Williams[4], aware of the need for such a counteracting factor, has proposed that the mechanism resides in the effects of pleiotropic genes, the favourable effects of which early in life outweigh in selective value the harmful effects they have later on. The age at which such harmful effects are permitted would be determined by the incidence of adult mortality. For example, birds can fly, and are thus less liable to predation than other homeotherms of similar size; their mortality rate is lower, and consequently senescence occurs at a later age.

Whether or not the appeal to pleiotropy is compelling, we attach importance to the rest of Williams's argument which, with slight modification of emphasis, can be stated in the following form: specific longevity is determined by (1) natural selection tending to prolong it and (2) the sum of all environmental hazards tending to curtail it.

As Medawar has pointed out, senescence results from: (1) extrinsic causes, including mechanical wear, and (2) intrinsic causes, which are genetically built in. Even in the absence of intrinsic senescence, there must be a period of time beyond which survival is improbable, because of chances of accidental death by predation, starvation, desiccation and so on, added to the effects of extrinsically caused senescence. We call these combined effects the hazard factor, which clearly varies in intensity between species. For potentially immortal elephants the hazard factor is probably far lower than that for potentially immortal fruit flies. If the hazard factor thus sets a limit to longevity even in a population of potentially immortal individuals, then late acting harmful genes can accumulate and intrinsic senescence can develop. In a real population, where intrinsic senescence has been established, observable specific longevity is determined by three components: (i) random accident, (ii) environmentally caused extrinsic senescence and (iii) intrinsic senescence. The hazard factor (which is a function of components (i) and (ii)) would, if acting alone, permit a greater specific longevity than exists in any population showing intrinsic senescence. The hazard factor prevents prolongation of life while any species remains in a particular niche (*sensu lato*). Should the niche change, or the species evolve (presumably both would occur simultaneously), then of course the hazard factor may change in such a way as to determine a longer or shorter specific longevity.

The hypothesis requires that it should be possible to prolong the life span of a species by breeding it in an environment where the hazard factor is lower than normal. Such an experiment would be difficult to carry out, because genetically controlled senescence, already present in a population, would limit the extent to which environmental improvement could immediately extend specific longevity.

A quicker answer might be obtained by the reverse procedure—in which the experimenter would impose an additional severe hazard by decreasing the normal life span for several generations. Then, according to the hypothesis, the subsequent life span of the experimental population should be shorter than that of a control population when both are tested in the environment of the control population. *Drosophila* would be a suitable experimental animal. In the simplest form of the experiment, all adults would be removed from the population after (say) 7 days of egg laying, only the eggs which they had by then laid being used to continue the population, the process being repeated for fifty or so generations. In this way, the "unlived" portion of the normal life span would not be exposed to differential selection, so that random mutations and gene interactions applicable to that period would be allowed to accumulate. Comparison of the life span of the resulting population with that of another, where adults had been left to breed and die normally, might provide an indication of the validity of the hypothesis.

Comfort[1] urges the need for research to decide whether or not there exists a single "leading process" as the cause of mammalian senescence. If the hazard factor hypothesis is valid, differences in specific longevity in different species are seen primarily as phenomena with ecological aetiology, and the existence of a single "general" cause of senescence seems unlikely.

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Effect of Neomycin on an Inhibitor of Spontaneous Tumours in Mice

I have already discussed the effect of liver extracts on the biological characteristics of spontaneous tumours in C3H/St mice. These effects were obtained by exposing the offspring of a tumour-bearing mother to a parenteral injection of a specially prepared liver extract. In other words, the extract was injected into a pregnant mouse and the ensuing offspring did not develop spontaneous tumours of mammary gland origin (adenocarcinoma) for several months; this is a striking effect on the characteristics of cancer[2].

I have emphasized[2] that two commonly accepted mechanisms are involved in experimental cancer. These are: (1) a mechanism involving an initiator or promotor for the origin of cancer, and (2) a mechanism for the continuation or survival of the tumour. In the case of the well known mammary gland tumours in mice, the presence of the milk factor or virus of Bittner is certainly important[1].

I have now found that spontaneous tumours occur in the offspring at ages comparable with those of the controls, and so mechanism (1) for the origin of cancer may not be affected by the treatment of the tumour-bearing pregnant females with liver extracts. But the continuation of the neoplastic condition is affected (growth rate and retrogressive changes) and therefore mechanism (2) involved in the continuation of neoplasia, may be involved as a result of the experimental procedure of injecting liver extract into a pregnant mouse.

Many tumours undergoing retrogressive changes become extremely soft, even though the liver extract is always injected peritoneally at sites remote from the neoplastic growth, which is always subcutaneous. Large areas filled with liquefied material develop in the tumours. These foci sometimes coalesce to form enormous cysts which can be drained by a hypodermic needle. Cultures of newly formed liquefied areas are sterile (according to tests carried out by Dr Phillips Gausewitz of the Scripps Memorial Hospital, La Jolla, California); but many of these soft areas become secondarily infected with the common bacteria usually found in a mouse colony, especially if a break occurs in the skin. In many cases the death of the tumour-bearing mouse is obviously affected by the presence of these infective organisms.

In an attempt to control the secondary infections in retrogressing cancerous tissue, perhaps only partially, and thus prolong the life of a tumour-bearing animal, I have investigated the effects of several antibiotics. I report here the effects of neomycin, given in drinking

water, on a tumour-bearing mouse that was receiving liver extracts.

