points for the groups of dogs at the three higher dose levels, at which the incidence of bone cancer induced by ^{226}Ra is high, fall on one line. Points for groups of dogs at the three lower dose levels do not fall on this line, and these dogs experience little life-shortening, decreased incidence of bone cancer, and increased incidence of the diseases of old age. Clearly, any simple interpretation of a proportionality of bone cancer to radiation dose is erroneous in this case.

Since radiation causes its damage through the free radicals H, OH, and hydrated electrons, any getters such as cysteine, thiamine, and related sulfur and selenium compounds protect against radiation-induced mutations. They may also be expected to protect against the mutations induced by ordinary metabolism and so slow down all the degenerative diseases of aging.

The steady-state theory of mutation interprets the waves in $-d \ln S_j/dt$ against age as clear evidence of heterogeneity in human inheritance with respect to protective reserves against the particular disorder j and strengthens such conjectures resting on different grounds.

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