Reports

Biological Equilibrium and the Origin of Cancer

Many biological variations that have occurred in a rather extensive series of experiments dealing with maternal age and characteristics of the offspring are quite unpredictable and, at least, partially unexplainable. These characteristics have involved susceptibility to various types of chemically induced neoplasias (*1–3*) as well as characteristics of a biological or physiological nature, such as age of first litters, litter spacings, litter sizes, and so forth.

The first unusual variation that occurred was the appearance of chemically induced neoplasias (methylcholanthrene was used) in mice of the Br descent at earlier and earlier latent periods in spite of the fact that a continuous selection toward resistance to tumors had been employed. The phenomenon of variation taking place counter to the trend of genetic selection was later verified in the 2NHO descent (*1*). "In this series a total of 3247 mice of the 2NHO descent have been injected subcutaneously with one milligram of methylcholanthrene at sixty days of age. The mice belonged to the F_1–F_{20} generations. A selection toward resistance to all chemically induced tumors was constantly employed. Fibrosarcoma at the site of the carcinogen and lung adenomas appeared to respond to selection between F_1–F_4. However, beginning with F_5 there was a reversal of susceptibility to these two tumors in spite of selection toward greater resistance. Adenomatous lesions near the pylorus and papillomas of the forestomach appeared in mice only during the intermediate generations F_3–F_{14}. Following a period of delayed latency for the appearance of fibrosarcomas as a result of selection toward resistance to such tumors, there was a progressively earlier appearance of such tumors counter to the trend of selection providing methylcholanthrene had been injected into both parents over many generations. This phenomenon of reversed susceptibility to induced tumors has occurred in *all* selected lines and must be considered the rule."

Another unexpected observation was that the latent period for the appearance of any specific type of tumor could not be increased by genetic selection toward resistance to chemically induced tumors; what actually occurred as a result of this method of selection was that one type of tumor was replaced by another histologically different tumor with a longer latent period (*2*). This study also led to the observation that, between the F_4 and the F_{20} generations of the pBr descent, the sum total of chemically induced tumors (percentage incidence) did not change—there was merely a shift in the histological types of tumors. The conclusion was reached that "in the genetic mechanisms involved in cancer, perhaps one or more factors control the origin of specific types of tumors, whereas another mechanism may be involved in the origin of the total number of tumors (all tumors at all sites taken together)."

Selection toward an earlier and earlier litter seriation descent (early maternal age) has also produced variation in the opposite direction of all specific types of tumors investigated: (i) squamous cell carcinoma of the skin, (ii) adenocarcinoma of the lungs, (iii) fibrosarcoma, (iv) adenocarcinoma of the mammary gland, (v) mixed tumors, and (vi) rarer tumor types at other sites (*3*).

The same phenomenon that variations sometimes take place counter to the trend of genetic selection has occurred several times in a polydactylous descent that was started in the F_1 generation of a cross between mice and the C_{57} blacks and the Brpb descent and has continued, up to the present time, to the F_{17} generation.

In this experiment (*4*), six separate descents have been continued. The selection has been based exclusively on maternal age—that is, the time at which the offspring were born. The classes are (i) less than 100 days, (ii) 101 to 200 days, (iii) 201 to 300 days, (iv) 301 to 400 days, (v) 401 to 500 days, and (vi) 501 to 600 days; each generation has been made up of at least 30 breeding brothers-to-sisters. One of the ideas behind this investigation was to determine the maximal variation possible by brother-to-sister matings beginning with the F_1 generation (high heterozygosity) and continuing until a high degree of homozygosity had been reached. Eventually the process of selection, now based on maternal age exclusively, will be reversed in order to determine whether any divergence in the present six independent descents is permanent or only of a temporary nature. Reversed selection is not indicated, however, until proof that biologic equilibrium for any character has been obtained.

The average ages for the production of first litters for the six "maternal-age" descents between F_1 and F_{17} have been in sequence 82.1, 73.9, 72.2, 68.8, 64.7, and 51.5 days. This again is variation counter to the trend of selection, the youngest maternal-age descent having their first litters later than females in the other older maternal-age descents.

The average litter spacings between the first and eighth litters (both sexes being kept together in all cases) have been in the six maternal-age descents, 28.5, 27.7, 27.7, 26.8, 27.0, and 24.4 days. This is a regression (straight line) curve, although with small slope counter to the trend of selection.

The average litter spacings for the same six maternal-age descents in sequence between the eighth and 14th litters have been 22.7, 23.9, 24.3, 25.1, 24.1, and 30.6 days.

Thus mice of the earliest maternal-age descent (less than 100 days) have their first litters later than do females of the other maternal-age descents; they have the poorest litter-spacings value in the early litters, but they improve in this characteristic between the eighth and 14th litters more than do females of the other four maternal-age descents. Mice of all separate maternal-age descents have their 14th litters at approximately the same age. In sequence, the average ages of mice for the birth of 14th litters were (i) 412.7 days, (ii) 411.7 days, (iii) 412.1 days, (iv) 408.3 days, and (v) 403.0 days.

The litter size of mice again demonstrates a compensatory mechanism. In the F_2 generation, the average litter size increased in all six maternal-age descents up to a maximal value in the fifth litter and then decreased until the lowest value was obtained in the last litter born to any female (in the 20th litter in the F_2 generation).

The descendants that are selected in

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an early litter (that is, at an early maternal age) descent when the litter size is maximal have smaller litters than do the females that were taken from a late litter (or late maternal age) descent where the litter size had been minimal. Here again is evidence of a compensatory mechanism influencing litter size.