Neomycin was given at the rate of 12 mg/kg body weight/day. As in previous investigations of the effect of the inhibitor on neoplastic growth[2,3], the liver extract was administered peritoneally. The preparation of the liver extracts has already been described[2,3]. Essentially, the extract is an alcohol soluble (80 and 100 per cent) moiety obtained by exposing the ground liver of several species (mouse, South African rat, cattle and horn shark) to alcohol. The lyophilized material is taken up in distilled water and refrigerated while not in use. Before use the extracts are warmed to room temperature to avoid the spasms associated with the injection of refrigerated materials. A small quantity of thymol is added to the extracts as a preservative, and the liver extracts in distilled water are pasteurized at 56° C for 30 min before being stored in sealed serum bottles.

A total of 334 C3H/St mice bearing spontaneous tumours (adenocarcinomata of mammary gland origin) was used. They were divided into four groups as follows: (1) sixty-three controls; (2) twelve given neomycin alone; (3) thirty-six given neomycin and inhibitor; (4) 223 given inhibitor alone. Results are presented in Fig. 1 which shows that there are obviously only two patterns of growth rate for spontaneous tumours in mice of the four groups. These data are based on successive increments of growth per unit of time. This means that all curves start at zero because the initial size of a tumour is always deducted from successive sizes in order to compute the increments of growth. The patterns are: (1) a single curve (solid line with dots) which was obtained from the effect of the liver inhibitor on the growth of the neoplasm and (2) a composite group of three curves made up of (*a*) the controls (solid line with triangles); (*b*) neomycin alone (short dashes); and (*c*) neomycin and the liver inhibitor (long dashes).

Obviously there is no difference between the growth rates of spontaneous tumours obtained in mice of one or the other class in group (2) (Fig. 1). The rate of growth of spontaneous tumours treated with liver inhibitor is considerably suppressed compared with any of the three classes in group (2).

Neomycin given in drinking water to a tumour-bearing mouse had no effect on the rate of growth of the spontaneous tumour (Fig. 1). Periodic injection of liver extract (three times a week) inhibits the growth of a spontaneous tumour of mammary gland origin in mice (Fig. 1). Finally, the administration of neomycin in the drinking water of a tumour-bearing mouse apparently "inactivated" the tumour inhibitor which had been administered peritoneally (Fig. 1).

Inactivation of an inhibitor of spontaneous tumours in mice is well documented, but considerably more research is needed before an explanation can be given. It is questionable whether neomycin could control completely the secondary infections of a spontaneous growth, for it exerts its antibiotic effect in the gut. It is possible that not all the biological effects of this drug are known. Furthermore, the nature of the inhibitor is far from clear. The term "liver extract" is not specific in view of the innumerable components in the liver and the variety of methods available for extraction. Other differences between liver extracts, which are associated with the species of animal used, age and so on, may be involved (my unpublished results). For example, extract of male liver is more inhibitory to spontaneous tumours than extract of female liver. It is also important to remember that the effectiveness of the inhibitor has been reported to change while the liver extract is being stored in distilled water under refrigeration[3]. Some of these changes seem to be cyclical; their meaning is unclear, although because the materials in the water form an emulsion or emulsoid, some of the changes may be associated with the aggregation of particles.

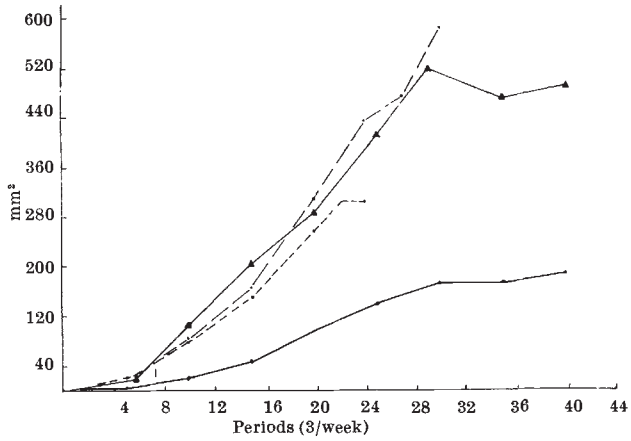

Fig. 1. Growth rates of spontaneous tumours (adenocarcinomata of mammary gland origin) in C3H/St mice expressed as increments in successive periods of time (three observations a week) expressed on the base line. ▲, Controls (sixty-three mice); - - -, mice treated with neomycin alone (twelve mice); — — —, mice treated with neomycin and the inhibitor (thirty mice); —●—, mice receiving the inhibitor alone (two hundred and twenty-three mice). Sizes of tumours are expressed on the vertical line; these were computed as the multiplication of the two longest diameter of the tumours.

Perhaps the use of neomycin will make it possible to reach an understanding of the nature of the tumour inhibitor which has been found in liver extracts.

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Role of Leucocidin and Triphosphoinositide in the Control of Potassium Permeability

LEUCOCIDIN is a product of *Staphylococcus*, consists of two proteins and is toxic to the polymorphonuclear leucocytes of rabbit and man. The study of the response of leucocytes to leucocidin has led to the unexpected finding that the changes that occur mimic those in excitable or secreting cells during membrane depolarization or stimulation by hormones[1]. Thus the permeability to cations but not other small molecules increases, protein in the cytoplasmic particles is secreted and calcium is accumulated in vesicles. It is probable that the primary response to leucocidin is the increased permeability to cations[1]. The changes in membrane structure that precede the altered cation permeability during membrane depolarization are unknown and the mode of action of leucocidin may be relevant. The study of the interaction of leucocidin with the isolated leucocyte membrane and with purified phospholipids led us to suggest that the primary action of leucocidin is to change the conformation of triphosphoinositide in the leucocyte surface membrane. This communication provides confirmatory evidence for this hypothesis.

The triphosphoinositide content of the leucocyte (32 mμmoles/g wet weight of packed cells) is about twelve times less than that of brain[3] although expressed as a molar fraction of the phospholipid, the triphosphoinositide