It is clear by the evidence now available that the characteristics of the offspring occurring in the maternal-age descents in the middle of the age distribution do not significantly change between the F_1 and F_{10} generations—it is only the offspring of the two extreme maternal-age classes which deviate, and this deviation is counter to the trend of maternal-age selection.

The obvious reason for such compensatory changes as those enumerated in the preceding pargraphs is to keep the species in equilibrium. If there were no such compensatory mechanism, it would be relatively easy for a species to drift into chaos. This would necessarily be so for any character that may be partially influenced by parental age and other factors. If the practice were continued for many generations for females to have their first child (or litter) earlier and earlier, irreparable damage to the species might be the result. Similarly, the practice of bearing young long after the normal reproductive period has been exceeded might also produce disastrous results.

The present experiment indicates quite convincingly that, unless the insult has not been too great for too many generations, a compensatory mechanism corrects for a deviation from the norm, and this variation takes place counter to the trend of selection.

In genetics there is a concept that a species is in equilibrium until a mutation occurs "to upset the applecart," after which a new equilibrium is established by incorporating into, or by discarding from descent, the new mutation. We no longer have to make the assumption that the species is in equilibrium (homeostasis). There is evidence, such as the present data, to prove that a mechanism actually exists. The nature of this mechanism is still in doubt, and we do not know how to influence it.

It is not my intention to review the literature dealing with equilibrium or homeostasis. To me it is not clear whether biological or genetic equilibrium is involved. To some investigators these two phenomena may be absolutely dependent on each other. This may be true, but certainly more data are needed for final analysis. The field of genetic homeostasis has recently been covered by Lerner (*5*).

Since so many types of biological characteristics, such as age of first litters, litter spacing, litter size, and various types of tumors, are kept in equilibrium, this mechanism must be of extreme biological importance. A species could probably not be kept in equilibrium unless the individuals who make up the species are also in equilibrium at least during the reproductive period.

The various types of cancers which arise in the mammalian body have, at least, one characteristic in common. Cancer arises because the organism has lost control of a definitive part. Perhaps during the aging process the mechanism that keeps the individual in equilibrium is disrupted, and as a result of this loss of control of all the parts cancer of one or more elements is able to originate and to grow at the expense of the rest of the body.

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References and Notes

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4. This work has been made possible, in part, by a grant from the National Cancer Institute, U.S. Public Health Service.
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Auditory and Aversion Thresholds of Rats for Bands of Noise

In the context of animal behavior theory, stimuli are often described as having both drive and cue value (*1*). Drive value refers to the ability of a stimulus to motivate behavior, and cue value refers to the ability of a stimulus to serve as a signal to the animal by virtue of its distinctiveness. In general, these two aspects of stimuli have been studied independently within the framework of two separate psychological disciplines, namely, learning theory and psychophysics. As a result of this, there are few studies comparing the cue and drive properties of stimuli, although it is obvious that the two properties are not unrelated in the case of most stimuli.

The purpose of the present study (*2*), then, was to develop a technique for comparing the drive and cue properties of a specific stimulus dimension—in this case, noise. More specifically, this research compares the auditory thresholds of rats for bands of random noise with the aversion thresholds of rats for the same bands of noise. The auditory thresholds were taken to represent the minimal cue value of white noise, and the aversion thresholds the minimal drive properties of white noise. Thresholds were obtained for a number of different frequency bands of noise so that both the shape of the functions and the distance between them could be compared. The following bands of noise were used: 250 to 500, 500 to 1000, 1000 to 2000, 3000 to 4000, and 4000 to 5000 cy/sec.

Acoustically, the apparatus for both threshold studies was the same, consisting primarily of a noise-generating system and a heavy Celotex enclosure 2 ft wide, 3 ft deep, and 6 ft high lined with fiber-glass insulation. The noise-producing system included a white noise generator, electronic switch, audio amplifier, attenuator, two UTC-4C variable band-pass filters, and a horn-type loudspeaker mounted inside the Celotex enclosure. Two test cages were used in the study; one for the determination of auditory thresholds and one for the determination of aversion thresholds. Both cages had the same over-all physical dimensions (7 in. wide, 10 in. deep, and 7 in. high); when in use (one at a time), they were mounted at the midline of the cabinet on steel rods. The sound field within each cage was relatively uniform (± 1½ db for all frequency bands).

Auditory thresholds were determined by means of a classical shock-avoidance technique. Six animals were first trained to turn a small wheel located at one end of the cage whenever a noise stimulus was presented. This was accomplished by giving the animal an electric shock by means of a shock grill floor if it did not turn the wheel within 2½ seconds of the onset of the noise. Whenever the animal responded within the 2½-second period, the noise was turned off and no shock was administered; if the animal did not respond within the 2½-second period, the noise continued and electric shock was administered until the rat turned the wheel. After the animal had been trained to respond to the cue or signal value of the noise, it was possible to determine the auditory threshold by varying the noise stimulus in 5-db steps around the threshold and recording the number of times the animal responded to each intensity. At the lowest intensi-

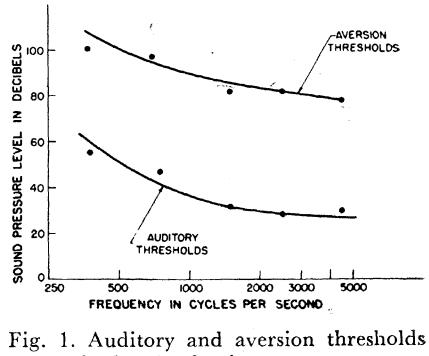

Fig. 1. Auditory and aversion thresholds of rats for bands of noise.